

Poster Session I

Diagnosis and differential diagnosis

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Diagnostic criteria for Susac syndrome
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Objective: Susac syndrome (SuS) is a rare, autoimmune-mediated, occlusive microangiopathy of the brain, inner ear, and retina, predominantly affecting young female patients. SuS is characterized by the clinical triad of encephalopathy with or without focal neurological signs, visual disorder due to branch retinal artery occlusions (BRAO), and vestibulo-cochlear deficits. Since clinical presentation, demographic aspects (such as age and gender) and diagnostic parameters (e.g. cranial magnetic resonance imaging (MRI) findings) may overlap, misdiagnoses as multiple sclerosis (MS), often occur. Our objective was to establish diagnostic criteria of either definite or probable SuS, to allow the earlier establishment of the correct diagnosis and initiation of an appropriate treatment and to facilitate the differentiation from MS.

Methods: The establishment of diagnostic criteria was based on the following three steps:

1) Definition of a reference group of 32 patients with an unambiguous diagnosis of SuS as assessed by the interdisciplinary experts of the European Susac Consortium (EuSaC) team;

2) Selection of diagnostic criteria, based on common clinical and paraclinical findings in the EuSaC cohort and on a review of the literature.

3) Validation of the proposed criteria in the previously published cohort of all SuS cases reported until 2012.

Results: Integrating the clinical presentation and paraclinical findings, we propose formal diagnostic criteria and recommend a diagnostic workup to facilitate the diagnosis of SuS. More than 90% of the cases in the literature fulfilled the proposed criteria for probable or definite Susac syndrome. We surmise that more patients could have been diagnosed with the recommended diagnostic workup.

Conclusion: We propose diagnostic criteria for Susac syndrome that may help both experts and physicians not familiar with SuS to make an early correct diagnosis, to prevent delayed therapies and to rule out important differential diagnoses such as MS.

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Time influences the performance of diagnostic criteria for multiple sclerosis
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Background: The McDonald criteria allow a diagnosis of multiple sclerosis (MS) in people with a clinically isolated syndrome (CIS) who have MRI evidence of dissemination in space and time. The performance of the McDonald criteria for the development of clinically-define MS (CDMS) has sometimes been evaluated in single-centre and multi-centre studies over follow-up periods of 2-3 years. Competing factors may influence the performance of MRI criteria in the longer term, including late relapses (beyond 2-3 years), identification of alternative diagnoses other than MS and the development of MS in people with normal MRI scans done at the time of CIS.

Objective: To investigate the effect of time on the performance of the McDonald 2010 in a prospectively recruited CIS cohort with long-term follow-up.

Methods: We studied 158 CIS patients (mean age 32.2 years, 107 (68%) female, 129 (82%) optic neuritis) who were followed up prospectively for the development of CDMS for up to 20 years. The McDonald 2010 dissemination in space and dissemination in time criteria were applied retrospectively to brain and spinal cord MRI scans obtained at the time of presentation (within 3 months of CIS) and a follow-up brain MRI after 3 and 12 months. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the McDonald 2010 criteria for a diagnosis of CDMS after 2, 5, 10, 15 and up to 20 years was calculated.

Results: 97 (61%) patients developed CDMS over a mean±SD follow-up period of 14.9±2.8 years. The median time to a second clinical attack was 18.5 months (range 1 - 214 months). Over time the specificity and accuracy of the McDonald 2010 criteria improved. The sensitivity/specificity/accuracy of the criteria for a diagnosis of CDMS was 94%/57%/68% at 2 years, 87%/69%/78% at 5 years, 82%/73%/78% at 10 years, 81%/76%/79% at 15 years and 81%/77%/80% at up to 20 years. The positive predictive value for a diagnosis of CDMS increased over time, while the negative predictive value decreased.

Conclusion: The duration of follow-up is an important factor when evaluating the performance MRI criteria in diagnostic criteria for MS. Validation of diagnostic criteria for MS should be done in longitudinal studies with at least 2 years of follow-up, and ideally 5 or more years given the notable increase in specificity between year 2 and 5.

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D Altman has nothing to disclose.
K Miszkiel has nothing to disclose.
F Barkhof acts as a consultant to Biogen-Idec, Janssen Alzheimer Immunotherapy, Bayer-Schering, Merck-Serono, Roche, Novartis, Genzyme, and Sanofi-Aventis. He has received sponsorship from EU-H2020, NWO, SMSR, EU-FP7, TEVA, Novartis, Toshiba. He is on the editorial board of Radiology, Brain, Neuroradiology, MSJ, Neurology.
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Evaluation of the sensitivity of the 2016 MAGNIMS MRI criteria for dissemination in space in children

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Background: The 2016 MAGNIMS criteria have made some recommendations to modify the dissemination in space (DIS) criteria, including:

(i) to add the presence of a lesion in the optic nerve,
(ii) no distinction needs to be made between symptomatic and asymptomatic MRI lesions,
(iii) requirement of ≥3 periventricular lesions. We aimed to retrospectively evaluate the increased in sensitivity of these three new DIS MAGNIMS criteria in a cohort of children with a confirmed diagnosis of MS.

Methods: We retrospectively recruited 62 children [median age at onset 13 (range 5-16), 42 females] with MS who had undergone baseline and serial clinical and MRI examinations over a minimum of 24 months. The involvement of the optic nerve was considered either on MRI, or visual evoked potentials (VEPs) or clinically (in case of presence of optic nerve pallor). A neuroradiologist, blinded to the diagnosis, scored the MRI scans, while the sensitivity of the 2010 McDonald and 2016 MAGNIMS DIS criteria at baseline was calculated.

Results: The mean length of follow-up was 4 years (range, 2-12 years). Fifty-five out of 62 children (89%) children fulfilled the 2010 McDonald DIS criteria at baseline. Three additional patients (58/62, 94%) fulfilled the DIS 2016 MAGNIMS criteria; this modest increase in sensitivity was due to the inclusion of lesions within the symptomatic region. The presence of an optic nerve lesion in 21 out of 62 children (34%) (5 confirmed on MRI, 9 on VEPs and 7 on fundoscopy) did not identify any additional cases. Similarly, the requirement of three or more lesions to define the involvement of the periventricular region in DIS did increase sensitivity; only one patient (who fulfilled both 2010 McDonald and 2016 MAGNIMS criteria) showed less than 3 lesions in the periventricular region; the remainder 57 children (57/62, 92%) showed ≥3 lesions.

Conclusion: The inclusion of symptomatic lesion may improve the sensitivity of DIS criteria in children, while the inclusion of optic nerve lesions in DIS did not influence the sensitivity of MRI criteria. The requirement of three periventricular lesions did not affect the number of patients who fulfilled the DIS criteria, but their role in increasing specificity in children should be evaluated by including cases who do not convert to MS. In general, alternative diagnosis should be looked for in children who at onset of clinically isolated syndrome do not have periventricular lesions.

Lesion topographies in the multiple sclerosis diagnostic criteria: a reappraisal

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Background: The MAGNIMS expert-opinion consensus on proposed modifications to the multiple sclerosis (MS) diagnostic criteria suggested increasing periventricular (PV) lesions from ≥1 to ≥3 and combining cortical and juxtacortical (JC) lesions into a single term (CJC). Additionally, corpus callous (CC) lesions are common in MS but are not included in the diagnostic criteria.

Goals: to assess the contributions of CJC and CC lesions to MS diagnosis and to compare the value of ≥1 vs ≥3 PV lesions in clinically isolated syndromes (CIS).

Methods: Study based on an ongoing CIS cohort. Baseline magnetic resonance imaging (MRI) was obtained 3-5 months after the CIS. We divided the study in two steps, selecting patients with sufficient information on baseline brain MRI to assess 2010 dissemination in space (DIS) and time (DIT), but taking the symptomatic lesions into account. Step 1. We evaluated the following lesion topography classifications in 657 CIS with stepwise Cox proportional hazards regression models considering 2nd attack as the outcome: ≥1 PV, ≥3 PV, ≥1 JC, ≥1 CJC, ≥1 CC, ≥1 infratentorial, and ≥1 spinal cord. Step 2: We established two DIS versions according to the PV lesion cut-offs of ≥1 and ≥3 and assessed their
Performance at 10 years with 2nd attack as the outcome (n=326), first individually and then combined with DTI. We also assessed these cases divided by age and by CIS topography.

**Results:** Step 1. The models [hazard ratios (95% CI)] favored ≥1 over ≥3 PV lesions [2.5 (1.7-3.6)] and CJC over JC lesions [1.4 (1.0-1.8)]. CC lesions were not selected. Step 2. DIS specificity with ≥1 PV lesions was slightly lower than with ≥3 (59.1 vs 61.4) and the same after adding DIT (88.6). Regarding age, ≥3 PV lesions improved DIS specificity over ≥1 PV lesions in the 40-49 years of age bracket (66.7 vs 58.3). This difference disappeared when adding DIT (83.3). Optic neuritis had a similar pattern when evaluating CIS topographies. The specificity for DIS with ≥1 PV lesions was 70.6 vs 76.5 with ≥3 PV lesions and 100.0 for both when adding DIT.

**Conclusions:** Our results comply with the MAGNIMS consensus recommendation of combining cortical and JC lesions into a single term when possible. CC lesions do not contribute to MS diagnosis. Concerning PV lesions, maintaining the current ≥1 PV lesion cut-off in the McDonald criteria does not compromise specificity in typical CIS cases, but attention should be paid to older patients or optic neuritis cases.

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**Brain and spinal cord imaging features in neuromyelitis optica spectrum disorder**

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**Background and aims:** Brain and cord MRI features of neuromyelitis optica spectrum disorder (NMOSD) patients are variables. Different studies have described typical white matter (WM) hyperintensities in the brain and spinal cord and new entities, such as short transverse myelitis (STM), can occur, thus complicating the diagnostic process. We evaluated the prevalence of typical and atypical focal hyperintense lesions of the brain and spinal cord in a multicentric, large cohort of NMOSD patients.

**Methods:** One-hundred and eighteen NMOSD patients according to 2015 Wingerchuck criteria and 30 age-, sex- and disease-duration matched multiple sclerosis (MS) patients underwent brain and spinal cord MRI at 3.0 Tesla in two different centers (Milan and Belgrade). Number and features of brain and spinal cord lesions were analyzed. Brain T2-hyperintense, T1-hypointense lesion volume (LV) and lesion probability maps were also obtained.

**Results:** The analysis of brain features showed that NMOSD patients had lower T2 and T1 lesion numbers and volumes than MS patients (p< 0.0001 for all). Cortical lesions on double inversion recovery sequences were detected in none of NMOSD patients and 60% of MS patients. Typical encephalic lesions were detected in 21% of NMOSD (14% brainstem periventricular/periaqueuductal lesions; 3.5% large hemispheric lesions; 1.6% diencephalic lesions; 1.6% cortico-spinal tract lesions). Thirty-five percent of NMOSD patients and 100% of MS patients had 2010 McDonald criteria for disease dissemination in space (p< 0.001). In addition, all NMOSD patients with WM lesions showed small non-specific brain lesions. In NMOSD patients, T2-hyperintense lesions were mostly located at the level of periventricular, subcortical, insular and periaqueuductal regions. The analysis of spinal cord features showed long transverse myelitis (LTM) in 39% of NMOSD patients and one MS patient (p=0.01). STM were detected in 27% NMOSD patients and 70 % of MS patients (p< 0.001).

**Conclusions:** Typical brain and cord lesions occur in a minority of NMOSD patients. A relatively high percentage of NMOSD patients satisfies 2010 McDonald criteria for DIS. These data prompt the development of better algorithms for the diagnosis and differential diagnosis of WM conditions.
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P291 Performance of 2010 McDonald criteria and 2016 MAGNIMS guidelines in the diagnosis of primary progressive multiple sclerosis

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Background: 2010 McDonald criteria for primary progressive multiple sclerosis (PPMS) have not been fully validated, while 2016 MAGNIMS MRI guidelines have not been studied in PPMS yet.

Goals: To assess sensitivity and specificity of 2010 McDonald and 2016 MAGNIMS criteria for PPMS applied to two University Centers retrospective cohorts.

Methods: Patients who were seen at University of California San Francisco and Verona University MS Centers for suspected PPMS were retrospectively identified from existing databases between November 2015 and October 2016. Data were obtained from review of patient charts with adequate documentation of clinical, MRI and cerebrospinal fluid (CSF) status to determine the fulfillment of 2010 McDonald criteria for PPMS and 2016 MAGNIMS guidelines for dissemination in space (DIS) at first visit at study centers. PPMS diagnosis was confirmed at last available visit using stringent criteria (DIS according to 2005 McDonald criteria, dissemination in time according to 2001 McDonald criteria, and exclusion of a better explanation as the “gold standard”).

Results: We included 108 patients with a mean follow-up duration of 10.1±6.6 years. 2010 McDonald criteria sensitivity for PPMS was 92.1% (95%CI: 84.5%-96.8%), while specificity was 57.9% (33.5%-79.8%). The highest combined values of sensitivity and specificity (91.8% [95%CI: 82.9%-96.9%] and 72.2% [46.5%-90.3%]) were achieved by combining 2016 MAGNIMS DIS criteria and the presence of oligoclonal bands or increased IgG index in the CSF.

Interpretation: Our findings suggest that 2010 McDonald criteria for PPMS diagnosis have high sensitivity, while specificity appears to be modest. The substitution of 2016 MAGNIMS criteria for DIS plus the incorporation of CSF status increased specificity without compromising sensitivity.

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P292 Brain microglial activation detected by TSPO PET at the pre-symptomatic stage of MS

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Introduction: Brain MRI of asymptomatic subjects sometimes shows incidental areas of high signal on T2-weighted sequences. This condition can be indicative of a radiological isolated syndrome (RIS) but is most often related to other aetiologies. The spatial distribution of T2-hyperintensities may help to distinguish inflammatory and non-inflammatory abnormalities, however a robust predictive imaging marker is still missing, especially for the earliest pre-symptomatic stages of MS. The detection of an abnormal microglial activation within hyperintense white matter (WM) areas or in normal appearing tissues (NAWM) could be predictive of MS but has never been investigated.

Methods: A 30-yr women (MP) was included as a control in an18F-DPA714 PET study in MS. We identified 3 brain WM T2-hyperintensities at baseline (0>3mm). She experienced 8 months later a clinical isolated syndrome (CIS), and brain MRI showed 3 new lesions. Spinal cord MRI was normal. The baseline 18F-DPA714 PET was quantified according to the non-invasive methodology recently described (Garcia-Lorenzo, et al. 2017, JCBFM) and expressed as distribution volume ratios (DVR). Results were compared to a group of 9 healthy controls with normal MRI and a similar high-binder polymorphism for the TSPO gene. Individual maps of microglial activation were also derived, expressed as percentages of volume with 18F-DPA714 activated voxels (PVAM).

Results: There was an increase of 18F-DPA714 DVR in baseline lesions (T2lesPVAM=11.11), compared to the white matter of healthy controls (WMM=0.99±0.06). A trend for an increased DVR was found both in the normal appearing white matter (NAWMMP=1.04 versus WMM=0.99±0.06), and in the grey matter (GMMP=1.42 versus GM=1.35±0.07).

Individual maps showed microglial activation both in T2 lesions and in the NAWM (PVAM in t2lesPVAM= 22.8% and in
Cancer, and 1 oral epidermoid carcinoma. None of these patients had PNS criteria. Three patients had non-small cell lung cancer, 1 breast onconeuronal antibodies using immunohistochemistry and cell-as paraneoplastic. Samples were tested for AQP4-IgG and plasm within 2 years of the NMOSD clinical onset were classified IgG positive NMOSD patients. Patients with a diagnosis of neo-nosed according established PNS criteria and to compare with the one of MS patients. 18F-DPA714 PET could identify the inflammatory component in incidental MRI hyperintensities. Whether it could predict clinical conversion to MS should be further investigated.

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Clinical and prognostic profile of paraneoplastic neuromyelitis optica spectrum disorders
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Background: Neuromyelitis optica spectrum disorders (NMOSD) mainly involve spinal cord and optic nerve in association with highly specific serum antibodies against the aquaporin-4 water channel (AQP4-IgG). Few series of NMOSD AQP4-IgG positive patients have been reported in relation with the presence of tumors. Nevertheless, these series have included benign tumors, don’t have applied established paraneoplastic neurological syndrome (PNS) criteria and have included limited clinical or follow-up data.

Objective: To define the clinical and paraclinical characteristics of AQP4-IgG positive patients with paraneoplastic NMOSD diagnosed according established PNS criteria and to compare with those of a cohort of idiopathic AQP4-IgG NMOSD patients.

Methods: We performed a retrospective, multicenter study. Data were collected from 2006 through 2016. We identified 186 AQP4-IgG positive NMOSD patients. Patients with a diagnosis of neoplasm within 2 years of the NMOSD clinical onset were classified as paraneoplastic. Samples were tested for AQP4-IgG and onconeuronal antibodies using immunohistochemistry and cell-based assays as described.

Results: Five (2.7%) AQP4-IgG positive NMOSD patients fulfilled PNS criteria. Three patients had non-small cell lung cancer, 1 breast cancer, and 1 oral epidermoid carcinoma. None of these patients had onconeuronal antibodies. Compared with idiopathic NMOSD, paraneoplastic NMOSD patients were more frequently male (60% vs 9%, p< 0.01) and older (mean age at onset 62 vs 40 years, p< 0.01). The clinical presentation was longitudinal extensive transverse myelitis (LETM) in 3 cases, and encephalitis/brainstem followed by sequential LETM (less than 1 month from first episode). None of the 5 patients presented episodes of optic neuritis. Paraneoplastic NMOSD patients exhibited, longer spinal cord lesions (mean vertebral segments affected: 13 vs 6, p=0.02), worse disability at onset and at last follow-up (p< 0.05) and higher mortality (60% vs 5%, p< 0.01).

Conclusion: Paraneoplastic NMOSD are more likely in older, male patients who present with LETM. Patients with this profile should be evaluated for the presence of an underlying cancer.

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DE and FG report no disclosures.

P294
Susac syndrome: clinical features, laboratory testing and treatment responses of 20 cases
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Background: Susac’s Syndrome is a rare, autoimmune angiopathy characterized by encephalopathy, hearing loss, and visual disturbance resulting from branch retinal artery occlusion. The diagnosis can be difficult to establish as the full clinical triad rarely occurs during the first presentation.

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Objective: The purpose of the study is to examine the demographics, clinical characteristics, treatment, and prognosis of patients with Susac syndrome.

Methods: 20 patients (7 male, 13 female) diagnosed with Susac syndrome from 9 centers were studied. Demographic and clinical features, diagnostic methods, clinical course, treatment strategies, and outcomes were analyzed. The diagnosis of Susac syndrome was based on clinical presentations, brain MRI, fluorescein angiography and audiometric tests.

Results: The mean age at presentation was 32 years (14-65). Only 4 patients presented with the complete clinical triad. Retinal artery occlusions were demonstrated in 16 patients. Audiograms showed sensorineural hearing loss in 17 patients. Nineteen patients showed central round callosal lesions on brain MRI’s. CSF analyses were performed in 18 cases. Elevated total protein was found in 15 patients, with a mean of 116 mg/dl (15-250). OCB was detected in 2 patients.

All patients were treated with an IV methylprednisolone (1000mg) for 3-10 days. Three patients only demonstrated clinical improvement after being further treated with 5 doses of IVIg. Ten patients responded to treatment, while 7 showed partial improvement and 6 showed no clinical improvement. After the acute phase, 6 patients were given a slow tapering of oral prednisone (ranging from 5 months to 7 years). The mean follow-up time was 2.7 years. Three patients that had not been treated with oral prednisone and one that had, later relapsed.

Conclusion: In this case series, only 20% patients presented with the classical clinical triad of Susac syndrome. The most common clinical manifestations at onset were central nervous system symptoms. Brain MRI’s showed corpus callosal lesions in 19 out of 20 patients. Since the clinical presentation of Susac syndrome can be ambiguous and the differential diagnosis is wide, the suspicion of Susac syndrome should be high if lesions are observed in the corpus callosum as well as coexisting auditory or retinal artery occlusions.

Although there is no guideline for treatment, early pulse steroid treatment, antithrombotic treatment and follow-ups for possible relapses are crucial.

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P295
Epidemiology of neuromyelitis optica spectrum disorders in Catalonia: a population-based study
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Background: Neuromyelitis optica spectrum disorders (NOMSOD) are responsible for long-term disability in adults and children. Though much has recently been learned about its pathogenesis, population-based studies regarding the epidemiology of NOMSOD are scarce, have shown variable prevalence rates and have been conducted before the implementation of the most recently proposed 2015 diagnostic criteria.

Aim: To estimate the incidence, prevalence and clinical features of NOMSOD in a Southern European white Caucasian population (Catalonia, Spain), based on the 2015 NOMSOD diagnostic criteria.

Methods: This was a population-based multicenter retrospective study. Between 2006 and 2015, adults and children with a first-ever diagnosis of NOMSOD according to the 2015 criteria were identified using multiple sources of data: aquaporin-4 antibody (AQP4-IgG) testing laboratory registry, identification of all those residents in Catalonia who during the study time period appeared through NMOSD (WHO ICD-9 code: 341.0) and contacting 41 hospitals (AQP4-IgG) testing laboratory registry, identification of all those residents in Catalonia who during the study time period appeared throughout Catalonia. Incidence rate was calculated for the period 01/01/2006 to 01/01/2016 dividing the number of patients with onset date of NOMSOD in this period by the total number of...
person-year at risk and prevalence rate was calculated for the date 01/01/2016. Serum samples were tested for AQP4-IgG by cell-based assay (CBA), immunohistochemistry or ELISA. Additionally, presence of antibodies to MOG (MOG-IgG) was investigated by CBA.

**Results:** Seventy-four patients were identified in a population of 7,522,596 inhabitants. Most cases were white Caucasian (81%), and female (76%) with mean age at onset 40.6 years (range 10-76). Fifty-four (73%) patients were positive for AQP4-IgG and 20 (27%), seronegative. Nine out of fifteen (60%) seronegative patients were positive for MOG-IgG. The incidence rate of NMOSD in the Catalan population was estimated to be 0.63 cases per 10^6 person-years and the prevalence 0.89 cases per 10^5 inhabitants.

**Conclusions:** This is the first population-based epidemiological study applying the 2015 NMOSD criteria. Prevalence and incidence rates confirm NMOSD as a rare disease in a predominant white Caucasian population.

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**Double seronegative longitudinally extensive transverse myelitis: preliminary study on 17 patients**

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**Background:** Longitudinally extensive transverse myelitis (LETM) is frequently associated to neuromyelitis optica (NMO) spectrum disorders. However some patients, despite a large work-up, remains negative for any diagnosis, including AQP4 and MOG auto-antibodies (Ab). For this double seronegative LETM patients, NMO criteria are not fulfilled, and data about natural history and treatments recommendation are lacking.

**Objectives:** To describe clinical, biological and radiological course of patients who experienced a first episode of double seronegative LETM.
Methods: We included patients for whom, despite a comprehensive work-up including MOG-Ab and AQP4-Ab, the final diagnosis was double seronegative LETM with brain MRI at admission not suggestive of multiple sclerosis. The minimum clinical follow-up required was 1 year. Clinical and radiological outcomes were assessed by EDSS, brain and spinal cord MRI at 6, 12, 18, 24 months, when available, and at last visit. The initial work-up including CSF analysis was collected.

Results: 17 patients fulfilled inclusion criteria: 11 women and 6 men. Mean age at episode was 38.6 years (range 16-80). Mean EDSS at nadir was 5.3 (range 1-8). The LETM localisation was as follows: 9 thoracic (53%), 4 whole spinal cord (23%), 2 cervical (12%) and 2 cervico-thoracic (12%). Mean number of white cells in the CSF was 62 (range 1 - 500). Intrathecal synthesis of IgG was positive for only 3/16 patients (19%). All patients received high dose intravenous steroids within a mean of 17 days. Nine patients received second line therapy: plasmapheresis (n=6), additional pulse of steroids (n=2) or IV immunoglobulins (n=1). Mean follow-up was 4.7 years (range 1-11). Improvement was reported for 12 patients (70.5%), with however a mean EDSS at 6 and 12 months at 3.79 and 3.53, respectively. 11 patients (65%) received an immunosuppressive treatment. Among them, only 6 patients were treated at first episode. Six patients (35.3%) (without immunosuppressive treatment) experienced a second relapse during the following year (mean interval: 7.9 months), and one patient at 17 months.

Conclusions: In this cohort, the majority of patients experienced incomplete recovery after a first episode of LETM. In addition, the high rate of relapse in the first year, suggests a more frequently chronic relapsing course than expected. Thus, immunosuppressive treatments should be considered after a first episode of double seronegative LETM.

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P297
Immunoglobulin free light chains in saliva: a new marker of multiple sclerosis?
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The complexity of multiple sclerosis (MS) requires different biomarkers in order to evaluate the disease in its various aspects. The common laboratory tests in MS are performed using cerebrospinal fluid (CSF), but the need of lumbar puncture makes CSF tests impractical to monitor disease activity and response to treatment.

In our search for the non-invasive diagnostic methods we hypothesized that immunoglobulin (Ig) free light chains (FLC) analysis in saliva may help to detect the immune-pathological changes in MS. This assumption relied on the reports indicating the changes in mucosal immunity in MS patients, and on a growing body of evidence of a diagnostic role of FLC in MS.

A new technique based on Western blot analysis was developed to study k and λ FLC monomers (M) and dimers (D) in the saliva. Normal saliva showed high proportion of dimeric FLC as compared to that in the serum. This finding might be explained by structural peculiarities of Ig in saliva: in contrast to most serum Ig, saliva IgA2 molecules incorporate the dimeric (not monomeric) light chains that may require production of larger amounts of dimeric light chains by the B cells synthesizing IgA2.

FLC M-D patterns in the saliva of MS patients were compared to those in healthy subjects. The intensity of the immunoreactive FLC was measured, and the FLC indices accounting for the total FLC level and for M/D ratios (k M/D index and λ M/D index) were computed. Most patients with active MS showed abnormally high FLC levels, or/and a high proportion of monomeric FLC. The reasons for such pathological FLC changes in active MS are not clear, but they might be due to peripheral B lymphocytes penetrating oral mucosa and producing larger amounts of monomeric FLC. Statistical analysis of these indices showed significant differences not only between active MS patients (n=27) and healthy subjects (n=28), but also between active MS patients (n=27) and those in remission (n=58).

The cut-off values were established to distinguish a healthy state from the pathological conditions in MS: total FLC level index = 17, k M/D index = 4.0, λ M/D index = 2.4. Most MS patients with active disease showed FLC indices above these cut-off values. The specificity and sensitivity of our technique for diagnosing the active MS was determined as 80% and 89%, respectively. The developed procedure may serve as a new non-invasive complimentary tool to evaluate the MS disease state and response to treatment.

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P298
Application of the 2015 diagnostic criteria for neuromyelitis optica spectrum disorders in a cohort of Latin American patients: the impact on diagnostic rates
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Background: The 2015 International Panel for neuromyelitis optica spectrum disorders (NMOSD) diagnosis (IPND) criteria were recently proposed. However, as there are no studies evaluating the application of the IPND criteria in Latin American populations, we aimed to assess whether these new criteria improve the diagnostic rate in a cohort of Latin American patients.

Methods: We reviewed medical records and applied both the 2006 and 2015 diagnostic criteria to all patients with final diagnosis of NMOSD in four centers from Argentina, Brazil and Venezuela. Patients with multiple sclerosis (n=915) or other well-established central nervous system inflammatory disease were excluded. Data on AQP4-ab status (by indirect immunofluorescence), gender, ethnicity, age and symptoms at onset, relapses, neuroimaging and immunosuppressive therapy were collected.

Results: A total of 104 patients were classified as NMOSD (2015 IPND). Of these, 64 (61.54%) patients fulfilled the 2006 NMO criteria (32 AQP4-ab positive, 17 AQP4-ab negative and 15 unknown). The rest of them, 38.46% (n=40, 33 were AQP4-ab positive, 5 AQP4-ab negative and 2 unknown AQP4-ab status) were reclassified as NMOSD by the 2015 IPND with a mean time to diagnosis of 5.25 (+12.57) months. Mean time to diagnosis was 7.89 (+14.18) months when using the 2006 IPND criteria (n=104) and 18.17 (+43.27) months when applying the 2006 criteria (n=64). Females with a mean age of about 37 years, white ethnicity and recurrent course predominated in all samples. Ninety-nine (95.1%) patients had at least 1 of the 3 major core clinical characteristics (optic neuritis (47.1%), transverse myelitis (31.7%) and both simultaneously (12%) and area postrema syndrome (13.4%)) as initial manifestation and 5 patients presented acute brainstem syndrome.

Conclusion: This study showed an increase of 38.46% in the diagnostic rate of NMOSD using the 2015 IPND criteria compared to 2006 NMO criteria, with a shorter mean time to diagnosis.

Disclosure
Nothing to disclose
**P300**

**New possibilities in multiple sclerosis imaging evaluation: studying the performance of Phase Sensitive Inversion Recovery (PSIR) in juxtacortical lesions**

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**Introduction:** Multiple Sclerosis (MS) is a demyelinating process that affects not only white matter, but also cortical gray matter. Cortical plaques can be classified by location and pathologic substratum. Juxtacortical lesions remain part of the differential diagnosis of cortical lesions, since the imaging differentiation can be challenging with the standard Magnetic Resonance (MRI) sequences. However, new pulse sequences have demonstrated better results in detection and differentiation of this lesions, like Double Inversion Recovery (DIR) and Phase Sensitive Inversion Recovery (PSIR), which shows accuracy 4.5 times greater than DIR in some studies.

**Objectives:** The study aims to assess the performance of PSIR in detection and differential diagnosis of cortical plaques in patients with diagnosis of MS, in comparison with FLAIR.

**Methods:** We retrospectively evaluated patients with diagnosis of MS confirmed by McDonald criteria (2010) who underwent MRI examination in our service between March 2016 and April 2017 and were studied with the sequences FLAIR and PSIR in a 3T equipment. The images were evaluated by two radiologists that quantified the number of lesions detected first in FLAIR sequence and after in PSIR sequence. After, they estimated how many lesions were reclassified using PSIR sequence. The incoherences in the first evaluation were solved by a third radiologist.

**Results:** 71 patients were included, with median age of 45.4 years and average of 12.7 years of disease evolution. 52 patients (73.2%) presented with juxtacortical lesions. Of this, 43 (82.7%) had lesions that were reclassified as leucocortical or cortical using PSIR, with a median number of 2.55 lesions per patient. 38 patients (54.3%) presented supratentorial lesions identified only in PSIR, with a median number of 1.44 lesions per patient. 23 patients (32.9%) presented infratentorial lesions identified only in PSIR, with a median number of 1.43 lesions per patient. PSIR sequence showed better detection performance than FLAIR in identifying MS lesions either in supratentorial or infratentorial compartment (p< 0.001 for both), detecting an average of 1.5 more lesions in supratentorial and 0.42 more lesions in infratentorial compartment.

**Conclusion:** The evaluation of MS lesions with PSIR shows greater performance for diagnosis and classification in comparison with FLAIR sequence, either in supratentorial or infratentorial compartment and its use should be encouraged in the clinical practice.

**Disclosure**

The authors declare no conflict of interests

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**MS Variants**

**P301**

**Myelin oligodendrocyte glycoprotein antibodies predict a favourable outcome in neuromyelitis optica related disorders**


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**Background:** Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been described in a subset of patients with neuromyelitis optica (NMO) phenotype. Previous data about disability outcome associated to MOG-Ab are limited and contradictory.

**Objective:** To investigate disability outcome associated to MOG-Ab in adults with NMO compared to aquaporin-4 antibody (AQP4-Ab) positive patients.

**Methods:** Multicentric retrospective study between January 2013 and January 2017, including 142 MOG-Ab positive, 176 AQP4-Ab positive and 53 double seronegative (DS) patients. Inclusion criteria were 1) the presence of at least one episode of transverse myelitis (TM) or optic neuritis (ON) for MOG-Ab and AQP4-Ab, 2) the presence of at least one episode of extensive TM or recurrent ON in DS. All patients were ≥18 years and had a minimum follow-up of 6 months. Survival time was defined as time to reach irreversible DSS (Disability Status Scale) 3.0 or visual acuity (VA) 0.2, sustained at least 6 months.

**Results:** Median age of onset was 37.4 (18.2-85.0) years, without differences among groups. A higher female to male ratio was observed only in the AQP4-Ab group (10:1 vs MOG-Ab 1.3:1 and
DS 1:1, \( p<0.001 \). MOG-Ab patients were more likely Caucasian (MOG-Ab 92.3% vs AQP4-Ab 76.9% vs DS 96.2%). After a median follow-up of 48.7 (6.1-556.6) months, patients were classified as follows: 39.1% NMO, 30.4% ON and 30.0% TM. When comparing patients with at least one episode of TM at last follow-up, MOG-Ab patients were at lower risk to reach DSS 3.0 than AQP4-Ab patients ( Hazard Ratio [HR] 0.55, 95% Confidence Interval [CI] 0.33-0.94, \( p=0.03 \)) and DS (HR 0.34, 95% CI 0.19-0.62, \( p<0.001 \)). Among those presenting at least one ON at last follow-up, MOG-Ab positive patients were at lower risk to reach VA 0.2 than AQP4-Ab (HR 0.44, 95% CI 0.22-0.89, \( p=0.023 \)) and DS (HR 0.43, 95% CI 0.17-1.01, \( p=0.05 \)).

Conclusion: In our study, MOG-Ab is associated to a good outcome in patients presenting with NMO or related disorders. This should be considered for future clinical trials.

Disclosure

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P302

Myelin oligodendrocyte glycoprotein antibodies spectrum disorder: clinical features and prognostic factors in a cohort of 150 adult patients


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Disclosure

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P303 Prognostic factor for therapeutic response of attacks in anti-AQP4, anti-MOG seropositive and NMO seronegative patients

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Background: Few data are available to define the best therapeutic strategy in treating attacks of NMO.

Objective: To define predictive factors for therapeutic response of the attacks in patients seropositive for anti-AQP4, anti-MOG or seronegative NMO.

Methods: We collected data from 5 referral centers included in the NOMADMUS project in France. Patients included should fulfill either NMOSD 2015 criteria or be positive for anti-AQP4/anti-MOG, be all free of any previous immunosuppressive drugs at the time of attack. To prevent biases, we considered only the very first attack for a given topography and the first treatment should be initiated during the first month. Therapeutic response was assessed using the EDSS score and was defined at 6 months by a complete regression of the symptoms (CR), a partial regression (PR) or the absence of response (NR).

Results: Seventy five patients were identified corresponding to 82 attacks. Mean age of first attack was 37 years including 43 myelitis (TM), 27 optic neuritis (ON), 8 ON+TM, one brainstem syndrome (BS), one ADEM and 2 BS+TM. Anti-AQP4 antibodies were found in 53 attacks and anti-MOG in 18 whereas 11 attacks were seronegative. Patients received the first treatment for their attack in a mean time of 13.7±19 days consisting in intravenous high dose steroid in 5 attacks at a mean dose of 5±2.8 grams. Second line of treatment was made in a mean time of 13.3±13.6 days following first line with steroids in 5 attacks, plasma exchanges in 24 attacks and IgIV in one. A third therapeutic line was proposed for 5 attacks. A CR was observed in 17 (20%) attacks, a PR in 45 (55%) and NR was observed in 16 (25%). In the univariate analysis, positivity for anti-AQP4 antibodies and the long delay between the first and the second line of treatment were two prognostic factors associated to a poor recovery. The dose of steroids and time to first line of treatment did not influence the recovery. No factor was identified independently in the multivariate analysis, probably due to the insufficient number of patients.

Conclusion: In this previously untreated population of seropositive AQP4+, MOG+ and seronegative NMO patients, AQP4-Ab positive status and delayed to second line treatment were both associated to poor recovery.

Disclosure

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N.C. has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva, with no relation to this study.

M.C. reports participation to advisory boards for Biogen, Novartis, Roche and

Ad Scientam, with no relation to this study.

E.M. reports participation to meetings and advisory boards for Biogen, Genzyme, Merck, Novartis, Roche and Teva, with no relation to the submitted work.

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A.K nothing to disclose

P304 Complement activation is associated with microscopic pathology in the placentas of women with NMO

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Introduction: An increased rate of preeclampsia and pregnancy loss has been reported in women with neuromyelitis optica (NMO) but mechanisms are unknown. Regulatory complement might represent the mechanism limiting injury in peripheral tissues induced by anti-aquaporin4 (AQP4) antibody binding to AQP4 antigen.

Objective: To establish a placenta registry for women with NMO and explore complement binding.

Methods: Pregnant women with NMO were prospectively enrolled in a longitudinal study registry. After examination for clinical purposes at the delivering hospital, placentas were transferred for detailed examination by the study placental expert. Each placental specimen was matched by maternal age and ancestry and gestational age at delivery with 2 specimens from mothers without neurologic or autoimmune disease. Medical records (maternal neurological record, delivery note, neonatal examination and delivering hospital gross pathology) and patient-reported reproductive history were also obtained.

Results: Placental specimens were obtained from 8 distinct states in the United States and in Europe. To date, 13 NMO pregnancies have been captured, with mean gestational age at enrollment of 31 weeks. At delivery, mean maternal age was 32.1 years, disease duration was 7 years, and gestational age was 38.1 weeks. One pregnancy resulted in preeclampsia and urgent delivery at 28 weeks, and one resulted in neonatal ventriculomegaly. There were no significant differences in gross or microscopic pathologic findings between the individuals with and without NMO. Immunofluorescence staining revealed an increase in CDA4 staining in NMO patients with placental microscopic pathology compared to those without (p<0.02). However, there was no...
compensatory rise in CD46 regulatory complement in these NMO placentas with pathology (P value >0.05).

**Interpretation:** Overall, these results suggest that dysfunction in the regulation of complement activation in women with NMO could give rise to microscopic placental pathology, resulting in adverse maternal and fetal outcomes.

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P305
**Neuromyelitis optica spectrum disorders: 20 year single centre observational data with treatment analysis**

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**Background:** Neuromyelitis optica (NMO) remains a diagnostic and therapeutic challenge for neurologists, especially when considering the restriction for medication access and antibody testing in many countries.

**Goals:** To present an update on our observational series (Bichuetti. Mult Scler 2009), including treatment analysis.

**Methods:** Single centre prospective observational cohort with retrospective analysis.

**Results:** we reviewed 1.748 medical records of patients followed from 1995 to December 31st, 2015. From 216 with possible NMO, 37 were excluded due to irretrievable information and 21 due to non-NMO diagnosis; 158 patients were included: 8 with monophasic NMO (mNMO) and 150 with relapsing NMO (rNMO). Mean age of onset was 33.6 for mNMO and 33.0 for rNMO, with median 8.3 years of disease duration for mNMO and 7.0 for rNMO; half of them were Afro-descendants in both groups. Both groups presented brain MRI abnormalities: 25% in mNMO and 48.7% in rNMO. 54.4% of the rNMO were anti-AQP4 positive and 82.7% fulfilled 2015 diagnostic criteria; all the mNMO were anti-AQP4 negative. One patient had concomitant autoimmune disease in the mNMO and 29 in the rNMO group. Six patients have deceased during follow-up, all from the relapsing cohort. 74.7% of the rNMO group presented the complete NMO syndrome (with 2 of the core symptoms: optic neuritis, longitudinal extensive transverse myelitis and/or area postrema syndrome), 10.7% relapsing myelitis and 14.7% relapsing optic neuritis. All patients in the rNMO group received at least one preventive treatment, including disease modifying therapies for multiple sclerosis (16), prednisone (101), azathioprine (100), mycophenolate (4), cyclosporine (2), methotrexate (20), cyclophosphamide (16), rituximab (2) or IV immunoglobulin (8). 70% of the treated rNMO presented an EDSS variation of 0 to 0.5, 12.7% 1.0 to 1.5, 6% 2.0 to 2.5, 4.7% 3.0 to 3.5 and 6.7% ³4.0.

**Conclusion:** 82.7% of patients treated with oral immunosuppressant, most of them azathioprine and methotrexate with or without prednisone, remained stable or with minimal EDSS variation during 8 years of follow-up. Early diagnosis and treatment implementation might contribute to this result that is important for those practicing in countries with restricted access to monoclonal antibodies.

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Nilton Amorim de Souza has nothing to disclose

Edenida Maria Lobato de Oliveira has received speaker fee from Teva, Biogen, Genzyme

P306
**Anti-MOG antibodies induce complement mediated demyelination in isolated optic neuritis and myelitis**

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**Background:** Recent studies indicate Anti-Myelin Oligodendrocyte Glycoprotein antibodies (MOG-IgG) as new serum biomarker of some forms of demyelinating diseases distinct both from classical Multiple sclerosis (MS) and from AQP4-IgG-mediated neuromyelitis optica spectrum disorders (NMOSD).

**Aims and Methods:** The aims of this study were 1) to evaluate, by a Cell Based Assay on HEK-293 cells stably transfected with human MOG, the frequency of serum MOG-IgG in a cohort of 57 adult patients with a first monosymptomatic episode of idiopathic autoimmune Optic Neuritis (ON) or Myelitis prospectively followed for a median period of 3.3±3.2 years; 2) to compare baseline clinical, laboratory and MRI features of patients with and without serum MOG-IgG; 3) to investigate the potential cytotoxic effect of MOG-IgG, obtained by immunoadsorption, on ex vivo rat optic nerve. Rat optic nerve was cultured on transwell porous supports for 24 h in CO2/O2-bubbled artificial cerebrospinal fluid (CSF), with human complement (HC) and/or MOG-IgG.
Results: Nineteen patients (33%) showed serum anti-MOG-IgG: 11 myelitis and 8 ON. MOG-IgG positive patients were older (p=0.001), had more severe disability at onset (p=0.0001), lower incidence of CSF IgG oligoclonal bands (31% vs 73%; p=0.003), lower number of brain MRI lesions (p=0.0001) and higher frequency of longer MRI spinal cord lesions (36% vs 5%; p=0.001) in comparison to MOG-IgG negative subjects. At follow-up, 42% of MOG-IgG positive patients satisfied MRI criteria for MS diagnosis vs 65% of MOG-IgG negative (p=0.07).

Rat optic nerve exposure to MOG-IgG and HC produced marked loss of myelin as a consequence of an oligodendrocytic damage, whereas astrocytes were not involved as demonstrated by normal Glial Fibrillary Acid Protein (GFAP) and AQP4 expression levels. No damages were seen in rat optic nerve cultured with either MOG-IgG or complement alone.

Conclusions: The peculiar clinical and paraclinical characteristics of MOG-IgG positive patients with ON and myelitis and the demonstrated complement-mediated cytotoxic effect of MOG-IgG on rat optic nerve oligodendrocytes, suggest that MOG autoimmunity is associated to an oligodendrocytes-mediated disease more similar clinically to NMOSD and pathologically to a pattern II variant of MS. Such a hypothesis warrant therapeutic considerations.

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P307
Ethnic differences in clinical manifestation and outcome of neuromyelitis optica spectrum disorder

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Objective: To determine if ethnic differences exist in the clinical features of neuromyelitis optica spectrum disorder (NMOSD).

Methods: Clinical and demographic data were retrospectively collected from 412 patients meeting 2015 NMOSD criteria in Germany, South Korea and USA.

Results: Of total 412 patients with NMOSD, 252 were Asian, 111 Caucasian, and 49 were Afro-American/Afro-European patients.

There was no significant difference in disease duration, time to immunosuppressive treatment, gender ratio, or anti-aquaporin4 positivity between ethnicity. The Asian and Afro-American/Afro-European patients had a younger age and higher frequency of brain involvement at onset than the Caucasian patients. The brain attacks during disease course occurred in 45% of Asian, 33% of Afro-American/Afro-European and 20% of Caucasian patients, but statistically significant difference was only found between Asian and Caucasian patients (p< 0.001). Patients who experienced severe attack (visual acuity<0.1 or EDSS>6.0 at nadir of attack) were more frequent in Afro-American/Afro-European patients (92%) than the Asian (68%) and Caucasian patients (61%) (p< 0.001). At last follow-up, patients with converted visual functional system (cVFS) score ≥ 3 were more frequently found in Afro-American/Afro-European (45%) than Asian (31%) and Caucasian patients (21%) (p<0.008), while the frequencies of EDSS > 6.0 were not significantly different. Mean time to EDSS ≥ 6.0 was shortest in Afro-American/Afro-European (3.1 ± 3.1 years) followed by Asian (4.6 ± 4.3 years) and Caucasian patients (7.4 ± 7.9 years), whereas mean time to cVFS score ≥ 3 was not significantly different among races.

Conclusion: Ethnic origins likely contribute to the clinical manifestations and outcomes of NMOSD. The Asian and Afro-American/Afro-European patients had a younger age of onset and higher frequency of brain involvement at onset than Caucasian patients. Afro-American/Afro-European patients experienced severe attack more frequently and reached severe disability more rapidly than Asian and Caucasian patients.
Clinical, MRI and laboratory features of myelin oligodendrocyte glycoprotein (MOG)-antibody-associated neurologic disease: a study of 259 cases

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Background: Antibody against myelin oligodendrocyte glycoprotein (MOG-Ab) can be detected in various demyelinating diseases of the central nervous system (CNS). Clinical findings of MOG-Ab+ neurologic diseases (~50 cases) have been reported, but its large scale cohort studies (~200 cases) including both adult and pediatric cases are lacking.

Objectives: To analyze the clinical, MRI and laboratory features of 259 MOG-Ab+ cases.

Material and Methods: We surveyed 369 MOG-Ab+ cases among 2910 consecutive cases whose samples were sent to our laboratory to test MOG-Ab with our in-house cell based assay (July 2015–March 2017).

Results: Of the 369 cases, the information of 259 cases were available. 125 (48.3%) were male, and the median age was 26 years (range 1–85) with 100 cases younger than 18 years old (38.6%). 129 (49.8%) had a relapsing disease, and MOG-Ab was detected in the first CNS event in 166. Median observation period was 19 months (3–444 months). In the latest events, the CNS lesions were localized in optic nerves in 147 (bilateral in 63), brain in 96 (42 with brainstem lesions, 17 with basal ganglia lesions), and spinal cord in 59 (33 with cervical cord lesions [40 (67.8%) had long cord lesions extending over more than 3 vertebral segments]. Major clinical diagnoses in the pediatric cases were multiple sclerosis/clinically isolated syndrome (22%), isolated optic neuritis (16%) and acute disseminated encephalomyelitis (15%), whereas in the adult cases, isolated optic neuritis (39.7%) was the most common followed by myelitis (8.3%), neuromyelitis optica spectrum disorders (8.3%), and cortical encephalitis (8.3%). In 129 relapsing cases, 34 had more than 4 relapses, and 43 experienced a relapse despite steroid therapy. In 205 whose cerebrospinal fluids were examined, 155 (75.6%) had pleocytosis, and the median cell counts were 16/microliter (0–854). Polymorphonuclear cells were observed in 125 (61.0%). Oligoclonal IgG bands were positive in 11.7% and myelin basic protein levels were elevated in 62.7% (median 118mg/dl, 40–38300). After the first clinical events, significant reduction in MOG-Ab titers over time predicted a monophasic course. EDSS and visual outcomes were generally good, whereas some had poorer outcomes mainly in relapsing cases.

Conclusion: The present study of MOG-Ab+ neurologic diseases showed age and MOG-Ab persistence and relapse may influence clinical phenotypes, course and prognosis of the disease, respectively.

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K. Fujihara serves on the advisory boards for Bayer Schering Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Alexon Pharmaceuticals, and Medimmune; has received travel funding and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Eisai Inc, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, Asahi Kasei Medical Co., Daiichi Sankyo, and Nihon Pharmaceutical; is on the editorial board for Clinical and Experimental Neuroimmunology; is an advisory board member for Sri Lanka Journal of Neurology; and received research support from Bayer Schering Pharma, Biogen Idec Japan, Asahi Kasei Medical, The Chemo-Sero-Therapeutic Research Institute, Teva Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Genzyme Japan, Ministry of Education, Science and Technology of Japan, and Ministry of Health, Welfare and Labor of Japan. Go to Neurology.org/nn for full disclosure forms.

P309
NMOSD relapses: an analysis of 328 episodes in 75 cases
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Introduction: We have recently undertaken a clinical survey of NMOSD across Australia and New Zealand; here we focused on...
a detailed analysis of relapse histories with the aim of better defining the clinical features of this condition.

**Methods:** We performed a clinical survey of NMOSD through 23 demyelinating disease clinics. Identification of cases was based on clinical criteria using features identified as being of high risk for NMOSD. Demographic and clinical information, including relapse histories, were recorded using a standardised questionnaire. NMOSD cases were defined using the 2015 Wingerchuk criteria.

**Results:** Of 177 cases of suspected NMOSD, 11 (6%) were excluded. NMOSD was confirmed in 75/166 (45%) cases. AQP4 antibodies were positive in 67/75 (89%) cases. Information for 328 relapses was available for analysis in the 75 cases. The most common types of relapse were transverse myelitis (48%) and optic neuritis (40%). Brainstem (9%), including area postrema (3%), and cerebral (1%) relapses were less common. Multifocal relapses were quite uncommon with optic neuritis and transverse myelitis being the most common combination (2%). Optic neuritis relapses were more common in cases with Asian ancestry (46/87 (53%) vs 85/241 (35%); p< 0.01). There was no significant difference in the pattern of relapses according to gender or serostatus. Analysis of month of relapse did not show any statistically significant variance from the expected distribution and there was no clear seasonal pattern. Area postrema syndromes were more common as a first relapse (9%) compared to overall and analysis of relapse by age suggested a predominance of optic neuritis prior to the age of 30 years with transverse myelitis being more common later. In 193/328 (59%) attacks IV steroids were given and 41/328 (13%) were treated with plasma exchange. Recovery data was available for 271 attacks and was full in 80 (30%), partial in 167 (62%) and nil in 24 (9%).

**Conclusions:** This cohort of NMOSD patients represents approximately 50% of the known cases in Australia and New Zealand. These data indicate that optic neuritis and transverse myelitis are the most common types of relapse and that simultaneous multifocal attacks are relatively uncommon. Attacks of optic neuritis predominate over spinal attacks under the age of 30 years, but this pattern is reversed thereafter. Optic neuritis may be more common in cases with Asian ancestry. Recovery is incomplete in the majority of relapses.

**Disclosure**


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**P310 Multiple sclerosis AHI1 genetic risk promotes IFNg+ CD4+ T cells**

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**Objective:** To study the influence of the Abelson helper integration site 1 (AHI1) locus associated with multiple sclerosis (MS) susceptibility on CD4+ T-cell function.

**Methods:** We characterized chromatin state of T-cells in the MS associated AHI1 linkage disequilibrium (LD) block. The expression and the role of the AHI1 variant was examined in T-cells from genotyped healthy subjects that were recruited the PhenoGenetic Project, and the function of AHI1 was explored using T-cells from Ahi1 knockout mice.

**Results:** Chromatin state analysis reveals that the LD block containing rs4896153, that is robustly associated with MS susceptibility (Odds Ratio = 1.15, p=1.65 x 10^-3), overlaps with strong enhancer regions that are present in human naïve and memory CD4+ T-cells. Relative to the rs4896153^A protective allele, the rs4896153^T susceptibility allele is associated with decreased AHI1 RNA expression specifically in naïve CD4+ T-cells (p=1.73 x 10^-14, n=213), and we replicate this effect in an independent set of subjects (p=2.5 x 10^-4, n=33). Functional studies then showed that the rs4896153^T risk variant and the subsequent decreased AHI1 expression was associated with reduced CD4+ T-cell proliferation and a specific differentiation into IFNγ-positive T-cells compared to those carrying the protective rs4896153^A allele. This T cell phenotype was also observed in murine CD4+ T-cells with genetic deletion of Ahi1.

**Interpretation:** Our findings suggest that the effect of the AHI1 genetic risk for MS is mediated, in part, by enhancing the development of pro-inflammatory IFNγ+ T-cells that have previously been implicated in MS and its mouse models.

**Disclosure**

The authors declare no conflict of interest. Research reported in this study was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number R01AI130547.
P311
Double inversion recovery MRI in the evaluation of the anterior visual pathway in patients with multiple sclerosis and neuromyelitis optica spectrum disorders

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Background: Double inversion recovery (DIR) magnetic resonance imaging can detect cortical lesions in multiple sclerosis (MS). The aim of our study is to evaluate the anterior visual pathway (AVP) using 3D-DIR sequence in a Japanese cohort of MS and neuromyelitis optica spectrum disorders (NMOSD).

Methods: We performed neuro-ophthalmological and neuroradiological analysis using 3D-DIR images from 14 patients (28 eyes) with NMOSD and 28 patients (56 eyes) with MS.

Results: Thirteen of 28 (46%) eyes with NMOSD and 19 of 56 (34%) eyes had history of optic neuritis (ON) in NMOSD patients and MS patients, respectively. 3D-DIR findings demonstrated that 13 of 13 (100%) eyes and 17 of 19 (89%) eyes had abnormal signal in the AVP with history of ON in NMOSD patients and MS patients, respectively, and 3D-DIR images reached the good performance for the diagnosis of ON (100% sensitivity and 100% specificity for NMOSD patients, and 89% sensitivity and 97% specificity for MS patients). The numbers of segments with optic chiasma and intracranial involvement were significantly higher in NMOSD patients compared to MS patients (P < 0.05). The length of abnormal intensity lesions in the AVP in NMOSD patients was significantly longer than in MS patients (P < 0.05). Moreover, length of abnormal intensity lesions on 3D-DIR images was inversely correlated with retinal nerve fiber layer thickness on optical coherence tomography examination in the whole cohort (P < 0.01).

Conclusion: The optic nerve DIR images demonstrated that the distribution of abnormal intensity lesions showed accumulation of archival lesions throughout the disease course, the length of lesions may be associated with retinal axonal damages, and the patterns of distribution and length in NMOSD patients was distinct and unique compared to those in MS patients. These data suggest that the optic nerve DIR images may be useful parameters in diagnosis of ON of NMOSD and MS patients.

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M. Hokari, A. Yokoseki, T. Wakasugi, F. Yanagimura, K. Yanagawa, Y. M. Nishizawa and O. Onodera have nothing to disclose.

P312
What could be the clinical and MRI spectrum of anti-MOG associated disorders?

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Background and aims: A broad spectrum of central nervous system inflammatory disorders has been recognised related to anti-myelin oligodendrocyte glycoprotein antibodies (MOG-Abs). We present clinical, MRI and cerebrospinal fluid (CSF) data of a patient cohort of anti-MOG-Abs positive Danish adults.

Methods: Case series: report of 16 patients. The serum analysis for anti-MOG Abs was performed by using a cell-based assay detecting antibodies of IgG1 class targeting full-length MOG in Oxford, UK.

Results: We have identified 7 female and 9 male with anti-MOG Abs between October 2015 and March 2017. The median age at onset was 33 (11-62). The mean follow-up was 92 (±70) months. Mean time to the second relapse was 25 (±23.6) months. Four patients had monophasic disease. The median number of relapses was 2.5 (range: 1-13). Frequent relapses (5-8-11-13) were observed in 4 cases, where the primary diagnosis was multiple sclerosis (MS) and disease modifying therapies were initiated. The clinical presentations included: optic neuritis in 5 cases; myelitis in 2 cases; optic neuritis and myelitis in 3 cases; myelitis and brainstem symptoms in 2 cases; optic neuritis and acute disseminated encephalomyelitis (ADEM) in 1 case; myelitis with ADEM in 1 case; combination of optic neuritis, myelitis and brainstem symptoms were observed in 2 cases. Brain MRI was repeatedly normal in 6 cases, but MS-like lesions in the corpus callosum and juxtacortical lesions were found in 3 cases. Spinal cord MRI showed longitudinally extensive spinal cord lesion in 9 cases. Furthermore, 4 patients had also short lesions in the spinal cord, and 4 patients had multiple lesions in the spinal cord. CSF revealed normal IgG-index in all 16 cases; only 2 patients out of 12 had oligoclonal bands (OCBs). Mononuclear pleocytosis was found in 9 cases with a median cell number 33.5 (1-195).

Conclusion: Our cohort represents a clinically heterogeneous patient population explaining the difficulty in establishing diagnosis. We observed a wide range of different MRI lesions characteristic to both neuromyelitis optica spectrum disorder and MS. The CSF results showed more clear difference from MS, and examination of anti-MOG-Abs should also be considered in MS cases without elevated IgG index and OCBs.

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Paediatric MS

P313
Disease course and immunotherapies responses in children with relapsing myelin oligodendrocyte glycoprotein antibodies (MOG-Ab)-associated disease


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Background: Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) are associated with a range of demyelinating disorders in adults and children. Current therapeutic strategies are largely center-specific, with no formal consensus guidelines. We therefore conducted this multicenter study to describe the disease course, and response to different treatment strategies in children with relapsing MOG-Ab-associated disease.

Methods: We retrospectively collected demographic, clinical, and radiological data of 102 patients with MOG-Ab associated relapsing disease, from 8 countries that are part of the EU Paediatric Demyelinating Disease Consortium. Patients were treated according to local protocols. Annual relapse rate (ARR) and Expanded Disability Status Scale (EDSS) before and on treatment were compared in patients receiving immunotherapy for over 1 year.

Results: 102 children were identified whose original diagnoses were neuromyelitis optica spectrum disorder (NMOSD, 43.1%), multiphasic disseminated encephalomyelitis (MDEM, 19.6%), and relapsing optic neuritis (RON, 17.6%). A total of 464 demyelinating events were reported in the cohort. Clinical events under the age of 9yrs were more likely to affect the brain, whereas events over the age of 9yrs were more likely to affect the optic nerve (p< 0.001). Brain MRI abnormalities were also more common in the younger group (p< 0.001). Disease modifying drugs (DMDs) were given in 52 (51%) children: 28 (53.8%) patients were treated with 1 DMD, 16 (30.7%) with two and 7 (13.5%) with 3 or more sequential DMDs. The treated group had a more severe phenotype than the untreated group, with higher total number of relapses and EDSS at last follow-up (p=0.0094 and P< 0.001 respectively). No changes in relapses frequency and EDSS were observed between the pre- and post-initiation of Interferon-beta and Glatiramer acetate, n=11). ARR was reduced by 0.8 with Azathioprine (n=20, p=0.0004), 1.3 with Mycophenolate mofetil (n=15, p=0.0028), and 1.6 with Rituximab (n=9, p=0.0008), but the EDSS remain stable with these DMDs. Regular IVIG (n=12) were associated with an improvement in ARR (1.7, p< 0.0001) and EDSS (mean improvement 1.0, 95%CI: 0.2466 to 1.753, p=0.0127).

Conclusions: Children with MOG-Ab associated disease did not seem to benefit from conventional MS treatments, whilst B-cells targeted treatments, and particularly IVIG, were associated with a significant reduction in relapse frequency.

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**P314**

Psychiatric morbidity develops after onset of pediatric multiple sclerosis: a Danish nationwide population-based study

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**Background:** Pediatric-onset multiple sclerosis (MS) affects life at a stage vital for social and educational achievements and psychiatric co-morbidity is common after MS onset. Few studies have examined psychiatric morbidity before MS onset.

**Objectives:** To assess the association of psychiatric morbidity before and after onset of MS in children.

**Methods:** In this nationwide study, detailed case ascertainment was performed on all pediatric MS cases, including chart review. For each MS patient we selected five controls using density sampling from the entire Danish population, and we matched controls to MS-cases by sex and birthdate. Outcomes were in-hospital diagnoses of psychiatric disorders, outpatient psychiatric consultations and psychiatric drugs. Hazard ratios (HR) including 95% confidence intervals (CI) were estimated using conditional logistic regression and cox regression.

**Results:** We identified 212 pediatric MS cases and 1,060 controls. No association with psychiatric morbidity was found before onset of MS (HR=0.8; 95% CI, 0.4-1.7). After MS onset, MS cases had significantly more psychiatric co-morbidity than controls (HR=2.6; 1.7–3.8; p<0.0001) and it was present in both boys and girls.

**Conclusions:** Psychiatric morbidity commences at onset of pediatric MS and affects children with MS almost three times more frequent than children without MS; accordingly, neuropsychological evaluation is highly recommended in newly-diagnosed children with MS.

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**P315**

Childhood multiple sclerosis is associated with reduced brain volumes at disease onset and brain growth failure

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Background: Recent studies showed that children with multiple sclerosis (MS) have failure of age-expected brain growth. However, the onset and extent of brain volume loss remains unclear. We aimed to evaluate brain growth in a European cohort of children with MS treated with basic disease-modifying and second-line therapies.

Goal: Longitudinal assessment of brain volumes in paediatric MS patients at disease onset and at 2 years follow-up (FU).

Methods: High-resolution MRI scans from 38 patients (mean age 14.6±1.7 years; 20 female) with paediatric MS at first attack and after 2 years from Germany and Austria were compared to controls from the NIH Paediatric MRI Data Repository (661 scans, 349 children; age 10-22). Normalized whole brain (WB), grey matter (GM), peripheral grey matter (pGM), white matter (WM) and ventricular cerebrospinal fluid (vCSF) volumes were measured using FSL SIENAX. Age- and sex-specific z scores were calculated based on controls.

Results: Paediatric MS patients had significant brain atrophy at disease onset (reduced WB (1634.8 cm³±61.4 vs. 1738.1±86.3; p<0.001), GM (901.8±56.6 vs. 973.1±71.6; p<0.001), pGM (707.5±50.0 vs. 780.6±60.1; p<0.001), and WM volumes (733.1±66.8 vs. 765.1±49.0; p<0.001)) as well as after 2 years compared to controls. The z scores of all brain structures were significantly smaller than zero at baseline (all p<0.001) and at 2 years FU (all p<0.003). Accordingly, vCSF volume was significantly reduced using FSL SIENAX.

Conclusion: Already at disease onset, paediatric MS patients show significant brain atrophy, affecting WB, GM and WM volumes compared to controls. In addition, patients continue to have accelerated WM and WB volume loss within 2 years compared to controls despite disease-modifying therapies. Marked brain atrophy already at disease onset and continuing brain volume loss over time indicate early neurodegeneration in paediatric MS patients.

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P316 Executive dysfunction in paediatric-onset multiple sclerosis: deficits above and beyond slowed processing speed
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Background: Cognitive impairment occurs in approximately 30% of individuals with paediatric-onset multiple sclerosis (MS). Executive functions (EF) seem particularly vulnerable to MS pathology, but given the importance of efficient information processing for coordination of EFs, it is unclear whether such deficits represent impairment distinct from slowed processing speed. We investigated performance on tasks of attention, inhibition, mental flexibility/abstraction, and working memory in young adults with paediatric-onset MS, controlling for task-specific response time.

Method: 43 patients (mean age = 19.60 ± 3.81; 31 female; mean disease duration = 6.16 ± 3.72) and 30 healthy controls (mean age = 17.70 ± 5.15; 21 female) were recruited from eight children’s hospitals across Canada and from the Children’s Hospital of Philadelphia, Philadelphia, PA, United States.

Results: After controlling for response time, MS patients demonstrated poorer accuracy than healthy controls on tasks of attention (p = 0.001), inhibition (p = 0.003), and working memory (p = 0.018). Accuracy on a measure of mental flexibility/abstraction (Conditional Exclusion Test) did not differ between groups (p = 0.075), however, post-hoc analyses revealed slower response times on this task in MS patients, which were retained when controlling for motor speed (p = 0.021). There were no significant group differences in response time for the attention, inhibition, and working memory subtests (p > 0.05).

Conclusion: Several domains of executive dysfunction, specifically attention, inhibition, and working memory, are apparent in young adults with paediatric-onset MS, and are distinct from...
processing speed deficits. Difficulties with abstraction and mental flexibility are less apparent and are more likely attributable to slowed processing speed.

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P317 Clinical significance of anti-MOG antibodies in the evaluation of children with a first demyelinating episode: prospective Spanish national cohort

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Objectives: To evaluate the utility of antibodies against the myelin oligodendrocyte protein (anti-MOG) antibodies predicting the clinical course of children after a first episode of acquired demyelinating syndrome (ADS).

Methods: Cohorts study of 124 children (< 18 years) followed prospectively from a first episode of ADS. Acute serum/CSF samples (< 3 months from disease onset) were investigated for aquaporin 4 (AQP4), MOG and neuronal surface antibodies. In patients with antibodies, follow-up serum samples were re-analysed every 4 months. Sixty-nine radiologic items were systematically analysed blinded to clinical and immunological data.

Results: 124 children (67, 54% female) median age 9.2 years (IQR 4.2-13.4) were included after a first episode of ADS (50 acute disseminated encephalomyelitis [ADEM], 29 optic neuritis [ON], 22 myelitis, 6 brainstem-cerebellar, 6 hemispheric, and 12 multifocal non-encephalopathic involvement). After a median follow-up of 12.2 months (IQR 6.9-24.1), 14 (11%) patients were diagnosed with multiple sclerosis (MS), 7 (6%) developed at least one clinical relapse but didn’t fulfill the criteria for MS (6 neuromyelitis optica spectrum disorders [NMOSD], 1 recurrent ON), and 103 (83%) individuals remained monophasic (48 ADEM, 1 NMOSD, 54 clinical isolated syndromes [CIS]). Anti-MOG antibodies were identified in 42/107 (39%) patients in whom acute samples were available (4 with concomitant glycine receptor [GlyR] antibodies). None of the patients harboured AQP4 or other antibodies. None of the 42 patients with MOG antibodies was diagnosed with MS at last follow-up, while 9/65 (14%) patients without these antibodies did, p<0.01. Six/7 patients who developed non-MS clinical relapses harboured MOG antibodies, p<0.01. Preliminary analysis of 20 patients comparing radiological variables at onset showed that patients with MOG antibodies had less frequent periventricular and tectum lesions, but more frequently diffuse cerebellum involvement (p<0.05). None of the MOG patients had new asymptomatic lesions on follow-up MRIs. These data, the dynamics of the antibodies, and the analysis of 30 more patients will be presented.

Conclusion: Our data support recent published data that MOG antibodies are associated with a non-MS disease course in children, and frequently associated with NMOSD.

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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Actelion, Amirall, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme and Teva Pharmaceutical.

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AR serves on scientific advisory boards for NeuroTEC and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer Schering Pharma, Sanofi-Aventis, Bracco, Merck Serono, Teva Pharmaceutical Industries Ltd., and Merck-Idoc, receives research support from Bayer Schering Pharma, and serves as a consultant for Novartis.

TA and GA share first authorship

MT and AS share last authorship

P318

Implications of the international paediatric multiple sclerosis study group consensus criteria for paediatric acute disseminated encephalomyelitis: a Danish nationwide population-based study

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Background: The International Paediatric Multiple Sclerosis Study Group (IPMSSG) has proposed new criteria for acute disseminated encephalomyelitis (ADEM) not evaluated in clinical practice.

Objectives: To assess epidemiological implications of the IPMSSG criteria for ADEM in a cohort study using prospectively collected data.

Methods: We identified all diagnosed cases of ADEM in Denmark during 2008-2015 from the Danish National Patient Register by International Classification of Diseases 10-codes assigned to acute demyelinating episodes. We subsequently reviewed all medical records to validate ADEM based on a senior paediatric neurologist’s opinion (A.P.B).

Results: We found 49 children up to the age of 18 with a verified diagnosis of ADEM (incidence rate 0.51 per 100,000 person-years); all had an abnormal brain magnetic resonance imaging (MRI). Only 18 (37%) fulfilled the IPMSSG criteria regarding encephalopathy and polyfocal neurological deficits. Children fulfilling the IPMSSG criteria had a slightly better outcome on follow-up than those children who did not fulfill the criteria, but the difference was non-significant. Among all 49 children with ADEM, 31% had clinical sequelae after a mean follow-up of 4.5 years. Surprisingly, none progressed to multiphasic ADEM or MS (mean follow-up: 4.5 years).

Conclusions: Among 49 children with ADEM, none converted to multiphasic ADEM or MS (mean follow-up: 4.5 years). Applying the IPMSSG criteria to all children with a diagnosis of ADEM leaves 63% of the cases without a diagnosis and lowers the incidence rate of paediatric ADEM.

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P319

Continuous accelerometry as a measure of physical activity impairment in paediatric-onset multiple sclerosis subjects versus healthy controls

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Background: Compared to adult-onset MS, paediatric-onset MS (POMS) patients exhibit a more inflammatory disease course with lower disability, more relapse, more progression of disability, and a higher rate of conversion to secondary progressive MS. This study aimed to objectively assess the impact of multiple sclerosis on physical activity and test the hypothesis that POMS patients exhibit a more inflammatory disease course with lower physical activity compared to healthy controls.

Methods: A total of 18 patients with POMS (11 females, 7 males, age range 6-21 years) and 16 healthy controls (9 females, 7 males, age range 7-17 years) were enrolled in the study. All patients were recruited from the Multiple Sclerosis Visual System (IMSVISUAL) Consortium. The study was approved by the institutional review board of the American Academy of Neurology and the University of Virginia. Physical activity was measured using a wrist-worn accelerometer (ActiGraph). The accelerometer was worn on the non-dominant arm and recorded activity during 24 hours per day for 7 days. The accelerometer data were analyzed using proprietary software (ActiLife). Physical activity was assessed using the actiGraph index (AGI), which is a measure of total activity. The AGI was calculated for each individual and compared between patients and controls. Results: The AGI was significantly lower in patients with POMS compared to healthy controls (p < 0.05). The AGI was also significantly lower in female patients compared to healthy controls (p < 0.05). Conclusion: Continuous accelerometry is a useful measure of physical activity impairment in patients with POMS. Physical activity is lower in patients with POMS compared to healthy controls. This finding is consistent with the hypothesis that POMS patients exhibit a more inflammatory disease course with lower physical activity.
a higher frequency of clinical relapses, a greater burden of infratentorial lesions, and an overall higher brain lesion volume. Despite this, POMS patients tend to have characteristically low levels of sustained disability within the first 10 years of disease. As a result, objective measures of physical disability are considered largely unreliable in this population. Continuous accelerometry represents a novel candidate measure for detecting mild physical disability in paediatric MS subjects.

**Design and Methods:** 21 POMS and 50 healthy controls were recruited from the University of Virginia’s Paediatric MS Clinic and the local community, respectively. Subjects completed surveys on physical activity (International Physical Activity Questionnaire (IPAQ)) and factors affecting activity levels (Modified Fatigue Impact Scale (MFIS), Beck’s Depression Inventory). All subjects completed timed walking tests (2-minute (2MW) and 6-minute (6MW) walks) and 7-day waist-worn continuous accelerometry.

**Results:** Baseline demographics of sex, age, race, and smoking history were not different between groups; however, POMS subjects had higher rates of obesity (p<0.01). POMS subjects had a median Expanded Disability Status Scale (EDSS) score of 1.5 (range: 0-3). Cases and controls reported similar physical activity levels as measured by IPAQ (p=0.61), but POMS subjects reported significantly higher levels of physical fatigue on MFIS (8.0 ±7.2 vs. 4.6 ±5.3; p=0.03). Of timed walking tests, the 6MW performance best distinguished POMS subjects from controls (p=0.027). There were no significant differences between groups on continuous accelerometry-derived measures, including daily steps, time spent in vigorous or moderate activity, and maximum step rate (MSR). In both groups, obesity negatively impacted subject MSR, but with a more pronounced effect in POMS subjects (r= -0.62; p=0.003).

**Conclusions:** POMS subjects subjectively experience more fatigue but do not report lower levels of physical activity compared to healthy peers. Timed walking tests are potentially useful measures in POMS, but 7-day continuous accelerometry did not distinguish POMS from healthy peers.

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M.D. Goldman: Nothing to disclose

**Objective:** To examine whether chitinase 3-like 1 (CHI3L1) and neurofilament light chain (NFL) in the CSF of a pediatric population predict acquired CNS demyelinating disease compared to non-demyelinating disease.

**Methods:** Children (< 18 years) referred to hospital for possible neurological inflammatory disease were retrospectively included from June 1, 2010 to July 1, 2016. All children had CSF evaluated for oligoclonal bands as part of the initial diagnostic work-up. Detailed case ascertainment was performed in all children by review of medical records. NFL and CHI3L1 were measured by enzyme-linked immunosorbent assays. Endpoints were differences in concentrations of CSF NFL and CHI3L1. Multiple regression, Kruskal-Wallis, Mann-Whitney, and receiver operating characteristics curves were used.

**Results:** We included 193 children and subsequently classified them into five groups based on clinical, biochemical and MRI data: demyelinating disease (n=33), children with normal diagnostic work-up (n=37), inflammatory neurological disease (n=49), other neurological disease (n=55), and systemic inflammatory disease (n=19). For demyelinating disease, the median age at onset was 15.0 years (range 2.5–17.9) and 52% were boys. Concentrations of NFL and CHI3L1 differed significantly between the five groups (p=0.0001). Further, CHI3L1 was significantly higher for demyelinating disease compared to all other groups, and NFL was significantly higher for demyelinating disease than the other groups except for systemic inflammatory disease. Children with acute disseminated encephalomyelitis (ADEM) compared to multiple sclerosis (MS) had significantly higher concentration of CHI3L1, and CHI3L1≥281 µg/L increased the risk for ADEM 6-fold.

**Conclusions:** This study provides class II evidence that CSF CHI3L1 and NFL are associated with acquired CNS demyelinating disease in children referred to hospital for possible inflammatory CNS disease. Further, CHI3L1 may be useful in identifying children with ADEM who have a high risk of relapse. We suggest that CSF CHI3L1 and NFL may be useful in predicting the disease course in children with possible inflammatory CNS disease who require spinal fluid examination.

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Chitinase 3-like 1 and neurofilament light chain in the cerebrospinal fluid predict pediatric acquired CNS demyelinating disease

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P321 Evaluation of teriflunomide in children and adolescents with relapsing MS: TERIKIDS phase 3 study design, enrolment update, and baseline data
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Background: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS. Teriflunomide 14 mg has shown consistent efficacy vs placebo in clinical studies in adults. There are unmet needs in the treatment of paediatric patients with MS. Patients with paediatric onset of MS represent 2-5% of all MS cases and can present with higher relapse rates and greater lesion burden compared with adult-onset MS.

Objective: To describe the design and provide an enrolment update for the phase 3, double-blind, randomized, placebo-controlled TERIKIDS study (NCT02201108) and open-label extension evaluating efficacy, safety, and pharmacokinetics (PK) of teriflunomide in children with relapsing MS (RMS).

Methods: Target recruitment: 165 patients aged 10-17 years with RMS meeting McDonald (2010) and International Pediatric MS Study Group (2013) criteria at screening, with ≥1 or ≥2 relapse(s) in the prior 12 or 24 months, respectively. Patients are being randomized 2:1 to teriflunomide or placebo, with adjustment to 14-mg adult-equivalent dose determined in a blinded PK run-in phase. The double-blind period will last 96 weeks or until a patient experiences relapse or exceeds protocol defined limits for enlarged/new T2 lesions, at which point patients have the option of entering an open-label period in which they receive teriflunomide. Primary endpoint: time to first clinical relapse after randomization. Secondary endpoints: proportions of relapse-free patients at 24, 48, 72, and 96 weeks; MRI and cognitive outcomes; and PK. Safety and tolerability will be evaluated by adverse event reporting at each visit.

Results: As of 5/5/17, 109 patients were randomized, with demographics as follows: 72 (66.1%) female; mean (SD) age, 14.7 (2.1) years; mean (SD) time since symptom onset, 2.24 (2.00) years. Of these, the majority (75.2%) had not received any MS treatment in the prior 2 years. Median (range) baseline EDSS score was 1.5 (0-4) and mean (SD) number of relapses within the previous 1 and 2 years was 1.5 (0.7) and 2.2 (1.1), respectively. At baseline, mean (SD) number of T2 lesions was 50.1 (38.2), and 58 (53.2%) patients had ≥1 gadolinium-enhancing lesion.

Conclusions: Paediatric patients enrolled in TERIKIDS to date have high levels of baseline disease activity and a relatively short disease duration. TERIKIDS will provide insights into efficacy, safety, tolerability, and PK of teriflunomide in the rare paediatric population with RMS.

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Natural course
P322 Risk of secondary progressive multiple sclerosis: a longitudinal study

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Objective: To determine the demographic, clinical and paraclinical features that influence the risk of conversion to SPMS.

Background: The ability to estimate individual risk of conversion to secondary progressive multiple sclerosis (SPMS) represents an area of unmet need. We have examined factors associated with SPMS conversion using a time-sensitive survival model, objective definition of SPMS and the multinational MSBase cohort.

Methods: Patients with adult-onset relapsing-remitting multiple sclerosis, at least three visits (with ≥6 months between the first and second visit and ≥3 months between the second and final visit), a minimum dataset and sufficient magnetic resonance imaging (MRI) data were selected from MSBase. The risk of objectively defined SPMS conversion was re-evaluated at multiple timepoints per patient using multivariable marginal Cox regression models. Sensitivity analyses with additional prognostic markers, minimum follow up requirements and stringent data quality standards were performed.

Results: 6,145 patients contributing 35,340 visits and 39,360 patient-years of follow up were included in the primary analysis. Older age (HR: 1.02, 95% CI: 1.01-1.04), longer disease duration (HR: 1.03, 95% CI: 1.01-1.05), a higher expanded disability status scale score (HR: 1.30, 95% CI: 1.21-1.41) and more rapid disability trajectory (HR: 2.58, 95% CI: 1.39-4.81) were independently associated with an increased risk of SPMS, while an improving disability trajectory (HR: 0.31, 95% CI: 0.12-0.88) was associated with a reduced risk of SPMS. Recent MRI evidence of disease activity in the brain, radiological evidence of lesions in the spinal cord and the presence of oligoclonal bands in the cerebrospinal fluid did not independently influence the risk of SPMS. Pre-baseline exposure to disease modifying therapy lowered the risk of SPMS in a larger cohort of patients for whom MRI data was not required (n = 15,717; HR: 0.70, 95% CI: 0.54-0.91).

Conclusion: Risk of SPMS increases with age, duration of illness and worsening disability, and decreases with improving disability. Recent MRI evidence of disease activity in the brain, spinal cord lesions and oligoclonal bands in the cerebrospinal fluid do not influence the risk of conversion to SPMS. Therapy may delay the onset of SPMS, although further work is required to confirm this result.

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Characteristics of radiologically isolated syndrome (RIS) national French cohort

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Radiologically Isolated Syndrome (RIS) is characterized by patients with incidental ﬁndings on brain or spinal cord MRI which are suggestive of demyelinating disease without Multiple Sclerosis (MS) signs and symptoms. The French RIS cohort is prospective and ﬁles are centralized and analyzed with a double-blind, standardized procedure. The aim is to conﬁrm diagnosis, to collect clinical, biological and imaging data to promote researches. This is a national prospective cohort, including 35 tertiary MS centers, gathering all RIS suspected cases since 2004. RIS ﬁles are identiﬁed in each center from the local MS Specialist. National coordinator collects all RIS cases and a double-blind MRI reading agrees for RIS status on imaging and patient medical history. French RIS cohort contains 222 ﬁles in december 2016: 161 Women (72.5%), 61 Men (27.5%), Mean age 36.4 years [9.97-14.1]. 32 ﬁles (14%) were classiﬁed as NON RIS and not included. On the 222 conﬁrmed RIS cases, MRI motives are very variable: headache 27%, migraine 15%, vertigo 9%, trauma 5.9%, pain 4.5%, ophthalmic 2.5%, ENT 8.6%, depression 4.1%, witness study 0.5%, MS family 3.2%, somatiform 1.4%, fatigue 4.1%, other disease monitoring 13.1%, miscellaneous 9.5%. During the mean follow-up of 34 months [0-244], 30% of the patients have converted clinically. Mean time for the seminal event: 43 months after the ﬁrst MRI [1.5-378.2], 25% of patients with a primary progressive MS, 75% of patient with relapsing MS (spinal cord 29.9%, optic neuritis 14.9%, brainstorm 4.5%, long tract 7.5%, other 17.9%). Twenty-three patients (34%) had temporal MRI dissemination before clinical conversion.

To date 41 patients (26.5%) has DT on brain MRI but have not clinically converted. The French prospective cohort has a standardized centralization with a yearly clinical, radiological and biological follow-up. The gathered prospective data does not seem to differ from those published in 2009 about a retrospective, smaller sample. It is important to improve the detection of patients and to better characterize some atypical neurological symptoms which could be considered as atypical forms of MS. To date, no treatment is available for RIS patients. These data need to be included and conﬁrmed in a prospective worldwide cohort effort. A European double blinded phase III study (TERIS) will start in 2017 which evaluate efﬁcacy of teriflunomide vs placebo in delaying the clinical event.

Disclosure


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Background: More precise methods to estimate prognosis for individual MS patients are needed. Model building, selection and external validation are key steps. However, small sample sizes, inadequate data standardization, short follow-up and lack of quantitative metrics have limited progress.

Objectives: Use advanced modelling and data mining techniques to assess baseline prognostic factors for MS disease progression in a pooled sample of RCT placebo arms.

Methods: Four RCTs of RRMS were combined in an integrated clinical trial database (IDB). Studies included AFFIRM (natalizumab registration trial), DEFINE and CONFIRM (dimethyl fumarate registration trials) and ADVANCE (peginterferon beta-zumab registration trial), DEFINE and CONFIRM (dimethyl fumarate registration trials) and ADVANCE (peginterferon beta-zumab registration trial). IDB data were used to build prognostic models for outcomes over 2 years of follow-up. LASSO and ridge regression, elastic nets, support vector machines (SVM) and dynamic nets were used to model time to disease progression confirmed at 24 weeks, in regression, elastic nets, support vector machines (SVM) and dynamic nets. A total of 434 subjects (27.4%) out of 1582 had progression in the combined endpoint over 2 years. PASAT, SF-36 PCS

Results: A total of 434 subjects (27.4%) out of 1582 had progression in the combined endpoint over 2 years. PASAT, SF-36 PCS and LCLA were the most important factors selected by the different competing algorithms, yet without consistent ranking of these 3 factors for prognostic importance. Model prediction performance was relatively poor (c-indices< 0.60) across all models including standard Cox regression and other definitions of progression.

Conclusions: Disagreement in prognostic factors ranking obtained by more powerful statistical tools confirmed the relatively poor prediction performance of baseline factors in modelling disease progression. The performance of the selected modeling approaches, including traditional regression methods, makes it important to explore alternative predictors, or use dynamic prognostic models which account for predictor changes during follow-up.

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Predicting MS disease progression remains a significant challenge: results from advanced statistical models of RCT placebo arms

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P325
Looking back: patients with “aggressive MS” (EDSS 6.0 at 10 years) in the Barcelona CIS cohort

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Background: Early identification of patients with an aggressive MS is key for personalized medicine.

Goals: to identify the baseline features of CIS patients that have reached a confirmed Expanded Disability Status Scale (EDSS) ≥6.0 at 10 years.

Methods: Study based on an ongoing CIS cohort. From this cohort, we selected patients with a CIS before February 15th, 2006 (10 years before database lock) and a minimum follow-up of 10 years (n=401). We divided patients according to their confirmed EDSS ≥6.0 status at year 10: yes, n=16 (4%); no, n=385 (96%) and compared their baseline characteristics, in terms of sex, age, CIS topography, oligoclonal bands (OB) status, and available number of T2 (n=390) and contrast-enhancing lesions (CEL) (n=168) at baseline. Regarding the lesion number variables, we performed a profile-likelihood analysis to identify the best clinically meaningful cut-offs discriminating EDSS status (50 and 25 T2 lesions and 10 and 5 CEL were selected). Sensitivity (Se), specificity (Sp), accuracy (Acc), positive and negative predictive values (PPV, NPV) and positive likelihood ratios (+LR) for these cut-offs were performed.
Results: Mean (SD) follow-up was 15.5 (3.4) years if EDSS ≥6.0 vs 14.3 (2.9) in the rest, p=0.125. Baseline characteristics such as sex and age and CIS topography showed no differences according to EDSS ≥6.0 status. However, we observed a higher proportion of spinal cord CIS in patients reaching an EDSS ≥6.0 [n=7 (43.8%) vs n=103 (26.8%), p=0.050]. OB were positive in 9/10 (90.0%) EDSS ≥6.0 patients compared to 212/324 (65.4%) who did not reach the outcome (p=0.028). The median (IQR) T2 lesion number was 72 (32-100) in patients with EDSS ≥6.0 compared to 7 (1-19) in those with lower scores (p<0.0001). Median CEL were 3 (2-25) in patients with EDSS ≥6.0 vs 0 (0-1) in the rest (p<0.0001). The diagnostic tests performances were as follows: Cut-off 50: [Se 63%, Sp 89%, Acc 87%, PPV 19%; NPV 98%; +LR 5]; cut-off 25: [Se 81%, Sp 81, Acc 81%, PPV 15%, +LR 4]; cut-off: 10 CEL lesions [Se 54%, Sp 97%, Acc 92%, PPV 50%, +LR 12 ]; cut-off: 5 CEL lesions [Se 46%, Sp 94%, Acc 90%, PPV 38%, +LR 7 ].

Conclusions: 1 out of 5 patients with more than 50 T2 lesions and 1 out of 2 with more than 10 CEL lesions at baseline will have reached an EDSS ≥6.0 at 10 years. Establishing a lesion number cut-off could aid in the early identification of patients at risk of reaching severe disability.

Disclosure

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C Nos reports no disclosures.

M Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Actelion, Amiral, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme and Teva Pharmaceutical.

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Miscarriage induces reactivation of inflammation in relapsing-remitting multiple sclerosis

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Background: While the influence of pregnancy in multiple sclerosis (MS) has been well established, there is no data on the effect of miscarriage on the short-term disease course.

Objective: To investigate the post-miscarriage clinical and radiological outcomes of women with relapsing remitting MS (RRMS).

Methods: An independent, multi-center retrospective study was performed by collecting data of women with RRMS who regularly attended four Italian MS centers. We compared pre- and post-miscarriage annualized relapse rate (ARR) and the number of Gd+ lesions as detected on the pre-conception and the post-miscarriage MRI scan, by analyses of covariance. Variables associated with post-miscarriage clinical and MRI activity were investigated using Poisson regression models. Each miscarriage was considered as a statistical unit.

Results: From 1983 to 2016 we observed 88 miscarriages (2 induced) in 69 women. The mean (SD) age at miscarriage was 34.3 (5.6) years. Miscarriage occurred after a mean time of 9.6 (3.4) weeks from the estimated conception date. Conception happened during treatment with disease modifying drugs (DMT) in 62 events out of 88 (45 interferon beta, 9 natalizumab, 6 glatiramer acetate, 2 FTY720). The post-miscarriage mean ARR (0.38+/-.053) was unchanged compared with pre-miscarriage ARR (0.47 +/-.068, p=0.29). The post-miscarriage mean number of Gd+ lesions (0.76 +/- 1.54) was significantly increased compared with the pre-conception MRI scan (0.36 +/-0.81, p=0.02). This finding remains unaltered after correcting for age at miscarriage, pre-conception and post-miscarriage DMT, time elapsed from the

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miscarriage to MRI scan. Occurrence of post-miscarriage Gd+ lesions was inversely correlated with the length of pregnancy maintenance (OR=0.78, p=0.01) and directly correlated with the pre-conception number of Gd+ lesions (OR=1.96, p=0.008).

**Conclusions:** Miscarriage induces disease reactivation possibly due to the recovery of the immunocompetence, as postulated in successful pregnancy in MS. We hypothesize that the inverse correlation between pregnancy length and the occurrence of new Gd+ lesions, might be explained by pro-inflammatory processes, essential for implantation and pregnancy maintenance, and by low production of estriol not yet reaching protective levels, both occurring at very early pregnancy.

**References**


**Disclosure**

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**P327**

**How common is truly benign MS?**

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The existence of benign multiple sclerosis (MS) remains controversial. Uncertainty remains about the frequency and pathological explanation for a favourable outcome in MS. However, identifying and studying individuals with benign MS has considerable implications for patient management and for our understanding of the biology of the disease. Most definitions of benign MS are centered on walking ability after 10-15y despite the far wider impact of MS on ability.

We screened a prevalent population of over 2,000 people with MS and found 275 individuals who had unlimited walking ability after 15 or more years from onset. We undertook detailed assessments in 56 of the individuals within this group (those recorded to have unlimited walking ability after the longest disease durations). Assessment incorporated scores of cognition, fatigue, mood, vision, bladder symptoms and arm and leg function. All patients were defined as having relapsing-remitting MS but they showed a wide range of relapse frequency and severity. In a group of 32 patients who fulfilled a contemporary EDSS-based definition for benign MS, less than 25% were found to be truly benign (defined as normal function in all domains). Patient-reported scores of MS-impact correlated strongly with the outcomes of clinical assessment but patients’ own perception of their condition was more benign than clinicians’. MR imaging was used to explore the biology underlying benign MS using both a global and a tract-based approach.

Our study highlights the low prevalence of truly benign MS (estimated here as < 4% of a prevalent population) and provides early insights into its phenotypic and imaging characteristics. This could inform on the biological mechanisms of a favourable outcome in MS.

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P328
Long term outcomes of neuromyelitis optica: a systematic literature review

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Background: There is limited literature regarding long term outcomes in neuromyelitis optica spectrum disorder (NMOSD) since the discovery of aquaporin-4 (AQP4) IgG.

Objective: To perform a systematic literature review on the long term outcomes in NMOSD in the era of AQP4 IgG.

Methods: We conducted a database search including Cochrane Collaboration Database, PubMed, SCOPUS, Web of Knowledge, and Embase through April 2017 using terms “neuromyelitis optica” or “Devic’s disease” and the following: “clinical features”, “outcome”, “natural history”, “prognosis”, “mortality”, “morbidity”, “incidence”, “prevalence”, “epidemiology”, and “demography”. We included English language studies that utilized 1999, 2006 or 2015, Wingerchuk criteria and reported results of AQP4-IgG.

Results: Twenty to thirty percent of patients had residual motor and visual disability after the initial attack; early disability was positively associated with long term disability. After 5-6 years, 11-18% of individuals had visual acuity of ≤ 20/200 in at least one eye and 7-23% were wheelchair confined. Nonwhites and Hispanics had higher relapse rates and worse outcomes. Younger patients and men had worse visual outcomes, whereas older patients had poor motor outcomes. Long term immunosuppressive treatment reduced attack-related disability. AQP4-IgG serostatus was not associated with outcome.

Survival improved in contemporary studies (91-98% survival after 5 years) compared to reports (68-75% survival) prior to discovery of AQP4-IgG. A higher attack frequency during the first 2 years, older age at onset, lack of recovery from first attack, blindness, and history of other autoimmune disease were associated with higher mortality rates, but race, gender and type of attack at onset were not.

Conclusion: Contemporary studies report more favorable outcomes than pre-AQP4-IgG series. Early disability predicts late disability, consistent with favorable effects of early treatment on disability. Outcomes are worse in nonwhites and Hispanics. Visual outcomes are worse in young onset and motor outcomes in late onset NMOSD.

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P329
Description of patients with benign multiple sclerosis in the treatment era

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Background: Despite targeting inflammation with current treatment regimens, many patients with multiple sclerosis (MS) continue to develop progressive disability. However, there is a subset of patients with benign MS who have minimal disability after decades of illness with less aggressive therapeutic treatments. The definition and prevalence of benign MS vary greatly between different study groups. We aim to describe patients from our clinic with benign MS, which we have defined as having MS for greater than or equal to 20 years and having an EDSS of less than or equal to 3.

Methods: A cross-sectional retrospective data analysis was performed on electronic clinical data collected from a state-level tertiary MS center after IRB approval. >90% of patients in the database had exposure to disease modifying agents.

Results: 31.3% of patients with MS for at least 20 years met our definition of “benign MS”. Patients with benign MS were diagnosed at a younger age, with median age of diagnosis of 29 versus 31 for those with a more active disease course (P=0.046). 88.5% of patients with benign MS were still characterized as having RRMS, compared to 15.8% of patients with MS for over 20 years with an EDSS greater than 3.0 (P<0.001). Only 1 out of 11 (9.1%) patients with PPMS for 20 years had an EDSS of less than 3. Of patients diagnosed with MS for over 20 years, those that met the criteria for benign MS were less likely to have failed a prior therapy (P<0.003), but were more likely to be on current disease modifying therapies (P=0.030). Patients with benign MS were also less likely to have been treated with aggressive agents (P<0.001).

Conclusion: Patients that met our definition of benign MS were diagnosed at a younger age than those with a more aggressive disease course. Patients with benign MS were less likely to have failed prior therapies, including aggressive agents, but were more likely to continue active MS disease modifying therapy, presumably because their disease had not advanced to a progressive course. The prevalence of 31.3% in our study population was higher than several other study groups despite more stringent criteria; this could reflect advances in MS treatment through disease modifying therapies.

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Andrew Bouley: nothing to disclose
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P330
Cognitive impairment can help to predict long-term disease course in benign multiple sclerosis patients: a 12 year follow-up study
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Background: definition of benign multiple sclerosis (BMS) remains controversial. Moreover, a sizeable proportion of classically defined BMS patients may be no longer benign (NLB) when re-assessed in the long-term.

Objectives: To provide a neuropsychological and MR assessment of BMS subjects in order to predict further disease course.

Methods: In 63 BMS patients (Expanded Disability Status Scale (EDSS) score ≤ 3.0 and disease duration ≤ 15 years) cognitive functioning was assessed through the Rao’s Brief Repeatable Battery. Forty-six patients underwent brain MR assessment with measurement of T2 and T1 lesion volumes (T2LV and T1LV), total and regional brain volumes and magnetization transfer ratio (MTr). After a mean follow-up of 12.6 ± 0.4 years, patients still having an EDSS score < 3.5 were classified as “still benign” (SB), whereas patients having an EDSS score ≥ 4.0 were defined as NLB. Possible prognostic predictors were assessed through a multivariate Cox survival analysis.

Results: Cognitive impairment (CI, failure of > 3 tests) was detected in 20 (31.8%). By the end of the follow-up, 20 (32.8%) were classified as NLB. In the Cox regression model, NLB status was related to the number of tests failed (HR=1.4; 95%CI 1.1 - 1.8; p=0.004) and, marginally, to EDSS score (HR=1.6; 95%CI 1.0 - 2.7; p=0.058). As for MR, NLB patients were characterized by higher mean T1-W lesion volumes (p=0.045) and marginally, lower NCV (p = 0.096). Patients were grouped on the basis of previously published clinical predicting score by adding 1 point each for male gender, EDSS score > 2.0 and CI. Patients with score 2-3 were at higher risk of NLB status at the follow-up (HR=3.5; 95%CI 1.5 - 8.6; p=0.005, accuracy=70.5%).

Conclusions: in BMS patients, the presence of CI and higher cortical and subcortical MR brain damage is related to higher risk of shifting to a non-benign course in the long-term. A thorough clinical, neuropsychological and MR assessment can help to predict further disease course in BMS patients.

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P331
Long-term treatment effect over disability progression in patients with relapsing multiple sclerosis
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Objective: To explore the conversion to secondary progressive multiple sclerosis (SPMS) in multiple sclerosis treated-patients seen from the first relapse and followed 18 years.

Methods: All patients that began treatment with Diseases Modifying Therapies (DMTs), between 1995 and 2002, have been prospectively followed. Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Score (MSSS) were obtained to calculate disability. Kaplan-Meier Survival analysis was used to estimate time for reaching EDSS=3.0, conversion to SPMS, EDSS=6.0, and time between the beginning of SPMS and EDSS=6.0. A Cox multivariate regression analysis was used to explore prognostic factors.

Results: 204 patients have been uninterruptedly treated for 13 years; initially with first-line DMTs, and in 88 patients with second-line therapies because treatment failure (43.1%). 53.4% of patients reaching an EDSS=3.0, 36.3% converted to SPMS; and 17.8% reached an EDSS=6.0 (estimated time: 14.1 years, 19.9 years and 17.2 years, respectively). A multifocal syndrome, an age older than 34 years at the beginning; and treatment failure, independently predicted the conversion to SPMS. Reaching an EDSS of 3.0 in less than 7 years predicted an early conversion to SPMS. All these variables did not influence the time to reach an EDSS of 6.0 once a patient was diagnosed of SPMS, which was 9.0 years.

Interpretation: A reduction in the rate of conversion to SPMS and a lower cumulated disability has been observed in our cohort with the current escalating treatment strategy. However, patients that converted to SPMS had similar characteristics to those of classical natural history studies.

Disclosure
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Epidemiology

P332
Increased incidence of psychiatric disorders five years before diagnosis in multiple sclerosis


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Background: The incidence and prevalence of psychiatric comorbidity are increased in multiple sclerosis (MS) compared to the general population. The prevalence of psychiatric comorbidity is higher than expected at MS diagnosis, but little is known about the incidence of psychiatric disorders before the diagnosis of MS. Elevated incidence rates before diagnosis could indicate that the increased burden of psychiatric comorbidity in MS reflects biologic effects such as inflammation or neurodegeneration.

Objective: To determine the incidence of psychiatric disorders five years before MS diagnosis as compared to a matched cohort without MS.

Methods: Using population-based administrative health data from the Canadian province of Manitoba, we identified all persons with incident MS between 1989 and 2012 using a validated algorithm, and a cohort from the general population matched 5:1 on year of birth, sex and region. We selected members of these groups with at least five years of residency before and after the first health contact for demyelinating disease (diagnosis date). We applied validated algorithms for depression, anxiety, and bipolar disorder to determine the annual incidence of these conditions in the five-year periods before and after the diagnosis date.

Results: We identified 1922 persons with MS and 11392 controls. As compared to controls, MS patients had an elevated incidence of depression (IRR 3.62; 95%CI: 2.49-5.27), anxiety (IRR 2.90; 95%CI: 2.13-3.96), and bipolar disorder (IRR 3.29; 95%CI: 1.78-6.08) in the diagnosis year. As early as five years before the diagnosis year, the incidence of depression (IRR 2.45; 95%CI: 1.46-4.11), anxiety disorders (IRR 1.72; 95%CI: 1.07-2.15) and bipolar disorder (IRR 1.72; 95%CI: 1.07-2.75) were also elevated. The incidence of psychiatric disorders in the matched population remained stable over time.

Conclusion: Compared to a matched general population cohort, the MS population has an elevated incidence of psychiatric comorbidity as early as five years before diagnosis.

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P333
A large cohort study of physical and psychological impacts of smoking on PwMS via the UK MS Register

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Background: Although the negative impacts of smoking on general health has long been known, research has shown there are significant issues related to outcomes and treatments for People with Multiple Sclerosis (PwMS) who continue to smoke. The MS Register has one of the largest collections of Patient Reported outcome Measures (PRoMS) data from PwMS in the UK.

Objective: Employ the largest collection of PRoMs ever used in such a study to inform clinical anti-smoking interventions to PwMS.

Methods: Three longitudinal PRoMs from the Register were used. The ‘baseline’ questionnaire (MSLife) has included questions about participant smoking status since 2014. The physical component of the Multiple Sclerosis Impact Scale (MSIS-29) was used to measure disability, and the Hospital Anxiety and Depression Score (HADS) to assess mental wellbeing; both of these have been repeating instruments since 2012. There are multiple responses per participant, therefore fuzzy logic was used to join MSIS and HADS responses where dates were closely matched to the smoking status at baseline.

Results: Total participants providing Smoking data and at least one valid MSIS n= 6021; from this cohort, there were 10,878 survey responses over a period of 3.1 years. Participants with smoking data and a HADS score, n= 6125 with 10,961 responses. Kruskal-Wallis H tests showed a statistically significant difference between the physical portion of the MSIS-29 score (χ²(2) = 147.68, p < 0.001) as well as the total HADS score (χ²(2) = 129.08, p < 0.001) for participants with different types of smoking status. Never smokers had a mean MSIS score of 48.4 (s = 19.9) and mean HADS of 28.1 (s = 7.6) while the same mean scores for smokers were 53.5 (s = 19.4) and 30.0 (s = 7.9).

Conclusion: In line with recent research, a change of MSIS of 7.5 has been found to be clinically significant. The higher average
score for smokers suggests a real increase in disability for smokers over non-smokers. This study showed a significant difference in self-reported physical disability and for PwMS according to their smoking status. Future work will include an analysis of variance to account for confounders and potential clinical inventions.

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P334
A nationwide survey of the influence of month of birth on the risk of developing multiple sclerosis in Sweden and Iceland

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Background: Previous studies have shown that the risk of multiple sclerosis (MS) is associated to season of birth with a higher proportion of MS patients being born in spring. However, this relationship has recently been questioned and may be due to confounding factors.

Objective: Our aim was to assess the influence from season or month of birth on the risk of developing MS in Sweden and Iceland.

Methods: Information about month of birth, gender and phenotype of MS for patients born 1940-1996 were retrieved from the Swedish MS registry (SMSR), and their place of birth were retrieved from The Swedish Total Population Registry (TPR). The corresponding information was retrieved from medical journals of Icelandic MS patients born 1981-1996 and their gender (Statistics Iceland). We calculated the expected number of MS patients born during each season and in every month and compared it with the observed number. Adjustments were made for gender, birth year and county of birth.

Results: We included 12020 Swedish and 108 Icelandic MS patients in the analyses. There was no significant difference between expected and observed MS births related to season or month of birth in Sweden or Iceland. Adjustments were made for birth year and birth place. However, similar results were obtained even without such adjustments. No significant differences were found in subgroup analyses including data of latitude of birth, gender, clinical phenotype and early MS onset ≤30 years.

Conclusion: Our results don’t support the previously reported association between season or month of birth and MS risk.

Disclosure

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Results: On 15 December 2016, clinical data from 40 centres, representing all French MS referral centres and networks, were aggregated: data from 56,401 patients were available. Standardized MRIs were produced by 15 MRI centres and 3005 sequences from 264 patients were available. Biological samples were collected in 12 centres from 548 patients. OFSEP covered 37% of MS patients in 2012 (from 0% to 100% by region, median=26%); in 2016, OFSEP coverage increase to 45% (from 3% to 100% by region, median=52%).

Discussion: Over the last 5 years, OFSEP has extended its diversity, quality and representativity. Its data are open to physicians and researchers, public and private entities, in France and abroad.

Disclosure

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Dr. Clanet has no financial disclosure to declare.

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Background: MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions), a network of 10 healthcare institutions in the United States and Europe, was designed around the concept of a Learning Health System (LHS), merging research with ongoing patient care by collecting standardized clinical and imaging data during routine medical visits.

Objectives: To report initial demographic and clinical characteristics of patients participating in MS PATHS.

Methods: During routine visits, patients used an iPad-based device, the Multiple Sclerosis Performance Test (MSPT), to self-administer an MS history, including disease severity measured by the Patient Determined Disease Steps (PDDS), 12 subscales of the Quality of Life in Neurological Disorders (Neuro-QoL) instrument, and an electronic adaptation of the MSFC: a processing speed test (PST), similar to the Symbol Digit Modalities Test; a manual dexterity test (MDT), similar to the 9-hole peg test; and a 25-foot walking speed test (WST), similar to the timed 25-foot walk. Standardized MRIs were acquired on Siemens 3T scanners and participants could elect to provide samples to a biorepository.

Results: Data from the first 2017 quarterly release indicate the MS PATHS cohort (n=1353) is predominately white (85%) and female (72%), with a majority self-reporting a relapsing remitting disease course (62%). The mean (SD) age was 48.9 years (12.0) and mean (SD) disease duration was 12.2 years (9.4). PDDS was normal (29%), mild (19%) or moderate disability (11%), gait disability (12%), early cane (10%), late cane (7%), bilateral support (7%) or wheelchair/scooter (6%). The mean (SD, range) PST was 45.9 correct (13.2, 4-86), mean (SD, range) MDT was 28.8 seconds (7.1, 17.2-55.8) and mean (SD, range) WST was 8.1 seconds (5.4, 2-52.5). Patient reported symptoms in the moderate to severe range on Neuro-Qol included fatigue (53.3%), lower extremity function problems (37.3%), upper limb function problems (24.5%) and sleep disturbance (19.9%). Updated data will be presented.

Conclusions: MS PATHS is the first LHS established in MS. Patient engagement has been strong with participation rates >90%, suggesting the MS PATHS cohort is likely representative of MS patients seeking care at MS centers. The unique combination of patient reported outcomes, quantitative performance measures, standardized MRI and laboratory data should enable collaborative research and accelerate efforts to achieve personalized medicine in MS.

Disclosure

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Author disclosures:

Ellen Mowry has received research funding from Biogen and free medication for a clinical trial from Teva Neuroscience. She is a consultant for Biogen, Genzyme, Merck Serono, Novartis, Sanofi Aventis and Teva Pharma.
Objective: Social relations mediate multiple environmental risk factors in multiple sclerosis (MS) such as diet, outdoor physical activity, smoking, and exposure to Epstein-Barr virus. We studied the social networks in participants of the Genes and Environment in Multiple Sclerosis (GEMS) study, persons who have at least one first-degree relative with MS.

Methods: In a cross-sectional design, we assessed the social networks of 1493 GEMS participants, 1378 asymptomatic and 115 with MS. We analyzed the personal social network structure, such as size and connectivity, and the network composition, such as the proportion kin and range of health habits. We examined the association of the network traits with the multiple sclerosis rating scale (MSRS), a self-reported measure of MS-related functional disability. In an exploratory analysis, we compared MS patients with asymptomatic family members. We used an ordinal logistic regression and controlled for age and sex.

Results: The composition of networks was associated with the MSRS score. The proportion of individuals perceived to have a negative health impact was associated with higher MSRS (adjusted odds ratio 3.77; 95% confidence Interval [CI], 1.53-9.27; p=0.004). Decreased ability to manage more distant relationships monthly or less frequently, was associated with higher MSRS (adjusted odds ratio 3.45; 95% CI, 1.61-7.14; p=0.001). Negative health habits, such as the proportion of people who do not exercise (adjusted odds ratio 2.05; 95% CI, 1.04-4.03; p=0.04), proportion who do not take medications (adjusted odds ratio 10.3, 95% CI, 1.62-65.55, p=0.01), and proportion who do not go to the doctor regularly (adjusted odds ratio 12.9, 95% CI, 1.65-100.62; p=0.01), were also associated with higher MSRS. Network structure was not related to MSRS score.

Interpretations: This is the largest characterization of social networks in individuals at-risk for a neurological illness. Characteristics of people around a person at-risk for MS are associated with that individual’s neurological function, highlighting the importance of the environment on manifestations of nervous system function.

Disclosure

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Background: In Germany approximately 6-9% of the People with MS suffer from primary progressive MS (PPMS) (1). In 2016 Westerlind et al. (2) reported a significant decrease in diagnosis of PPMS in Sweden. In this abstract we analyse data in the German MS-Register with regard to the findings of Westerlind et al.

Methods: Data from the German MS-Registry was extracted in May 2017. Only patients with a confirmed disease course and who were born between 1946 and 1980 were analysed (N=33,804).

Birth and diagnosis cohorts were defined in line with Westerlind et al. Statistical analyses included Age-Period-Cohort Models based on cubic regression splines. Adjustment for sex, diagnosis delay and the date of entry into the registry was made.

Results: 57.3% of our analysed patients with PPMS were females and mean age was 51.2(±7.73) at time of analyses. Mean age at diagnosis was 42.7(±9.72). Crude estimates of PPMS prevalence ranges from 19% for the late 1940s birth cohort to less than 2% for the late 1970s birth cohort. Age-Period-Cohort modes reveal that this decline seems to be occurring due to a temporal trend (drift). The underlying temporal trend is described best by the birth cohort only (p<0.001). The 95%-confidence bounds for trends in the date of diagnosis however are too narrow to replicate the substantial effects reported by Westerlind et al (p=0.71). The variables age at diagnosis (p=0.001), gender (odds ratio 1.8;p< 0.001) and diagnosis delay (p<0.001) were also found to be significant while the entry date into the register was not (p=0.91). Sensitivity analyses by regional strata show coherent results.

Conclusions: Our analyses found strong temporal trends as reported by Westerlind et al.. The causal reasons for these effects are still unclear. Since the Swedish and German data suggest that the date of birth is a strong explanatory variable, epidemiological reasons must be considered as causal factors. Conversely the date of diagnosis which was highly relevant in the Swedish data may also account for epidemiological factors, but primarily for those related closely in time to the disease onset. Westerlind et al. also suggested clinical reasons like changing criteria to diagnose PPMS patients playing a role. That hypothesis was not supported by the German data. Our findings were adjusted by all relevant covariates, were homogeneous among regional strata, and did not depend on the collection date.

Disclosure
Conclusions: Head trauma in adolescence, particularly if repeated, is associated with a raised risk of subsequent multiple sclerosis, possibly due to initiation of an autoimmune process in the central nervous system. This further emphasises the importance of protecting young people from head injuries.

Disclosure
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P340
Clinical characteristics and treatment patterns of relapsing-remitting multiple sclerosis patients with high disease activity
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Background: While there is no consensus on definition, patients with relatively high disease activity (HDA) relapsing-remitting multiple sclerosis (RRMS) present with periods of frequent relapses and/or brain lesions. To determine the adequacy of current treatment, it is essential to understand the clinical characteristics of HDA-RRMS patients and treatment patterns.

Objectives: Describe the clinical characteristics of patients with RRMS and their treatment patterns, and compare these across categories of disease activity sourced from a real-world multiple sclerosis (MS) outcomes registry.

Methods: A cohort of 6,647 adult RRMS patients enrolled in the Swedish population-based MS register between 1996-2015 (inclusive) was followed from the date of disease modifying drug (DMD) initiation until discontinuation or last recorded visit. Time to first DMD switch was analysed with a Cox proportional hazards model, where switch was defined as the initiation of a new DMD within 6 months of discontinuing the initial DMD. All other patients were censored with no event at the end of follow-up. Estimates were adjusted for age, sex, initiation year, and type of DMD. Patients were classified into three subgroups at DMD initiation: active disease, defined as the presence of a relapse or T2 lesion, HDA-R defined as 2 relapses observed within 1 year of each other, or Highly Active RRMS (HA-RRMS) defined as 9 or more T2 lesions or at least 1 gadolinium-enhanced T1 lesion. Patients not fulfilling any subgroup criteria were classified as the low activity (LA) comparator group.

Results: Across the four disease activity groups, mean (standard deviation) age ranged from 69% to 75%. Median Kurtzke Expanded Disability Status Scale at DMD initiation was 1.5 for all groups except HA-RRMS, where the median was 2.0. Interferon was the most commonly initiated DMD but was considerably less common in the HA-RRMS group. Relative to the LA group, the adjusted hazard ratio (95% confidence interval) of DMD switch was 0.88 (0.81, 0.94), 0.87 (0.79, 0.96), and 1.17 (1.04, 1.32) for patients with active disease, HDA-R, and HA-RRMS, respectively.

Conclusions: These analyses suggest clinically relevant differences across the different definitions of disease activity studied here. Those with HA-RRMS appear to have a higher risk of DMD switch, indicating that satisfactory treatment options may not be available for these patients.

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KG provided consulting services to Merck as an employee of PAREXEL.
BA provided consulting services to Merck as an employee of PAREXEL.
JH has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker’s fees from Biogen, Novartis, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, BiogenIdec, Merck-Serono, TEVA, Sanofi-Genzyme and Bayer-Schering. His MS research is funded by the Swedish Research Council and the Swedish Brain Foundation.
SW is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany

P341
Factors impacting mortality rates in a large French Canadian MS population: a review of 4 decades of data
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Background: Several studies have concluded that the lifespan of a person with multiple sclerosis (MS) is 6 years less than that of the general population. However these studies did not reflect the latest advancements in disease-modifying therapies. Little is known about the impact of factors such as gender, disease course, date of onset by decades, or age at onset on longevity.

Methods: The Montreal-based CHUM MS Clinic was established in 1975. Since its inception, cohorts of 3771 patients have been followed and, in April 2016, their vital status was obtained through the provincial health care system database. Mortality rates, per 1000 person-years, were estimated according to gender, disease course at baseline, and age at onset. Follow-ups were carried out from the first clinic visit until death, or up to April 2016.

Results: This cohort consists of 3771 patients with a median follow-up of 13.7 years, representing 55,339 person-years. A total of 482 (13%) patients were deceased at the end of the follow-up period. The overall mortality rate was 8.7 per 1000 person-years.
The mortality rate was higher among men (11.6 per 1000 person-years) than women (7.6 per 1000 person-years). Disease course at baseline generally influenced mortality. Mortality rates were 5.5 among patients who had a persistent clinically isolated syndrome (n=750), 7.2 among those with a relapsing course (n=2465), 18.2 among those with secondary progressive (n=127) and 19.1 per 1000 person-years among patients with primary progressive course (n=429). In a subgroup of subjects who started their follow-up at the clinic within a maximum of 3 years after onset, age at onset was strongly related to mortality. Mortality rates were 2.9, 4.3, and 11.6 per 1000 person-years respectively among patients who were ≤20, 20-40, and >40 years at onset.

Discussion: Our observed results are in agreement with those published from similar cohorts in Canada and in Europe. Striking differences in mortality rates were observed according to gender, disease course at baseline, and age at onset. As the lifespan of the MS population increases, so does the need for global strategies for the care of aging MS patients.

Conclusion: This work is a first step in a study on the impact of aging in MS. Further work will be conducted on other factors that may impact mortality such as comorbidities, lifestyle, and treatment.

Disclosure
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P342
Understanding the timing of environmental exposures in the risk of MS
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The prevalence of multiple sclerosis (MS) is not uniform, with a latitudinal gradient present in most studies in both hemispheres. Genetic factors are thought to play a role in the gradient as are environmental factors such as ultraviolet radiation and decreased levels of vitamin D affecting the immune system. Understanding the drivers of this gradient may allow a better understanding of the environmental factors involved in MS pathogenesis.

The New Zealand national MS prevalence study (NZMSPS) is a cross-sectional study of people with definite MS resident in New Zealand on census night, 7 March 2006. Of 2917 people with MS identified, the age-standardized prevalence was 73.1 per 100,000. A latitudinal gradient was observed with MS prevalence increasing three-fold from the North (35°S) to the South (48°S). The gradient was non-uniform; females with relapsing-remitting/secondary-progressive (RRMS/SPMS) disease have a gradient 11 times greater than males with primary-progressive MS. MS was significantly less common among those of Maori ethnicity.

The study confirmed the presence of a robust latitudinal gradient of MS prevalence in New Zealand. These results indicated that the environmental factors that underlie the latitudinal gradient act differentially by gender, ethnicity and MS phenotype.

If the latitudinal gradient is altered by lifetime migration, from the place of birth, to the location on census night and preliminary analysis from this study suggests that the latitudinal gradient may be established very early in life (0-4yrs). Then migration complicates the established clear latitude profiles. Establishing the critical life periods in MS pathogenesis is very important for development of prevention strategies. If the gradient is driven by UVR exposure in the years prior to the clinical manifestations of MS then appropriate guidance on sun exposure/vitamin D supplementation can be directed at young adults. If however the gradient is driven by environmental factors at or around birth then the same messages need to be directed towards pregnant women and very early childhood.

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P343
Determining the incidence of MS in a Swedish county - overcoming challenges in using registry data
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Background: The incidence of multiple sclerosis (MS) has been estimated for some local areas in Sweden; 4.3/105, 5.2/105 and 6.4/105 person years, all analysed by year of onset and by checking medical records. A recent study of the national incidence showed an unexpectedly high figure: 10.2/105 person years (2001-08) assessing incidence of MS diagnoses from the Swedish MS register (SMSreg) and the National Patient Register (NPR) in combination. However, since information about reported year of onset/year of clinical diagnosis are lacking in NPR, to calculate MS incidence by data from NPR obviously has some limitations.

Objectives: The aim of this study was to carefully examine MS-incidence by year of onset in the county of Värmland, a defined geographic area and to investigate sensitivities and specificities of an MS diagnosis in SMSreg and NPR.

Methods: Patients with an ICD-code for MS, living in Värmland were identified from the SMSreg (485) and NPR (435) registries. Patients medical records, identified from NPR, were scrutinized regarding ICD-code and year of onset.

Results: The linked registers showed that out of the 900 patients, 435 patients were registered in NPR only. After detailed review of medical records, the diagnosis in 15% of MS patients in the NPR turned out to be false, a recorded diagnosis most often due to a initial suspicion of MS that eventually failed to be confirmed, or due to technical errors regarding coding. In addition, patients with a true MS diagnosis were missing in the SMSreg.

After scrutinizing individual records, 290 individuals (209 SMSreg, 81 NPR) remained with the ICD-code MS and with an onset 2001-13, and the adjusted average annual incidence in the
counties was 8.7/10^5 person years (CI 95% 7.7 - 9.7), 12.7 for women (CI 95% 10.9-14.4) and 5.0 for men (CI 95% 3.9-6.1).

Conclusion: Calculating occurrence of MS by data from administratively collected data can be associated with some problems. The accurate calculation of MS incidence in the county of Värmland, analysed by year of onset and scrutinized medical records, indicates that previous local surveys may have missed a complete coverage, or the earlier reported national incidence figures may be exaggerated due to methodological issues.

Disclosure

Dr Hillert has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker’s fees from Biogen, Novartis, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, BiogenIdec, Merck-Serono, TEVA, Sanofi-Genzyme and Bayer-Schering.

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The prevalence of multiple sclerosis in the United States: a population-based healthcare database approach

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Background: Within the US, the prevalence of multiple sclerosis (MS) is poorly understood and inadequately characterized, but such information is important to support planning of health services and advocacy efforts. We aimed to develop a case definition to identify people with MS using health claims databases, and to apply this definition across the US to generate robust population-based MS prevalence estimates.

Methods: An MS case definition was developed and validated in three independent administrative databases. We applied this definition to identify MS cases between 2008 and 2010 using the following health care databases: Optum, Truven, Department of Veterans Affairs (VA), Kaiser Permanente Southern California (KPSC), Medicare and Medicaid. We estimated the three-year cumulative prevalence, and standardized to the 2010 US population.

Results: Among individuals with at least one health claim for demyelinating disease, the case definition had a sensitivity of 86%, specificity: 76-82%, and positive predictive value: 96-98% when compared to physician-adjudicated diagnoses. The unadjusted cumulative prevalence of MS for 2008-2010 for the private insurance databases was 208 per 100,000 (95% CI: 205-211) for Optum and 208 per 100,000 (95% CI: 207-210) for Truven. The cumulative prevalence for the national VA health care system was 177 per 100,000 (95% CI: 174-181), and for KPSC was 110 per 100,000 (95% CI: 106-114). The female: male ratio for MS prevalence was about 3:1 across databases and a US geographic prevalence gradient was found. A final integrated national MS cumulative prevalence estimate will be generated and stratified by age, sex and geographic region.

Conclusion: The US national cumulative MS prevalence rates for 2008-10 are the highest reported to date and provide a contemporary understanding of the disease burden. Our rigorous algorithm-based approach to estimating prevalence is novel, efficient and has the potential to be used for other chronic conditions.

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A population-based assessment of “no evident disease activity” (NEDA) in multiple sclerosis

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Background: Prior studies of “no evident disease activity” (NEDA) in relapsing remitting multiple sclerosis (RRMS) have
focused on clinic-based cohorts which may have been impacted by referral bias. In this study we evaluated NEDA in a population-based RRMS cohort.

**Methods:** We identified all incident cases of RRMS in Olmsted County between 2000-2011 using a medical records linkage system. Retrospective chart review was conducted to determine the persistence of NEDA following RRMS diagnosis. NEDA failure was defined as evidence of new MRI activity, a relapse, or disability worsening as measured using the expanded disability status scale (EDSS). Kaplan-Meier survival analysis was used to determine NEDA survival probability.

**Results:** There were 93 incident cases of RRMS with 82 individuals having sufficient follow-up to determine persistence of NEDA. Median age at RRMS diagnosis was 34.5 years (range, 16-60) with female predominance (2.3:1). Prior to NEDA failure 44 of 82 (54%) did not receive any disease modifying therapy (DMT) while the remainder were treated primarily with first-tier, injectable DMT (37/38). NEDA was maintained by 63% at 1 year, 38% at 2 years, 19% at 5 years, and 12% at 10 years based on evaluations performed during routine clinical care. Disability measured by EDSS was no different at 10 years in patients maintaining NEDA versus those that failed NEDA at one year (p=0.3).

**Conclusions:** Maintenance of NEDA beyond 2 years is infrequent among a population-based cohort of newly diagnosed RRMS patients and similar to prior clinic-based cohorts suggesting these studies were not impacted by referral bias. NEDA maintenance at one year was not associated with disability outcome at 10 years.

**Disclosure**

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**P346**

**Use of the new oral disease-modifying therapies among the multiple sclerosis population in British Columbia, Canada over a five-year period (2011 - 2015)**


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**Background:** Three oral disease-modifying therapies (DMTs) for multiple sclerosis became available in Canada between 2011 and 2014 (fingolimod, dimethyl fumarate (DMF), and teriflunomide). An understanding of their uptake at the population-level is needed to guide future pharmacovigilance research.

**Objective:** To describe the uptake of the new oral DMTs by sex and age, and to compare their use with that of the established first generation DMTs.

**Methods:** In this retrospective cohort study, we used prospectively collected population-based health administrative data (1996-2015) from British Columbia, Canada to identify persons with multiple sclerosis (PwMS) using a previously validated algorithm based on hospital and physician generated diagnostic (International Classification of Disease) codes. Using province-wide drug prescription records, we estimated the rate of new users for each oral DMT and the proportion of PwMS who used each DMT among all those living in British Columbia, annually and over five years (2011-2015). The analyses were also stratified by age group and sex.

**Results:** Between 2011 and 2015, among an average of 12,272 PwMS in British Columbia, there were 1,019 new users of at least one oral DMT, equivalent to a rate of 16 (95%CI: 15.6-17.7) per 1,000 PwMS per year. The proportion of PwMS using fingolimod increased from 2.4 (95%CI: 1.6-3.5) to 19.4 (95%CI: 17.1-21.9), DMF from 6.2 (95%CI: 5.0-7.7) to 39.5 (95%CI: 36.2-43.0), and teriflunomide from 4.2 (95%CI: 3.2-5.5) to 16.0 (95%CI: 13.9-18.4) per 1,000 PwMS during the first year that each drug became available until 2015. Conversely, use of the first-generation, non-oral DMTs (beta interferon and glatiramer acetate) decreased by 31% from 1608, or 133.5 (95%CI: 127.5-139.7) per 1,000 PwMS, in 2011 to 1,117, or 87.0 (95%CI: 82.2-92.0) per 1,000 PwMS, in 2015. The uptake or use of the oral DMTs did not differ between men and women. PwMS aged <45 years were more likely than those aged >45 to fill a new prescription for an oral DMT and to be current users of any DMT.

**Conclusion:** The uptake and use of the new oral DMTs increased substantially over the first 2 to 5 years after their introduction. With the increasing uptake and use of the new oral DMTs it will be important to monitor their risks and benefits in the real world, population-based setting.

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P347
Incidence and follow-up of acquired demyelinating syndromes in Dutch children - update of a nationwide and prospective study
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Introduction: Acquired demyelinating syndromes (ADS) are a group of auto-immune mediated demyelinating disorders of the central nervous system in children. For a subgroup of children, the demyelinating event can be the first presentation of multiple sclerosis (MS). A nationwide, multicentre and prospective cohort study was initiated in the Netherlands in 2006, with a reported ADS incidence of 0.66/100,000 per year and an MS incidence of 0.15/100,000 per year in the period between 2007 and 2010. In this study, we give an update on the incidence and the long term follow-up of ADS in the Netherlands.

Methods: Children < 18 years old were eligible when presenting with a first attack of demyelination and were consecutively included from January 2006 to May 2017. Clinical data were collected at inclusion. Available serum was tested for anti-MOG antibodies (MOG-ab). Diagnoses were reviewed by an experienced team in consensus with the International Paediatric MS study group 2012 diagnostic criteria.

Results: Between 2011 and 2016, 154 ADS patients were identified. Of these, 52 were diagnosed with MS (34%). This results in a minimal ADS incidence of 0.74/100,000 per year and a minimal MS incidence of 0.25/100,000 per year in this period. From 2006 to 2017, a total of 256 ADS patients were identified. During follow-up (median 43 months, IQR 18.84-71.25), 147 patients (57.4%) were diagnosed with monophasic disease, 92 patients with MS (35.9%) and 17 patients (6.6%) with multiphasic disease other than MS. The last group consisted of 2 (11.8%) multiphasic disseminated encephalomyelitis, 6 (35.3%) acute disseminated encephalomyelitis followed by recurrent optic neuritis, 5 (29.4%) neuromyelitis optica spectrum disorders, 1 (5.9%) multiphasic MOG-disease not further specified and 3 (17.6%) chronic relapsing inflammatory optic neuropathy.

MOG-ab were absent in MS patients, but present in about 26% of monophasic patients (18/52). In patients with multiphasic disease other than MS, 71.4% (5/7) were positive for MOG-ab. In 80 MS patients the EDSS score at follow-up was available (median follow-up time 56 months, IQR 32.0-73.75). EDSS score of 4.0 was reached in 4/80 patients (5%).

Conclusion: The incidence of ADS in children in the Netherlands has increased in the past few years, mainly due to an increase in the MS incidence.

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P348
The association between disease activity and disability progression in patients with relapsing-remitting multiple sclerosis
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Background: Relapsing-remitting multiple sclerosis (RRMS) is the most common disease course of multiple sclerosis (MS) patients. Levels of disease activity among RRMS patients vary, with a proportion of RRMS patients experiencing high disease activity (HDA). It is critical to understand the association between disease activity and disease progression over time.

Objectives: Measure the association between disease activity and Kurtzke Expanded Disability Status Scale (EDSS)-based confirmed disability progression (CDP) in RRMS patients.

Methods: A cohort of 3,212 adult RRMS patients enrolled in the Swedish population-based MS register during 1996-2015 (inclusive) was followed from the date of disease modifying drug (DMD) initiation until CDP, DMD discontinuation, or last recorded visit. Time to first 6-month CDP was analysed using a Cox proportional hazards model, where CDP was defined as a confirmed baseline EDSS increase of at least 1 EDSS point for patients with baseline EDSS≥5.5 or an increase of at least 0.5 for those with baseline EDSS<5.5, with a confirmed increased EDSS score 3-6 months later. All other patients were censored with no event at the end of follow-up. Estimates were adjusted for age, sex, initiation year, and type of DMD. Patients were classified into three subgroups at DMD initiation: active disease, defined as the presence of a relapse or T2 lesion, HDA-R defined as ≥1 relapse or T2 lesion observed within 1 year of each other, or Highly Active RRMS (HA-RRMS) defined as ≥2 relapses or T2 lesions observed within 1 year, and type of DMD. Patients were classified into three subgroups at DMD initiation: active disease, defined as the presence of a relapse or T2 lesion, HDA-R defined as ≥1 relapse or T2 lesion observed within 1 year of each other, or Highly Active RRMS (HA-RRMS) defined as ≥2 relapses or T2 lesions observed within 1 year, and type of DMD. Patients were classified into three subgroups at DMD initiation: active disease, defined as the presence of a relapse or T2 lesion, HDA-R defined as ≥1 relapse or T2 lesion observed within 1 year of each other, or Highly Active RRMS (HA-RRMS) defined as ≥2 relapses or T2 lesions observed within 1 year, and type of DMD.

Results: Across the four patient groups, mean (standard deviation) age ranged from 34 (10) to 37 (10) years, and percentage of females ranged from 69% to 75%. Median EDSS score at DMD initiation was 1.5 for all groups except HA-RRMS, where the median was 2.0. Interferon was the most commonly initiated DMD but was considerably less common in the HA-RRMS group.

Conclusion: The incidence of ADS in children in the Netherlands has increased in the past few years, mainly due to an increase in the MS incidence.

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Relative to the LA group, the adjusted hazard ratio of CDP was 1.04 (p=0.82), 1.07 (p=0.74), and 1.08 (p=0.72) for patients with active disease, HDA-R, and HA-RRMS, respectively.

**Conclusions:** In this initial analysis, no evidence of differences in disease progression was observed among patients with varying levels of disease activity. Analyses are ongoing and upcoming results will be enhanced with marginal structural modelling to account for time-dependent confounding.

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KG provided consulting services to Merck as an employee of PAREXEL.

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**P349**

**Sex related differences of fetal maternal cross-talk modify phenotypic characteristics in women with multiple sclerosis**

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**Objectives:** To investigate the possible role of differences determined by the sex of the fetus on disease related characteristics among women affected by multiple sclerosis (MS). Background. Gender related differences in MS incidence and disease characteristics are usually attributed to hormone dependent factors. However, several studies recently proposed a more complex fetal maternal interaction which is dependent also by the sex of the fetus.

**Design and Methods:** We included women affected by MS according to McDonald revised criteria at the outpatient service for MS and related diseases of the Neurological Department of the University of Palermo. By means of a structured questionnaire we collected information about disease course and to fertile life characteristics including the sex of the fetuses in pregnancies occurred before or after the diagnosis of MS. We calculated differences between subgroups of the cohort according to the following variables: age at onset, number of relapses within the first three years of the diseases, complete recovery after the relapse, time from pregnancy to the first relapse, rate of relapses during the postpartum period, frequency of oligoclonal band in the cerebrospinal fluid at diagnosis (OB). Calculations were made comparing three subgroups of patients: MS women who did not have pregnancies before the onset of the disease, women who had a male child before onset and women who had a female child before onset of MS. Results. We included 322 women affected by MS, 136 of whom had a pregnancy before disease onset. Mean age at disease onset was 29.5 years (26.5 in women with no previous pregnancy, 36.4 in those with a female child, 36.2 in those with a male child). Relative risk of symptoms onset within the first year after delivery was 2.5 times higher in women who had a pregnancy with a male child compared to women who had a female child (95% CI 1.00-6.24, p= 0.04). Time to first symptom was longer in women who had a female child (96 months) compared to those who had a male child (92.5 months), p< 0.05). There was a higher frequency of OB in CSF of women who had a female child compared to those with a male child (96% vs. 81.7 %, p= 0.016).

**Conclusions:** This study support the hypothesis that the immune cross-talk between the mother and fetus are modified by the sex of the fetus, and may consequently contribute to determine different clinical features in women affected by MS.

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**P350**

**Harnessing electronic medical records to advance research on multiple sclerosis**

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**Background:** Electronic medical record (EMR) systems hold various data types, included easily extractable structured data and unstructured data requiring more sophisticated extraction procedures. Although research was never a primary goal of EMR system architecture, clinicians and researchers increasingly have the
opportunity to leverage clinical data for research-based analyses. However, no matter how large the datasets are, health-related research requires high-quality information and validation. While previous EMR studies successfully identified patients and extracted data, none have assessed the quality of these EMR real-life data compared to well-curated research databases.

**Goals:** To

1. use the University of California, San Francisco (UCSF) EMR system in order to identify patients with specific neurological disease, multiple sclerosis (MS), and extract their clinical data,
2. compare EMR-extracted data with gold-standard data from research to demonstrate that information extracted from EMR is of high-quality and can be used for health-related research, and
3. compare the EMR MS population characteristics to expected MS natural history.

**Methods:** A classification algorithm to identify MS patients in the UCSF Health System EMR was implemented under an IRB-approved protocol and clinical data algorithmically extracted and de-identified. Classification specificity and extraction performance were assessed by manual clinician record review. EMR data was compared to research cohort data in a subset of patients.

**Results:** We identified 4,142 MS patients with 95.9% sensitivity. Clinical data were extracted from free-text with high positive predictive values. We showed good concordance between EMR and research values for Expanded Disability Status Scale (EDSS) and Timed-25-foot walk (ICC=0.87 and 0.79 respectively) and for MS subtype (Kappa=0.65). We replicated several expected epidemiological features of MS: higher EDSS for patients with progressive forms compared to relapsing-remitting patients (p< 2.2x10-16) and for male compared to female patients (p=1.1x10-18); and an increase of EDSS with age at examination (p=1.3x10-229) and with MS duration (p=1.7x10-86). We also replicated an expected decrease in lymphocyte counts and increase in liver enzyme testing following fingolimod initiation.

**Conclusions:** Large real-world cohorts algorithmically extracted from EMR data are expanding opportunities for clinical research in MS

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**P351**

**Comparison of case-mix in multiple sclerosis patients participating in randomized control trials, prospective observational studies, and multiple sclerosis partners advancing technology and health solutions (MS PATHS)**

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**Background:** MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) plans to enrol approximately 10,000 MS patients from 10 healthcare institutions in the US and Europe. The large population, broad inclusion criteria (MS or CIS, no exclusions) and high participation rates (>90%) raise the potential for more representative populations and more generalizable research findings compared to randomized control trials (RCTs) or prospective cohort studies.

**Objectives:** To compare socio-demographic and clinical characteristics of MS PATHS patients with MS patients from six Biogen-sponsored RCTs and the EPIC (Expression, Proteomics, Imaging, Clinical) prospective cohort study.

**Methods:** Descriptive statistics were used to describe MS PATHS (n=1353), the pooled RCTs (n=6574) and EPIC (n=579) at baseline. The characteristics within each cohort were: age (yrs), sex, MS duration (yrs), relapses in last 12 months, 9-Hole Peg Test (9HPT) (sec) and Timed 25-Foot Walk (T25FW) (sec). Pairwise comparisons of MS PATHS patients vs. RCTs and EPIC were made with Wilcoxon rank sum tests and chi-squared tests. Standardized differences were also assessed. Pairwise c-statistics were made with Wilcoxon rank sum tests and chi-squared tests. Standardized differences were also assessed. Pairwise c-statistics were made with Wilcoxon rank sum tests and chi-squared tests. Standardized differences were also assessed.
were estimated from multivariate logistic regression models to address overall similarity.

**Results:** MS PATHS mean (SD) age was 48.9 (12.0), higher than the RCTs [37.4 (8.9)] and EPIC [43.0 (9.8)]. Mean disease duration was 12.2 (9.4) in MS PATHS, compared with 7.7 (6.5) and 9.0 (8.8) in the RCTs and EPIC, respectively. The percent of patients with zero relapses in the last 12 months was higher in MS PATHS (47.3) and EPIC (58.0) vs. RCTs (1.4). For MS PATHS, RCTs and EPIC, the 9HPT means (SD) were 28.8 (7.1), 22.7 (11.2) and 21.9 (5.3), whereas T25FW means (SD) were 8.1 (5.4), 6.7 (6.9) and 6.0 (6.2). All standardized differences were >10% and all p-values were < 0.05, except for sex. MS PATHS multivariate c-statistics for membership was 0.88 vs. RCTs and 0.82 vs. EPIC, showing the overall uniqueness of the MS PATHS cohort.

**Conclusions:** MS PATHS patients were older with longer disease duration, less active disease and worse functional performance compared to patients enrolled in RCTs and EPIC. Given the high participation rate, the MS PATHS cohort is likely representative of MS patients seeking care at MS centers. MS PATHS provides an opportunity to answer key clinical questions that might be generalizable beyond findings from RCTs and other selected cohorts.

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**MS and gender**

**P352**

Assisted reproductive technologies and relapse risk: a new case series and pooled analysis of existing studies

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**Introduction:** Assisted reproductive technologies (ART) are increasingly used, and five case series to date have reported an increase in relapses after ART in women with multiple sclerosis (MS). Small numbers and variation in study design have limited broader conclusions.

**Objective:** To contribute an independent case series to the literature, and to perform aggregated (pooled and meta-) analyses.

**Methods:** Our independent cohort (BWH) included 16 adult women with MS reporting ART exposure; in 12, ART occurred after MS onset. Clinical data were confirmed from medical records. The data were then pooled with 5 published case series from France (N=28), Germany (N=29) and Argentina (N=16). To compare relapse rates (RR) prior to ART across the centers we used chi-square analyses. To compare annualized RR (ARR) in the 3 months (3M) after ART with ARR in the 12M and 3M (excl. Germany) prior, we used Wilcoxon signed-ranked test for paired samples. We then adjusted for age, disease duration (fixed effects), and site- and subject-level repeated observation, using mixed Poisson regression models. Finally, we performed a meta-analysis using non-parametric Wilcoxon paired tests comparing relapses pre- and post- ART.

**Results:** In 22 BWH cycles, ARR in 3M after ART (Mean: 0.18 ± 0.85; Median: 0; Range: 0-4) was significantly higher than ARR in 3M prior (Mean: 0.55 ± 1.41, Median: 0; Range: 0-4; p=0.42) or 12M (Mean: 0.27 ± 0.55, Median: 0; Range: 0-2; p=0.58) prior ART. This was true in adjusted models as well. In the pooled analyses (N=85, mean age 32.7 years), mean ARR in 12M prior to ART ranged from 0.19±0.40 (Argentina) to 1.0±1.36 (France) (p<0.001). ARR in 3M after ART was significantly higher (p<0.01 for each) than in the 12M prior to ART in all clinical scenarios. ARR 3M after ART was also significantly higher compared to 3M prior (Germany excl.) for all ART events; events with ART failure but not success; use of GnRH agonists but not antagonists, nulliparous women; events with no DMT use or with DMT stopped >3M prior to ART, and events with DMT started within 3M after ART. These results remained significant in adjusted models. The meta-analysis confirmed a trend towards increased relapse rate in the 12M after ART relative to the 12M before (mean difference 0.36, 95% CI -0.25;0.96).

**Conclusion:** These pooled data support an increase in ARR following ART in women with MS. Reasons for local variation in ARR after ART, including relapse risk and ART dosing, will be pursued.

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**P353**

Pregnancy incidence and therapy exposure in relapsing forms of MS: a 12-year retrospective multicentre analysis

Objective: To retrospectively determine the incidence of pregnancy and therapeutic exposure in women with relapsing MS between 2005-2016. 

Methods: We identified all women with relapse-onset MS who were of childbearing potential (aged 15-45) in the MSBase Registry between January 2005 and October 2016. Unadjusted and adjusted annualised pregnancy incidence rates were calculated overall and by epoch (2005-2010; 2011-2016).

Demographic, clinical information, and disease-modifying therapy (DMT) exposure during pregnancy were also assessed.

Results: 9,098 women of childbearing potential were identified with 38,671 patient-years of follow-up. 1,178 (12.9%) women recorded 1,521 pregnancies. The annualised incidence rate (IR) of pregnancy rose from 0.040 between 2005-2010 to 0.044 between 2011-2016. Pregnancy incidence rates were highest in 25-35 year olds (0.07) and lowest in 40-45 year olds (0.006). Higher EDSS scores were associated with reduced pregnancy incidence (adjusted IRR 0.96; p< 0.001).

635 (41.7%) of reported pregnancies were conceived on therapy, increasing annually from 26.5% in 2006 to 61.7% in 2016. By class: 487 (76.7%) pregnancies were conceived on injectable therapy (55% interferon-beta; 21.7% glatiramer acetate), 38 (6%) on oral therapies (21 fingolimod (3.3%); 17 dimethylfumarate (2.7%)), 106 (16.7%) on monoclonal antibodies (104 natalizumab (16.4%); 2 rituximab (0.3%)), and 4 (0.6%) on azathioprine. Annualised IR of pregnancy by DMT class were similar; injectable therapy IR 0.23 (95% CI 0.22, 0.24); monoclonal antibody IR 0.25 (95% CI 0.23, 0.28) and oral therapy IR 0.26 (95% CI 0.22, 0.32).

The median duration of DMT exposure during pregnancy was 30 days (IQR: 9, 50).

Conclusion: We report an increase in pregnancy incidence rates over the past 12 years. We further report an increasing number of pregnancies conceived on therapy, with a significant proportion conceived on pregnancy class C/D drugs. We caution that the increased incidence of pregnancy reported may be due to conservative patient monitoring and reporting in an era where many pregnancies were conceived on class C/D drugs, rather than an increase in pregnancy rates per se. The annualised incidence of pregnancy by therapeutic class is comparable, as is the duration of DMT exposure during pregnancy.

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PD served on editorial boards and has been supported to attend meetings by EMDSereno, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

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FG Has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall.

DS Received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck-Serono.

VVP Served on scientific advisory boards for Biogen, Novartis Pharma and Novo-Sanofi-Genzyme; has received travel grants and consultancy fees from Biogen, Bayer Schering, Sanofi Aventis, Merck Serono, Sanofi-Genzyme and Novartis Pharma; has received research grants from Bayer Schering.

AS did not report any disclosures

COG Received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen GSK, Teva and Novartis.

FV Is an advisory board member for Teva, Biogen, Merck Serono and Novartis.

SV reports no disclosures

SH Received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering.

MS Has participated in, but not received honoraria for, advisory board activity for Biogen, MerckSerono, BayerSchering, Sanofi Aventis and Novartis.

RA did not report any disclosures

JP did not report any disclosures

JLSM Has accepted travel compensation from Novartis, Merck Serono and Biogen, speaking honoraria from Novartis, Sanofi, Merck Serono, Almirall, Bayer and Teva and has participated in a clinical trial by Biogen.

OS did not report any disclosures

GI Had travel/accommodation expenses funded by Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi Aventis, and Teva.

CS did not report any disclosures

JO Served on scientific advisory boards for Biogen, Genzyme and Novartis; has received speaker honoraria from Biogen, Bayer-Schering, Genzyme, Merck-Serono, Novartis and Teva and research grants from Biogen, Merck Serono, Novartis and Teva.

CS Received travel assistance from Biogen Idec and Novartis

KM, KN, RH are employees of Biogen

HB Served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck Serono, Novartis and Biogen.

This study was supported by the MSBase Foundation and Biogen.
Objective:

1. to assess MS disease activity during pregnancy after alemtuzumab (ALZ) treatment.
2. to document pregnancy outcomes in ALZ exposed pregnancies [ALZ< 4 months before the last menstrual period (LMP)]

Background: More than 25% of women with multiple sclerosis (MS) and high disease activity experience relapses during pregnancy. Data on relapse activity during and after pregnancy in ALZ treated women are scarce.

Methods: 22 women with ALZ treatment before pregnancy were prospectively enrolled into the German Multiple Sclerosis and Pregnancy Registry. Detailed information on the course of MS (relapses before ALZ, during ALZ, pregnancy and postpartum) and obstetrical information was obtained with a standardized questionnaire.

Results: 10 pregnancies were exposed to ALZ [last ALZ < 4 months before LMP]; the remaining 12 unexposed pregnancies became pregnant > 4 months after the last ALZ infusion. The mean age at conception was 30.0±4.1 years. So far 15 infants are born with a mean birthweight of 3407g ± 356g. One newborn whose mother received the last ALZ 2 months prior to LMP had hydropsplenia and one newborn whose mother received the last ALZ one day before LMP had hypospadias. One pregnancy ended in a spontaneous abortion. The remaining pregnancies are ongoing and their outcome will be reported.

Conclusion: Depleting antibodies as ALZ might be an interesting option for women with MS and high disease activity, who plan a pregnancy, as the drug itself is cleared shortly after the exposure but the biological effect continues. However, more information on the occurrence of secondary autoimmune disorders and the specific interaction with pregnancy is needed.

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A. I. Ciplea: Has nothing to disclose
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P355

X chromosome wide association analysis identified a novel FRMPD4 locus that differentially effects MS risk by sex

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Multiple sclerosis is characterised by a significant sex imbalance with an increasing female to male ratio of 3:4:1 for relapse onset MS. Characterising the role of the X chromosome in MS will enable a unique biological perspective on MS aetiology. However, the vast majority of GWAS studies have either not assessed or under assessed the X chromosome, as most of the analysis pipelines are designed for autosomal loci. The availability of a recently developed software (XWAS) that is specifically designed for X chromosome analysis has allowed us to assess the role of the X chromosome variants in MS onset.

We therefore conducted an X-wide association analysis using the ANZgene MS GWAS data (2482 MS cases and 4304 controls) as a discovery sample involving 6,518 SNPs and replicated using Australian MS exome array data (583 MS cases and 411 controls). We identified a significant association in FRMPD4 (rs6641026) that showed different effects by sex. In the discovery stage, the MS risk OR for males was 2.06 (P=1.84x10^-6), while the OR for female was 0.94 (P=0.35). In the validation stage, the OR for males was 5.09 (P=0.03) while the OR for females was 0.83 (P=0.38). The combined test for differentiated effect size between sex was significant after multiple testing (P=3.9x10^-6). This gene functions as a positive regulator of dendritic spine morphogenesis and density, and is required for the maintenance of excitatory synaptic transmission. The finding of an association with MS risk only in males may suggest a significant parent of origin effect or suggest a gene dosage effect is important and may be protective in females. This gene thus has high biological plausibility for involvement in MS risk. The differential effect by sex requires more research to elucidate the mechanisms.

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P356
Infertility diagnosis and treatment in women with and without multiple sclerosis

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Background: Data regarding infertility diagnosis and treatment in women with multiple sclerosis (MS) compared with women without MS are lacking. This study compared the prevalence of infertility and infertility treatments administered to women with and without MS based on US retrospective commercial claims analysis.

Methods: IMS Health Real World Data Adjudicated Claims - US data were used to identify a cohort of US women with MS (ICD-9-CM diagnosis code: 340.xx), aged 18-55, with a minimum of 1 year continuous insurance eligibility from 1/1/2006 to 31/12/2015. The number of women with MS meeting the eligibility criteria was 117,041. A comparator group of women without MS was also selected (n=1,422,836). Exact matching was used to control for baseline age, geographic region and index year quarter. Rates of infertility diagnosis, infertility treatments and live birth between the matched samples (n=96,937 in each group) were compared. Infertility treatments that were evaluated included oral infertility medications (clomiphene and/or letrozole), injectable medications for controlled ovarian stimulation (COS), defined as ≥1 gonadotropin (Gn) and an ovulation trigger, either human chorionic Gon or Gn-releasing hormone (GnRH) agonist, and other infertility treatments (Gn without trigger or GnRH antagonists).

Results: The mean (standard deviation) duration of follow-up available was 3.77 (2.36) years for women with MS and 3.82 (2.43) years for women without MS. A greater proportion of women with MS had a diagnosis of infertility compared with women without MS (8.52% vs 8.08%; p=0.0006). A lower proportion of women with MS used any infertility treatment compared with women without MS (1.01% vs 1.19%; p=0.0002). Of patients receiving infertility treatments, over half received oral infertility medications without Gn (MS 54.9% vs non-MS 54.8%); the remainder received injectable COS medications (MS 22.9% vs non-MS 25.0%) or other treatments (MS 22.3% vs non-MS 20.2%). The proportion of women using each of the individual infertility treatments was significantly lower in women with MS compared with women without MS (p<0.05, except for GnRH antagonists). The rate of live birth was lower in women with MS than in women without MS (5.00% vs 6.98%; p<0.0001).

Conclusions: Women with MS were more likely to have a diagnosis of infertility, were less likely to use infertility treatments and were less likely to have a live birth compared with women without MS.

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NCE is an employee of Health Services Consulting Corporation. Health Services Consulting Corporation received funding from EMD Serono, Inc.* to run the analysis.
BH and ALP are employees of EMD Serono, Inc.*, Rockland, MA, USA. *A business of Merck KGaA, Darmstadt, Germany.

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P357
Neonatal and delivery outcomes of babies to mothers with multiple sclerosis in Sweden

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Background: Clinical onset of multiple sclerosis (MS) often presents during early adulthood and thereby during women’s fertile years. How pregnancy influences the course of MS has been investigated quite extensively and even though the inflammatory activity is increased during the first three months post-partum; overall, pregnancy does not seem to have a deteriorating effect on the disease course. Therefore, women have been encouraged not to influence their family planning by MS and the patient’s focus has switched from the mother’s disease to the offspring’s wellbeing.

Objective: Effects of maternal MS on neonatal and delivery outcomes are explored to define areas of improvement in care.

Method: For this retrospective study we used data from female patients registered in the Swedish MS register (SMSreg) and female controls who were matched by Statistics Sweden on age and residential area from the general population. Data on neonatal and delivery outcomes were obtained from the Swedish Medical Birth Register (MFR). Categorical outcomes were analysed with Chi-squared test, continuous outcomes with Mann Whitney-U test if not normally distributed, and with a t-test when normally distributed.

Results: By July 2015, data on 6,887 women with MS including information on delivery and neonatal outcomes were available in the MFR. To these 130,495 women with pregnancies were matched from the general population.

Neonatal outcomes
Significant differences were seen in all investigated variables; birth weight (p<10^-4), and the birth length (p<10^-4) being smaller in babies to mothers with MS. The initial APGAR score (one minute after delivery) in babies to mothers with MS was slightly reduced with 8.73 compared to 8.77 in babies to mothers without MS (p<10^-4), but were similar at 5 minutes and 10 minutes.

Delivery outcomes
Significantly more assistance during delivery, especially vacuum extractions (p<10^-4) and elective or acute caesarean section (p<10^-4), was performed in mothers with MS compared to controls. Labour was induced artificially in 6.46% of deliveries in MS cases compared to 4.88% in controls (p<10^-4).

Conclusion: The observed difference in women with MS are small but in line with reports from other countries showing that women with MS in Sweden need special attention during labour to ensure the mother’s and the new-born’s safety and health.

Disclosure

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**MS symptoms**

**P359**

Randomized controlled trial of two group programs in multiple sclerosis: 12-month (long-term) follow-up effects on fatigue and self-efficacy

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**Objective:** To determine whether multiple sclerosis (MS) participants in Fatigue: Take Control (FTC) experienced decreased fatigue and increased self-efficacy compared to those in MS: Take Control (MSTC), a general MS education program.

**Background:** Fatigue is a common symptom in MS. FTC is a structured group program based on the Fatigue and MS guideline. Our multicenter trial with did not find greater effects on fatigue or self-efficacy in FTC compared with MSTC at 6 months. We now report findings for the subset of subjects followed for 12 months.

**Design and Methods:** 218 MS subjects with Modified Fatigue Impact Scale scores (MFIS) >24 were randomized to FTC or MSTC at 4 sites, each with 6 weekly 2-hour small group meetings with trained facilitators. FTC focused on fatigue management with education and behavior change including goal setting and emphasis on engagement. MSTC consisted of reading a different pamphlet on MS before each session and discussing it at the session. Outcomes were the MFIS and MS Self-Efficacy Scale (MSSE) completed at baseline, program completion, 6 months later and 12 months later at one site.

**Results:** These results are from the 74 subjects who completed 12-month follow up at one site, of 77 subjects randomized at the site. MFIS and MSSE scores at baseline, program completion and 6-month follow-up did not differ. At 12 months, mean MFIS scores (-8.9 and -2.5, respectively, p< 0.032) but not MSSE scores (+32 and -13, respectively, p> 0.63) improved more in FTC than in MSTC, with the MFIS improvement in FTC achieving a 7-point clinically significant change.

**Conclusions:** In comparison to a general MS education program, a structured fatigue-specific group program improved fatigue in MS participants at 12 months but not at program completion or 6 months, suggesting behavior change takes time and the need to follow participants for at least 12 months.

**Disclosure**

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P360
Abdominal massage in the self-management of constipation in people with multiple sclerosis

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Neurogenic bowel dysfunction (NBD) occurs in 50-80% of people with Multiple Sclerosis (PwMS). Causes include decreased mobility, polypharmacy, decreased colonic transit time, poor sensation and altered ano-rectal sphincter tone. There is evidence that despite substantially affecting quality of life, constipation continues to be a symptom often not discussed with clinicians due to embarrassment, lack of knowledge and perception of limited management options.

Advice plus abdominal massage is a potential self-management intervention for the relief of constipation. We report on the results of a randomised controlled trial comparing abdominal massage plus self-help information on bowel management to self-help information (AMBER).

Methods: 191 patients with MS and constipation were recruited from 12 centres across the UK. Those randomised to the intervention group were shown how to do the massage, provided with training materials (e.g. DVD) and information on bowel management; the control group received information only. All participants received weekly support telephone calls during the 6 weeks of intervention. The primary outcome was the Neurogic Bowel Dysfunction score at Week 24 and secondary outcomes included bowel diary data.

Results: Both groups reported improvement in symptoms with a significant mean difference in frequency of faecation between the groups at Week 24 (mean change 0.62, 95% CI, 0.03, 2.21, p=0.039) in favour of the massage group. Massage was primarily undertaken by the participant themselves. At 6 weeks 78/87 (89%) were continuing with the massage, 59 (75.6%) were undertaking the massage themselves and 11 (14.1%) required a carer to do the massage (8 did not complete this question) with a mean of 5.4 hours (SD1.75) per week. At Week 24, 77/87 (88%) participants were still in the study and of these 51 (66.2%) were continuing with the massage with 1 (1.3%) requiring a carer to undertake the massage, spending a mean of 3.2 hours (SD 2.83) per week. Of those continuing 45 (57.1%) felt benefit, 6 (7.8%) did not feel a benefit and one did not respond. Reasons for discontinuation included no perceived benefit 8 (8.4%), 5 (6.5%) found it too difficult, 1 (1.3%) because of carer burden and 12 (14.9%) provided no reason.

Conclusion: Abdominal massage plus information is an intervention that could be part of a self-management bowel care regimen providing superior improvement to information alone for some PwMS.

Disclosure
None

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P362
Cognitive impairment and brain atrophy in multiple sclerosis: a 10-year follow-up study
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Objectives: To explore cognitive impairment and identify associated magnetic resonance imaging (MRI) biomarkers in patients with multiple sclerosis (MS).

Methods: MRI of the brain was performed in 81 of the patients. Cognitive tests were performed in 74 of the patients at time of inclusion, and repeated after 5 and 10 years. Cognitive testing was performed using the Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Selective Reminding Test (SRT) delayed recall and SRT long time storage. Cognitive impairment at baseline was defined as scoring less than 1.5 SD compared to a healthy control group on two out of four cognitive tests. MRI was acquired on 1.5 T scanners. Global and tissue-specific volumes were calculated at each time point, and atrophy changes were longitudinally assessed, using a direct measurement approach, by calculating percentage volume changes between different time points. Statistical analysis was performed using a mixed linear model.

Results: At baseline we defined 37 (46%) of the patients as cognitively impaired (CI). The patients defined as CI had significantly lower whole brain volume (WBV) (p=0.003), grey matter volume (GMV) (p=0.002) and cortical volume (CV) (p=0.007); and significantly greater ventricular volume (p=0.009) and T1 (p=0.01)/T2 (p=0.007) lesion volume than the cognitively preserved (CP) patient-group at baseline. No significant differences were found between the CI and CP patient-group over 10 year follow-up.

We examined the cognitive test and found that PASAT showed a significant decline over 10-year follow-up (p=0.003), a trend was seen for SDMT to be significantly declining over the follow-up (p=0.057). Worsening SDMT score was correlated to total subcortical deep grey matter (SDGM) atrophy (p=0.001), and specifically atrophy of the putamen (p<0.001), pallidus (p<0.001) and thalamus (p< 0.001) were significantly correlated to worsening SDMT score.

Conclusion: This study shows that cognitive impairment is a common symptom in MS, with almost 50% of the patients affected at baseline in our data. We found significantly greater atrophy of WBV, CV and GMV at baseline in the CI patient-group, but no accelerated atrophy of the CI patient group over the 10-year follow-up. PASAT and SDMT scores decreased over time. Atrophy of total SDGM volume, specifically putamen, pallidus and thalamus, showed a significant correlation to worsening SDMT score.

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P363
Factors that affect computerized cognitive screening in people with MS: diurnal variation, location and practice effects
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Summary: MSReactor is a longitudinal study to monitor psychomotor function, attention and working memory in MS patients. Computerized cognitive screening is stable over repeat home based testing, and factors are identified which impact cognitive screening.

Introduction: Cognitive Impairment (CI) is common in MS. CI in MS can impact quality of life, and MS patients with CI are less likely to be employed and have reduced social functioning. Cognitive testing in routine clinic practice that is practical, does not require trained staff and is sensitive to changes over time remains a current unmet need. Computerized cognitive batteries (CCB) monitor for changes in select cognitive domains and can fill this gap. To be effective in monitoring for cognitive change, CCBs must be consistent in repeat testing, and systematic factors that impact testing be identified.

Methods: We enrolled 400 patients (390 RRMS) over 14 months, who agreed to 6 monthly testing at the clinic, in addition to the choice to complete tasks at home (1-3 monthly). The web-based MSReactor platform efficiently screens psychomotor speed, attention and working memory.

Results: Over 80% chose to complete home testing. Acceptability of tasks remains high, with over 70% happy to repeat tasks and only 5% anxious about the tasks. Using linear mixed models to examine testing conditions, there was a 2.5-6% difference in task performance between initial clinic test and subsequent clinic test. Reaction times for initial home based tasks were 3% faster than those recorded at the initial clinic session. In repeat home testing,
performance in the psychomotor and attention tasks were stable across the first 5 home tests, whereas working memory reaction times decreased by 0.8% for each subsequent test. Factors that affect testing were identified. Reaction times for tasks done in the morning were 6-7% slower than those done in the afternoon or night. EDSS affected performance with a 1-unit increase resulting in a 1.5-2.0% slowing in reaction time on all tasks. Location of testing also affected performance, with tests performed at home faster than those done in the clinic (p< 0.05).

**Conclusion:** Computerized cognitive monitoring is stable across repeat testing, following an initial familiarization period, making it suitable for unsupervised cognitive monitoring. Diurnal variation and location of testing effects on task performance in particular should be considered in future study designs utilizing CCB platforms.

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**P364**

Fatigue acceptance mediates cross-sectional and longitudinal associations between fatigue and sleep disturbance in multiple sclerosis

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**Background:** Fatigue is reported in 50-90% of people with multiple sclerosis (MS) and has been found to co-occur with sleep disturbance. However, the mechanisms underlying and influencing the relationship between fatigue and sleep disturbance are poorly understood. Fatigue acceptance (i.e., a person’s engagement in daily activities despite fatigue, and willingness to experience fatigue without avoidance or resistance), may play a role in helping individuals cope with fatigue and reduce its negative impact on sleep.

**Objectives:** To investigate cross-sectionally and longitudinally:

1. fatigue acceptance as a mediator between fatigue severity and sleep disturbance; and
2. fatigue severity as a moderator between fatigue acceptance and sleep disturbance.

**Method:** Participants were 136 individuals with MS from across the US participating in a longitudinal survey study. Measures for the present study included: the Fatigue Short Form from the Patient Reported Outcomes Measurement Information System (PROMIS), and the Activity Engagement and Fatigue Willingness subscales from the Chronic Fatigue Acceptance Questionnaire, collected during Year 1 (Y1); and the PROMIS Sleep Disturbance Short Form, collected during Years 1 and 6 (Y6). Mediation and moderation analyses were carried out using the PROCESS tool for SPSS.

**Results:** Activity engagement significantly mediated the effects of fatigue severity on sleep disturbance at Y1 (Indirect effect: B=0.21, CI=0.05-0.39) and Y6 (Indirect effect: B=0.21, CI=0.06-0.40), respectively accounting for 51% and 76% of the total effects. Fatigue willingness was not associated with Y1 or Y6 sleep disturbance (p>0.05). Fatigue severity did not moderate the effects of fatigue acceptance on sleep disturbances (ps > 0.05).

**Conclusion:** Results support a path through which acceptance of fatigue explains the concomitant and prospective relationships between fatigue and sleep disturbance in MS. From a clinical standpoint, psychological interventions, particularly those aimed at promoting individuals’ participation in meaningful activities despite fatigue, may serve to provide short- and long-term benefits in sleep and warrant future investigation.

**Disclosure**

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Dr. Ivan Molton: Nothing to disclose.

**P365**

Self-reported sleep disturbance and cognitive function in MS: mediating effects of depressed mood and fatigue

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**Background:** Sleep disturbance is reported in approximately 50% of individuals with multiple sclerosis (MS) and has a negative impact on cognitive function in this population. However, the mechanisms underlying the relationship between sleep disturbance and cognitive function are poorly understood.

**Objective:** The purpose of this study was to examine the relationship between sleep disturbance and cognitive function, and to examine the potentially mediating effects of depressed mood and fatigue.

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Dr. Mark Jensen: Nothing to disclose.
Method: The sample included 100 individuals with MS receiving care in a university-affiliated MS center. Cross-sectional data were obtained from: self-report measures of sleep disturbance (Item 3 of the 9-item Patient Health Questionnaire [PHQ]), depressed mood (Items 1 and 2 of the PHQ), fatigue (Fatigue Severity Scale), and cognitive function (MS Neuropsychological Screening Questionnaire [MSNQ]); and objective cognitive assessments of verbal memory (California Verbal Learning Test - II [CVLT]), visuospatial memory (Brief Visuospatial Memory Test - Revised [BVMT]), and processing speed (Symbol Digit Modalities Test [SDMT]). Meditational analyses were used to model the total, direct, and indirect effects of sleep disturbance on objective and perceived cognitive function, controlling for relevant covariates.

Results: The total effects of sleep disturbance on cognitive function were significant for the CVLT (β=-5.72, t=-2.22, p=0.02) and MSNQ (β=-8.20, t=3.00, p=0.004), but not the SDMT or BVMT (all p>0.05). Additionally, because the CVLT was not correlated with the PHQ (r=0.12, p=0.25) or FSS (r=-0.08, p=0.47), mediation effects were only examined for the MSNQ. The indirect effects of sleep disturbance accounted for 53% of the variance in the MSNQ, with significant mediation for both depressed mood (β=0.11, CI=0.03, 0.24) and fatigue (β=0.08, CI=0.01, 0.17).

Conclusion: Depressed mood and fatigue represent pathways through which sleep disturbance relates to perceived cognitive impairment. Rehabilitation-focused psychological interventions that target these mediating factors may help address perceived cognitive impairment in MS.

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P366
Repeatability and validity of neurophysiological correlates of fatigue in people with multiple sclerosis
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Background: Fatigue has been widely recognized as a debilitating symptom of multiple sclerosis (MS). An improved understanding of the neurophysiological basis of MS fatigue could underpin the development of new therapeutic approaches for fatigue management.

Aim: To assess the repeatability of neurophysiological correlates of MS fatigue and measure differences in neurophysiological function between people who are experiencing high and low levels of MS fatigue.

Results: 40 patients with relapsing remitting MS (20 fatigued [MS-F]; 20 less-fatigued [MS-LF]) according to Fatigue Severity Scale and 20 healthy controls (HC) were recruited. On separate days, maximum voluntary contraction force (MVC) and submaximal quadriceps contractions at 40% MVC to task failure were performed. Electrical stimulation was performed to assess neuromuscular transmission and contractile properties of muscle fibers. Transcranial magnetic stimulation was used to quantify corticospinal excitability (short intracortical excitability [SICI], cortical silent period [SP] and cortical voluntary activation (CVA). Repeatability was measured using Intraclass Correlation (ICC).

Conclusion: The results demonstrate neurophysiological deficits associated with fatigue severity between MS-F and MS-LF, which are consistent with evidence of impairment within cortical and subcortical function areas. This study shows it is possible to obtain reproducible measurements of lower-limb neurophysiological function in people with MS. This could provide new insights into the underlying cause, as well as presenting new opportunities for studying mechanisms underpinning the positive effects of therapeutic interventions.

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Depressive symptoms are associated with more negative functional outcomes than anxiety symptoms in persons with multiple sclerosis
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Background: Mood dysfunction, specifically anxiety and depression, are common in persons with MS (PwMS) and both...
depression and anxiety have negative impact on functional status. However, no study to date has examined the differential impact of depression and anxiety on functional outcomes in PwMS.

**Objective:** We aimed to examine the differential effects of depression and anxiety, measured by the Hospital Anxiety and Depression Scale Anxiety subscale (HADS-A) and Depression subscale (HADS-D), on functional outcomes in PwMS. The functional outcomes investigated were employment status, fatigue, as measured by the Fatigue Severity Scale (FSS), physical disability, as measured by the Expanded Disability Status Scale (EDSS), and cognition/processing speed, as measured by the Symbol Digit Modalities Test (SDMT).

**Methods:** A retrospective chart review identified 133 PwMS with data on all variables of interest. Exploratory structural equation models (SEM) were conducted to examine whether HADS-A or HADS-D subscale better related to functional outcomes in MS, while simultaneously controlling for their shared variance and also the effects of demographic factors, specifically age, years of education, gender and time since MS diagnosis in years. The fit of the model to the data was examined with typical fit indices used in SEM: chi square, comparative fit index (CFI), root-mean-square error of approximation (RMSEA), and standardized root-mean-square residual (SRMR).

**Results:** HADS-A and HADS-D scores were strongly positively correlated with each other (r = .53, p < .05). Controlling for covariates, anxiety was negatively associated with EDSS (β = -.28, p < .05). In contrast, depression positively correlated with FSS scores (β = .47, p < .05), EDSS (β = .30, p < .05) and negatively associated with SDMT scores (β = -.23, p < .05). Additionally, the predictors explained 2.6% of the variability in vocation, 24.1% in fatigue, 14.3% in EDSS and 21.4% in SDMT. The resulting model was a good fit to the data (χ²(8) = 4.26, p < .05, CFI = 1.00, RMSEA = .03, SRMR = .03). However, the model did not account for variance in employment status.

**Conclusion:** Depression, as measured by the HADS-D, has a significant negative impact on functional outcomes in PwMS, with a greater impact than anxiety. This data further supports the importance of identifying and treating depressive symptoms in PwMS.

**Disclosure**

In the last two years, Dr. Morrow has received honoraria for speaking, consulting, and advisory board participation from Biogen Idec, EMD Serono, Genzyme, Novartis, and Roche. She has acted as site principal investigator for clinical trials for Novartis, Genzyme and Roche. She has received investigator initiated trial funding from Genzyme. Drs. Blair and Santo have nothing to disclose. Ms. Gill has nothing to disclose.

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**P368**

**Neuroradiological characterization of multiple sclerosis patients with chronic pain**

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**Aims:** Pain is one of the most disabling symptoms in patients with multiple sclerosis (MS). Chronic pain in MS patients is often neuropathic in nature, although a clear-cut distinction with nociceptive pain is not easy. The aim of our study was to analyze the MRIs of MS patients with chronic pain in order to explore possible associations with lesion sites, on a voxel-by-voxel basis.

**Materials and Methods:** We enrolled patients aged ≥18 years with MS in accordance with the 2010 McDonald criteria. All patients with a clinical diagnosis of depression or peripheral nerve disease were excluded. Neurostatus-certified neurologists assessed Kurtzke’s Functional Systems and EDSS. We defined “persistent pain” as a frequent or constant pain lasting longer than 3 months. Patients meeting criteria for persistent pain were included in the “Pain Group” (PAIN+). The other patients were included in the “No-PAIN Group” (PAIN-).

**Results:** We enrolled 208 MS patients (140 F, mean age 55.2 ± 9.4 years; 176 RR, 28 progressive MS; mean EDSS 2.0±2.0). In both groups (PAIN+ group: 96 patients and PAIN- group: 112 patients) the total lesion volume (mL) and lesion number were recorded for each subject. To detect the association between lesion localization and persistent pain, images were analyzed with the Voxel-based Lesion Symptom Mapping (VLSM) method implemented in the nonparametric mapping (NPM) software included into the MRIcron. (Rorden et al., 2007).

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**Discussion and conclusions:** Right dorsolateral prefrontal lesions may induce hypalgesia, whereas posterior periventricular lesions may induce hyperalgesia in MS patients. It can be hypothesized that the hypalgesia mechanism induced by the right dorsolateral prefrontal lesions in patients with SM may be similar to those occurring in Alzheimer’s disease and the opposite of those occurring in patients with MS in accordance with the 2010 McDonald criteria. All patients with a clinical diagnosis of depression or peripheral nerve disease were excluded. Neurostatus-certified neurologists assessed Kurtzke’s Functional Systems and EDSS. We defined “persistent pain” as a frequent or constant pain lasting longer than 3 months. Patients meeting criteria for persistent pain were included in the “Pain Group” (PAIN+). The other patients were included in the “No-PAIN Group” (PAIN-).

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Background: Reduction of brain volume occurs in clinically active disease and correlates with progressive disability in multiple Sclerosis (MS). Although dysarthria is highly prevalent in MS, it only becomes clinically relevant in advanced stages of the disease. The relationship between early sub-clinical markers of dysarthria and overall disease severity is poorly understood.

Aim: To examine the relationship between an objective marker of speech performance and validated clinical scores for disease severity in non-dysarthric subjects with relapsing-remitting and secondary progressive MS.

Method: An experienced neurologist scored patients according to the Expanded Disability Status Scale (EDSS) and the Scale for the Assessment and Rating of Ataxia (SARA). Acoustic analysis was used to investigate the diadochokinetic speed in “as fast as possible” repetition of the meaningless word /pa/ta/ka/. Brain images were acquired using 3 Tesla magnetic resonance. Images were automatically segmented using FreeSurfer (5.7) to determine volumes for whole brain (excluding ventricles) and cerebellum. Lesions were automatically segmented by the lesion prediction tool version 2.0.15 for SPM (Statistical Parametric Mapping software). Statistical correlations were processed in SPSS (v 23.0) controlling for age. After adjustment for multiple comparisons, a p<0.01 was considered for statistical significance.

Results: We assessed 35 MS patients with normal speech (i.e. SARA score sub-score 0-1; age=47.7±12years; disease duration=13.2±8.4). Diadochokinetic rate (mean=5.63±0.83 syllables per second) directly correlated with EDSS (Spearman’s rho=0.454, 2-tailed p=0.007; median EDSS=3.5, interquartile range=3.5) and SARA (rho=0.515, p=0.002; SARA median=9, interquartile range 11.975), but not with whole brain volume (p=0.022), lesion load (p=0.032) or cerebellar volume (p=0.037).

Conclusion: Changes in acoustic markers can be detected before overt dysarthria in MS and reflect overall disease severity. Larger and longitudinal studies are needed to understand if those markers can help monitoring disease progression.

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P370
Cognitive flexibility in multiple sclerosis patients may be dependent on information processing speed
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Background: In many patients multiple sclerosis (MS) is associated with cognitive deficits. Previous studies indicated that cognitive flexibility and executive functions are impaired in MS patients. The aim of this study was to examine cognitive flexibility in MS patients compared to healthy controls, to evaluate associations with MRI changes and to study cognitive flexibility over a time-course of two years. We present preliminary results regarding cognitive flexibility.

Patients and Methods: 38 MS patients and 38 matched healthy controls were tested. Patients (22 female, 16 male, mean age 40.6 ± 9.7 years; 35 relapsing-remitting MS, 3 secondary progressive MS) did not differ significantly from controls in age, gender and education. Mean disease duration in patients was 11.1 ± 6.1 years. Both groups were tested using the Trail Making Test forms A and B (TMT-A, TMT-B), that tests for information processing speed and cognitive flexibility, Wisconsin Card Sorting Test (WCST), testing for executive functions, and the Regensburger Test of word fluency. We used paired t-tests for comparing patients to controls.

Results: Patients did not differ significantly from controls in ten categories of the WCST. Patients were significantly slower in completing TMT-A than controls (34.6 s ± 16.2; 27.3 s ± 10.5; p = 0.019) and in completing TMT-B (69.5 s ± 58; 56.4 s ± 19.4; p = 0.04, s = seconds). Word Fluency did not differ between patients and controls with respect to the change of lexical categories, but the patients performed significantly worse in changing between semantic categories: correct words after 1 minute 15 ± 3.2; 16.7 ± 3; p = 0.038; after the 2nd minute 7.6 ± 2.1; 9.1 ± 2.5, p = 0.003 and after the two minutes: sum of correct words 22.6 ± 3.8; 25.7 ± 4.7; p = 0.003.

Conclusion: Reduced information processing speed and reduced cognitive flexibility have been described as core deficits in MS patients. Our results indicate that when MS patients are pressed time as in the Trail Making Test and the changes of categories in the word fluency test, their performance gets significantly worse due to a reduced information processing speed. Deficits in cognitive flexibility have to be interpreted in tandem with the information processing speed.

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P371
Association between self-reported upper limb, lower limb and cognitive functioning and functional performance in MS PATHS (multiple sclerosis partners advancing technology and health solutions) patients

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Background: Objective measures of upper limb, lower limb and cognitive function are commonly used to assess MS patients. Although these measures provide an assessment of function and disability, they may not reflect how patients perceive their own ability.

Objective: To understand how patients’ perceptions of upper extremity, lower extremity and cognitive function are related to objective functional performance measures.

Methods: MS PATHS is a collaborative network of ten healthcare institutions in the US and Europe. During routine office visits, patients used the Multiple Sclerosis Performance Test (MSPT), an iPad-based device, to complete 12 scales from the Quality of Life in Neurological Disorders (Neuro-QoL) instrument and electronic adaptations of the MSFC: a processing speed test (PST); manual dexterity test (MDT); and walking speed test (WST). The relationship of the subjective self-reported scales and objective functional scales was assessed using scatterplots and Spearman’s rank correlations.

Results: The sample comprised 1353 patients. Mean (SD) age was 48.9 yrs (12.0), mean (SD) disease duration 12.2 yrs (9.4), 72% were female and 85% were white. Mean (SD, range) Neuro-QoL upper extremity t-score was 43.3 (9.3, 22.3-56.8), mean (SD, range) Neuro-QoL lower extremity t-score was 44.6 (10.7, 15.7-62.3) and mean (SD, range) Neuro-QoL cognitive function t-score was 45.3 (9.6, 22.9-68.3). Mean (SD, range) PST was 45.9 correct (13.2, 4-86), mean (SD, range) MDT was 28.8 secs (7.1, 17.2-55.8) and mean (SD, range) WST was 8.1 secs (5.4, 2-52.5). There were generally strong correlations (p < 0.001) between Neuro-QoL upper extremity t-scores and the MDT (r_s=−0.56), and Neuro-QoL lower extremity t-scores and the WST (r_s=−0.48). A weaker correlation was observed between Neuro-QoL cognitive function t-scores and the PST (r_s=0.29, p < 0.01).

Conclusions: Consistent with previous findings, self-reported cognitive status shows a weak correlation with cognitive performance measures (Benedict et al. 2008). This suggests the PST provides important information in determining when more comprehensive evaluations are needed to clarify the impact of cognitive dysfunction on QoL, function and employment. The stronger correlations observed between Neuro-QoL scores and the functional performance measures of upper and lower extremity function confirm the utility of the self-reported assessment, but their modest range indicates self-report and performance yield distinct information.

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Factors associated with fatigue in the NARCOMS registry

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Background: Fatigue is a common symptom reported by persons with MS and is considered one of the most disabling symptoms by 15%-40% of persons. Fatigue is associated with reduced quality of life and social participation.

Objective: To characterize fatigue and satisfaction with social participation in participants with respect to demographic and clinical characteristics using the Patient-Reported Outcome Measurement Information System (PROMIS®) instruments.

Methods: The North American Research Committee on Multiple Sclerosis (NARCOMS) registry semi-annual update in the fall 2016 included the PROMIS® domains of fatigue and satisfaction with participation in social roles (SPSR). The raw score was converted to the T-score to allow for comparison with the US general population. Demographic and clinical characteristics were obtained from the participant’s enrollment and Fall 2016 semi-annual surveys. Disability status was measured using Patient Determined Disease Steps (PDDS). Descriptive statistics and
Pearson correlations were used to summarize characteristics. Multivariable linear regression was used to examine the impact of characteristics on fatigue and SPSR.

**Results:** Of the 7006 respondents to the Fall 2016 semi-annual survey, 6293 (89.8%) participants completed both PROMIS® domains. Participants were primarily female (79.4%) and Caucasian (91.7%) with a mean (standard deviation [SD]) age of 59.9 (10.2) years. Median (25%, 75%) PDDS was 4 [early cane] (1, 6). The mean (SD) Fatigue T-score was 56.8 (11.0), and the mean (SD) SPSR T-score was 45.2 (10.6). There was a strong inverse correlation between fatigue and SPSR ($r=-0.828$, 95% confidence interval: [-0.836, -0.820]). Participants with normal (0) or mild (1) PDDS levels reported fatigue severity and SPSR at the mean of the general population. However, moderate (2) or greater (3-8) PDDS levels were associated with higher than average fatigue and lower SPSR. Minimal differences by gender and age were observed for the fatigue and SPSR. Multiple factors were associated with greater fatigue including, older age at diagnosis ($p<0.0001$), greater disability ($p<0.0001$) and increasing level of depression ($p<0.0001$).

**Conclusion:** Participants report high fatigue levels and low levels of satisfaction with participation in social roles. Fatigue is a multidimensional symptom and a better understanding of factors associated with fatigue could impact intervention studies, clinical care and enhance quality of life.

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**Clinical assessment tools**

**P373**

**Factors driving social withdrawal across multiple sclerosis disease types**

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**Background:** Multiple sclerosis has the capability to affect every aspect of the sufferer’s life including working ability, personal and social relationships. Social withdrawal may be considered to be a particularly deleterious consequence, but whether this is due to disease related impairments or psychological disability remains unclear. Furthermore, it is not known whether there are different factors driving social withdrawal in those with different disease types.

**Objective:** To determine the disease related and psychological factors which dictate social withdrawal across different MS disease types.

**Method:** Self-report instruments for physical and psychological impact (MSIS), pain (NPS), vision (MSVQ-7), bladder dysfunction (SF-QUALIVEEN), fatigue (NFI-Summary), spasticity (MSSS), anxiety and depression (HADS), coping (MS coping scale), hope (MS hope scale), self-esteem (Rosenberg) and self-efficacy (USE-MS) and social withdrawal (SWS), were administered concurrently to patients with definite MS as part of the TONiC study, a multicentre, UK study of factors affecting quality of life in MS. Subject characteristics including disease type were determined by a clinician at study enrolment. Summed raw scale scores were converted to interval level data by application of the Rasch measurement model. Factors explaining the variance in social withdrawal were determined by linear regression modelling ($p<0.01$).

**Results:** 3186 records were available for analysis. 73% were female, 65% had relapsing (RRMS), 12% primary progressive (PPMS) and 22% secondary progressive (SPMS) disease, 35% were fully ambulatory (EDSS 0-4), 38% EDSS 4.5-6.5, 7% EDSS 7.0-7.5, 5% 8.0-9.5. In RRMS, there were four significant factors ($p<0.001$, $R^2=0.68$): self-efficacy ($\beta=0.388$), physical impact ($\beta=0.364$), depression ($\beta=0.162$) and psychological impact ($\beta=0.107$). In PPMS, two main factors ($p<0.001$, $R^2=0.77$) of physical impact ($\beta=0.508$) and self-efficacy ($\beta=0.271$) were identified. In SPMS, the same main two factors ($p<0.001$, $R^2=0.59$) of physical impact ($\beta=0.503$) and self-efficacy ($\beta=0.316$) were seen.

**Conclusion:** High physical impact and low self-efficacy were the two factors consistently driving social withdrawal across MS disease types. Interestingly, fatigue, pain, spasticity, bladder dysfunction, visual impairment, anxiety, coping, hopelessness and self-esteem were not relevant.

**Disclosure**

Mills RJ, Caldu R and Young CA declare no conflicts of interest for this work. The TONiC study was supported by unrestricted grant support from NIH, MND, Multiple Sclerosis Society of Canada, Biogen, Genzyme, Merck, Novartis, Roche, Teva.
Background: Accurately assessing and predicting disability in people with multiple sclerosis (pwMS) is challenging for clinicians. The Expanded Timed Get Up and Go (ETGUG) is an adaptation of a timed up and go performance test that has been used to predict fall risk in a geriatric population.

Objective: Our objective was to evaluate the utility of the ETGUG in predicting disability among a large sample of pwMS in New York State, particularly compared to other assessment measures.

Methods: Participants (n=355) were part of the New York State Multiple Sclerosis Consortium (NYSMSC); a 20-year longitudinal registry. The ETGUG, Timed 25-foot walk (T25FW) and Expanded Disability Status Scale (EDSS) were compared using Spearman’s Rank correlations. Receiver operator characteristic (ROC) analyses with 80% specificity were carried out to determine the ETGUG and T25FW cutoff score and associated sensitivity predicting an EDSS score of ≥4.0.

Results: Of the 355 subjects, 121 (34.1%) had an EDSS score of 4.0 or higher. Both ETGUG and T25FW were highly correlated with EDSS (r=0.730 and r=0.729, respectively, p-value<0.001). Correlations with EDSS were stronger for both ETGUG and T25FW among subjects with an EDSS score≥4.0 than among pwMS with EDSS scores of <4.0 (ETGUG: r=.728, T25FW: r=.682 in the more disabled group; versus ETGUG: r=.433, T25FW: r=.447, respectively). At the predetermined specificity, an ETGUG score of ≥23.5 seconds had a 91.7% sensitivity of identifying subjects with an EDSS of ≥4.0, while completing the T25FW in ≥6.4 seconds had a lower sensitivity at 82.7%.

Conclusion: The ETGUG is a more sensitive predictor of disability than the T25FW in this sample. Prospectively captured data is required to determine the sensitivity of the ETGUG to longitudinal change and its usefulness in predicting disability progression and risk of falling especially in the patients with higher disability.

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P375
Intensive neurorehabilitation is associated with improved gait kinematic analysis in progressive multiple sclerosis

Introduction: The involvement of gait impairment is the main cause of disability in progressive multiple sclerosis (MS). In addition to validated clinical tests, kinematic measures of gait may provide useful information for the customization of rehabilitative intervention. We explored their usefulness in evaluating clinical improvement after intensive neurorehabilitation in progressive MS.

Methods: Seventeen subjects with progressive MS, (7 females), median age 49.7 (37-68), median expanded disability status scale-EDSS 5.9 (3.5-6.5), underwent testing of functional independence measure-FIM, walking speed with the 10-meter walk test-10MWT, walk endurance with the 6 minute walk test-6MWT, Berg balance scale-BBS at hospitalization (T0) and after a 4-week intensive neurorehabilitative program (T1).

Clinical measures were correlated with gait parameters (step frequency-cadence, velocity, cycle length, cycle acceleration, symmetry index of postero-anterior acceleration) collected during the 10MWT using a pocket-sized device combining accelerometers and a magnetometer, placed over the L5 vertebra with an elastic belt.

Results: At both time points, cadence correlated with FIM (T0: Pearson’s r 0.546, p=0.023; T1: r 0.638, p=0.006), 6MWT (r 0.803, p=0.001; T1: r 0.563, p=0.036), BBS (T0: r 0.675, p=0.003; T1: r 0.518, p=0.033). Velocity correlated with FIM (T0: r 0.590, p=0.013; T1 r 0.673, p=0.003), 6MWT (T0: r 0.773, p<0.002; T1: r 0.641, p=0.014), BBS (T0: r 0.596, p=0.011; T1: r 0.577, p=0.015). Cadence and velocity increase correlated with FIM improvement (r +0.501, p=0.040 and r +0.488, p=0.047, respectively), while 10MWT was significantly correlated with 6MWT at T0 (r -0.728 e p=0.007) and T1 (r -0.766 e p=0.001) and BBS at T0 (r -0.593 e p=0.015).

Conclusion: Cadence and velocity correlated with all clinical measures whereas 10MWT showed correlation only with 6MWT and BBS, suggesting that quantitative gait kinematics correlate with clinical measures better than 10MWT. Cadence and velocity improvement seems to reflect the increase in functional independence in daily activities rather than in walk endurance. These data suggest the feasibility and usefulness of gait testing with a wearable device in the clinical setting and prompt larger validation studies.

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Can we trust self-reported walking distance when determining EDSS scores? - A part of the Danish MS Hospitals Rehabilitation Study


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Introduction: In multiple sclerosis (MS) the expanded disability status scale (EDSS) is, despite well-known limitations, widely accepted as the main assessment tool and gold standard when describing disease severity and progression. Although the EDSS is highly dependent on patients walking capacity, self-reported statements about walking distance are ordinarily acceptable. However, this may lead to imprecise EDSS scoring due to potential patient mis-judgement and relatedly inappropriate treatment decisions. Nonetheless, surprisingly little is known about the concordance between self-reported and actual walking distance in MS. Thus, the purpose of this study was to compare the self-reported statements on walking distance provided during EDSS assessment with actual standardized walking performance.

Materials and Methods: 303 patients with MS and an EDSS ≥4, who was part of the Danish MS Hospitals Rehabilitation Study, were asked to estimate their walking distance according to the EDSS walking classification within the EDSS range 4.0-7.5 (>500 m; 300-500 m; 200-300m; 100-200 m; 20-100 m; 5-20 m; 0-5 m). Subsequently, they performed a maximum walking distance test, which was terminated when the participant was totally exhausted or passed 500 m. Finally, patients underwent a full neurologic examination by a trained Neurologist including EDSS determination based on patient’s actual walking performance.

Results: Complete datasets were collected from 273 out of 303 enrolled patients. A total of 145 patients (53%) misjudged their actual walking distance, by one category or more. Of those that misjudged, 73 % were underestimating. Persons using a walking aid tended to misjudge their walking ability. In most cases, difference between self-reported walking and actual walking affected the EDSS by ±0.5 point, however in a smaller subgroup misjudgments led to EDSS variabilities by more than ±1.0 point.

Discussion: This analysis demonstrated variability between patient reported and actual walking distance. Particularly persons using walking aids tended to misjudge their walking ability. In most cases, difference between self-reported walking and actual walking affected the EDSS by ±0.5 point, however in a smaller subgroup misjudgments led to EDSS variabilities by more than ±1.0 point.

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and reveals changes in daily function not otherwise captured by more traditional disability metrics.

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**P378**

**Convergent validity of acceleration-derived parameters from iPad®-based walking and balance testing**

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**Background:** There is growing interest in measuring the motor performance of individuals with multiple sclerosis (MS) using wearable devices. Walking and balance are of particular interest, due to their being frequently impaired in MS. We have previously developed a walking speed assessment module incorporated into an iPad®-based neurological performance test [MSPT]. In addition to the traditional outcome measure of walking time, data from the accelerometer and gyroscope within the iPad® can be collected, yet the validity of these measurements is not established.

**Goals:** To determine the convergent validity of parameters derived from the accelerometer and gyroscope in the iPad® to characterize gait and postural instability in MS patients, compared to walking speed and posturometry.

**Methods:** MS patients with gait disturbance performed walks under various conditions (Timed 25 Foot Walk [T25FW], comfortable pace walk on the GAITRite® gait analysis system, and treadmill walking in the Computer Assisted Rehabilitation ENvironment [CAREN] system) while wearing the iPad® on the back at the sacral level. Standing balance (eyes opened and eyes closed) was also assessed using a Tetrax® balance analysis platform while wearing the iPad®. Associations between acceleration-based iPad® parameters, instrumented measures of walking speed and balance, and self-report measures of walking balance, and confidence were assessed.

**Results:** Data from 49 participants were analyzed (age 55.5 ± 7.5 years, 57% women, 61% progressive disease course, 55% using a cane or walker). Significant correlations were observed between walking speed (under all 3 conditions) and many iPad® acceleration-derived parameters (Spearman r > 0.5), with stronger correlations in participants walking without an assistive device (some with r > 0.7). Significant correlations were also observed between the Stability score from the Tetrax® system (eyes closed condition) and most acceleration-derived parameters (Spearman r > 0.5), with stronger correlations among participants who used a cane or a walker (some with r > 0.7). Moderate associations between iPad® parameters and patient-reported walking and balance status were detected (r > 0.3).

**Conclusions:** Our results suggest satisfactory convergent validity between acceleration-based parameters derived from the iPad® and instrumented measures of walking speed and postural stability, although performance varies depending on the level of walking impairment.

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P379
McArdle sign: a specific sign of multiple sclerosis
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Filippo Savoldi has nothing to disclose.

Background: McArdle’s sign (McS) refers to rapidly reversible motor weakness induced by head flexion in patients with multiple sclerosis (MS).

Objective: We quantified McS in finger extensors using a torque measuring device and assessed its specificity for MS.

Methods: We enrolled 25 healthy controls (HC) and 76 patients with detectable finger extensor weakness, 52 with MS, 24 with other myelopathies (OM), 5 with peripheral nerve lesions (PNL); patients were not selected for having McS. We evaluated McS blinded to diagnosis by measuring change in finger extensor strength in successive trials of head extension and flexion, first clinically and then with a torque measuring device. McS was clinically rated from 0 (absent) to 3 (marked). In the quantitative measurement, the patient applied maximum extension strength of 4 fingers on a bar using isometric (against fixed object) and isoinertial (against a constant resistance) maneuvers; we averaged the percentage decrease in strength over 4 trials.

Results: Baseline strength was similar in the 3 patient groups. The median clinical McS was 1 (range 0-3) in MS patients, 0 (0-2) in OM, 0 (0-1) in HC and 0 in all PNL (P < 0.001). The isometric and isoinertial maneuvers provided similar quantitative results, but the isoinertial maneuver had superior diagnostic performance. Head flexion resulted in 17% (±17%) isoinertial strength reduction in MS patients versus 1% (±6%) in OM, 1% (±5%) in HC and -3% (±10%) in PNL (P < 0.0001). A multivariate regression analysis eliminated confounding by baseline strength. Receiver operator curves were generated to assess the diagnostic properties of the test; the area under the curve was 0.82 in MS versus HC and 0.83 in MS versus OM for isoinertial testing. A 10% drop in strength with flexion was 100% specific and 62% sensitive for MS compared to OM and a 6% drop 92% specific and 73% sensitive for MS compared to HC. Quantitative McS correlated with clinical McS by referring physician and technician (r = 0.58, p < 0.001). McS correlated with Expanded Disability Status Scale (r = 0.41, p = 0.02) and pyramidal score (r = 0.49, p < 0.001) in patients with MS, but was evident in some patients in very early phases of MS and minor disability.

Conclusion: McS, when defined as >10% neck flexion-induced reduction using isoinertial finger extension on a measurement device is highly specific and moderately sensitive for a diagnosis of MS. McS may facilitate diagnosis of MS in certain clinical situations.

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P380
How useful is the Hospital Anxiety and Depression Scale (HADS) in multiple sclerosis?
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Background: The Hospital Anxiety and Depression Scale (HADS) has been validated for use in people with multiple sclerosis (MS). However, scores on the depression subscale may be influenced by physical factors because of one question: “I feel as if I am slowed down.”

Objective: To determine the usefulness of the HADS with and without the “slowed down” question in detecting depression and predicting cognitive dysfunction.

Methods: A sample of 193 people with confirmed MS completed the HADS. Previously established cut-off scores for the HADS depression subscale with and without the “slowed down” question included were used to classify depressed participants. The Minimal Assessment of Cognitive Functioning in MS battery was administered to all participants. Two linear regression models were conducted to determine predictors of information processing speed, learning/memory, and executive function. In model 1 predictors included HADS - depression with the “slowed down” question, HADS - anxiety, EDSS, physical domain of the modified Fatigue Impact Scale (m-FIS), age, and premorbid IQ based on the Wechsler Test of Adult Reading (WTAR). In model 2 the “slowed down” question was excluded from the HADS - depression. Statistical significance was set at p = 0.05.

Results: The mean age of the sample was 43.62 years (SD: 10.67) and consisted of 136 (70.5%) females. The HADS - depression with and without the “slowed down” question detected similar rates of depression (30.6% vs. 31.6%, respectively). The internal consistency of the HADS - depression was similar with and without the “slowed down” question (Cronbach alpha: 0.80 and 0.80, respectively). Based on model 1, significant predictors of processing speed were EDSS, premorbid IQ, and HADS - depression; of memory EDSS, age, premorbid IQ, and HADS - depression; of executive function age, premorbid IQ, and HADS - depression. After removing the “slowed down” question in model 2, HADS - depression no longer predicted processing speed and memory. The only significant correlation between the EDSS and the individual HADS - depression questions was with the psychomotor slowing item (r = 0.20, p = 0.009).

Conclusion: Removing the “slowed down” question from the HADS - depression subscale does not influence its internal consistency. The
depression subscale is a better predictor of cognition with the question included, however, this relationship may be driven by factors other than depression.

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**P381**  
Subclinical motor impairment assessed by an engineered glove correlates with MRI brain damage in radiologically isolated syndromes  
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**Background:** The increasing use of magnetic resonance imaging (MRI) in the diagnostic work-up has contributed to identify asymptomatic subjects with unpredicted brain abnormalities suggestive of multiple sclerosis (MS), defined as subjects with radiologically isolated syndrome (RIS). Recently an engineered glove measuring finger motor performance has been demonstrated to provide reproducible parameters able to discriminate healthy controls (HC) and people with MS at early stage, detecting subclinical impairment not revealed by classical scales.  

**Objective:** To quantitatively assess finger motor performance in RIS subjects with respect to HC and its relationship with MRI.  

**Methods:** 17 RIS subjects (age=37.3±10.0 y, 11 F) and 17 matched HC performed a repetitive sequence of finger opposition movements with their dominant hand at maximal speed and bimanually metronome-paced (2Hz). Different parameters were calculated: RATE (number of touches per second) at maximal speed and Inter Hand Interval (IHI, the time difference between the corresponding touch onsets in the two hands) for the bimanual trial. All subjects underwent conventional and diffusion tensor imaging (DTI) to obtain global lesion volume (LV), fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD).  

**Results:** In RIS subjects RATE was significantly lower (2.6±0.5 vs. 3.4±0.9 Hz, p=0.005) and IHI higher (25.6±10.8 vs. 17.5±6.7 ms, p=0.006) than HC, indicating movement slowing and bimanual coordination impairment. DTI was also significantly altered (FA: 0.42±0.02 vs. 0.44±0.01, p=0.02; RD: 0.58±0.04 vs. 0.55±0.02, p=0.005; AD: 1.13±0.02 vs. 1.11±0.02, p=0.04). At multivariate analysis RD (OR=1.1, p=0.01) and RATE (OR=0.7, p=0.02) were independently retained in the model providing the greatest discrimination between groups (C=92%). IHI of RIS subjects correlated with LV (r=0.42), RD (r=0.55) and FA (r=0.43). In the follow-up 8 out of 17 RIS subjects had a clinical event; the time to the first event was shorter for those in the highest IHI quartile (HR=3.3, p=0.09).  

**Conclusions:** RIS subjects showed subtle motor impairment related to diffuse brain damage. Greater bimanual coordination impairment led to shorter time to the first clinical symptom, suggesting the importance of quantitative evaluation of fine motor performance. The engineered glove is a useful tool for a better characterization of subtle clinical impairment in MS.  

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**P382**  
Reliability and validity of a new, sensor-based system for gait analysis in patients with multiple sclerosis  
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**Background:** Gait abnormalities are common in multiple sclerosis (MS) and contribute to disability but may not be easily detected in the early stages of the disease.  

**Objective:** We evaluated reliability and validity of a new, sensor-based system for gait analysis in a large group of patients with MS (PwMS) with different disability stages, and healthy controls (HC).  

**Methods:** PwMS admitted to the University outpatient clinic or to inpatient rehabilitation, age >18 years, EDSS ≤ 7.0 and given informed consent were included in the study. Healthy volunteers (hospital staff, relatives and medical students) served as controls. The automatic gait analysis system *eGaIT* ("embedded gait analysis using intelligent technology") consists of a small sensor device (accelerometer and gyroscope) laterally attached to both shoes and enables data capturing and analysis, wireless data transfer, feature extraction and gait parameter calculation by pattern recognition algorithms. PwMS and HC were asked to perform the 25-foot walking test (25FWT) two times in a self-selected, comfortable speed (25FWT_slow), followed by two times in a speed as fast as possible (25FWT_fast). Reliability was assessed by correlation analysis between results of the two 25FWT recordings (in slow and fast speed) for different gait parameters (stride length, gait speed, swing time, cadence). Validity was estimated by...
1) comparing PwMS with HC, and
2) PwMS subgroups with different disability levels (EDSS ≤ 3.5 and EDSS ≥ 4.0).

Results: Between January 2016 and August 2016, 102 PwMS (68% female, mean age 43.0 ± 11.6 years, median EDSS 4.0), and 22 HC (45% female, mean age 34.3 ± 15.6 years) were investigated. Upon comparison of datasets from the first and second measurement, data highly correlated in both, PwMS (i.e. stride length 25FWT_slow, r=0.90, p< 0.001; 25FWT_fast, r=0.91, p< 0.001) and HC (25FWT_slow, r=0.75, p< 0.001; 25FWT_fast, r=0.54, p= 0.03). For all parameters investigated, we found statistically significant differences between HC and PwMS as well as between PwMS subgroups with lower (n=44) versus higher disability (n=58). These differences were more pronounced for 25FWT_fast (i.e. cadence, p< 0.001) than 25FWT_slow (cadence, p=0.03).

Conclusion: The eGaIT system is a reliable and valid tool for instrumented gait analysis in PwMS that may easily be administered and objectively supports the clinical workup by detection of gait abnormalities even in the early stages of MS.

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P383
Risk factors for cognitive impairment in multiple sclerosis as defined by the symbol digit modalities test: a retrospective analysis of the University of Calgary Multiple Sclerosis Clinic Database
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Background: Cognitive impairment is common in multiple sclerosis (MS) and is an independent risk factor for decreased employability, social functioning, and health-related quality of life. This retrospective study aims to identify risk factors associated with cognitive impairment using the Symbol Digit Modalities Test (SDMT).

Methods: We identified 1,886 MS patients (1,371 female and 515 male) in the University of Calgary MS Clinic Database who completed the SDMT at least once. Multivariable logistic regression was used to analyze factors associated with cognitive impairment (SDMT score < 50) at baseline. Among 1,218 (64.6%) patients who completed at least one follow-up SDMT, we analyzed factors associated with time to a clinically meaningful decline in cognitive function (decrease in SDMT score ≥4) using multivariable Cox proportional hazards regression. Risk factors included age, education, gender, disease course, disease duration, and Expanded Disability Status Scale (EDSS) score. A p value < 0.05 was considered statistically significant.

Results: At baseline, 892 (47.3%) patients were cognitively impaired (SDMT score < 50). Older age, less education, male gender, and higher EDSS were independently associated with increased odds of cognitive impairment. Categorical analysis revealed that patients with an EDSS score ≥2.0, age ≥55 years, male gender, and disease duration ≥20 years were at higher risk of having a baseline SDMT score < 50. Longitudinal data was available for 1,218 patients. Mean ±SD follow-up time was 2.3 ±1.1 years (range: 3.2 months-5.1 years). Decline in cognitive function (decrease in SDMT score ≥4) from baseline was observed in 421 (34.6%) patients. Median time to decline in cognition was 3.5 years (95% CI: 3.2-3.8). Male gender and normal baseline cognitive function were independent risk factors for cognitive decline. Among 664 patients with normal baseline cognition, 262 (39.5%) experienced a decline in cognitive function. Median time to decline in cognition was 3.1 years (95% CI: 3.0-3.7).

Conclusion: Routine screening for cognitive impairment with the SDMT may be particularly useful in patients with an EDSS score ≥2.0, age ≥55 years, male gender, or disease duration ≥20 years, as these patients are at higher risk of being cognitively impaired. Male patients, and those with normal cognitive function at baseline, appear to be at higher risk of experiencing a clinically meaningful decline in cognition within approximately 4 years.

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P384
Fully automated detection, segmentation and quantification of mean cross-sectional area of the spinal cord
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Background: The role of upper spinal cord atrophy in multiple sclerosis (MS) has been demonstrated in multiple studies in recent years. Mean Upper Cervical cord cross-sectional area (UCCA) was shown to correlate significantly with EDSS scores, used to
differentiate neuromyelitis optica (NMO) from MS, and also to separate groups of progressive vs relapsing-remitting patients. Precise manual measurement is a difficult and error-prone task, due to the small size of the spinal-cord cross-section with respect to voxel-size in MRI. Consequently, there is a high demand for automated quantitative measuring tools.

Methods: We implemented a fully automated atlas-based approach for detection and segmentation of the spinal cord from T1-weighted MPRAGE-MR Images. The atlas image has been labeled manually with landmarks for the spinal cord location and positions of intervertebral discs. For processing individual images, the atlas is first registered non-linearly to the image. Subsequently, the registered landmarks are used to control an iterative watersh-ed-based segmentation process of the spinal cord. Quantification is then carried out by fitting a bi-modal Gaussian mixture model with partial volume modeling to the histogram, which gives a precise volume measurement of the cord. Mean cross-sectional area (MCSA) is obtained as the ratio of volume to the centerline of the segmented spinal cord section. MCSA can be evaluated individually for each vertebral section.

We have evaluated our method on a cohort of 45 MS patients and 10 age-matched controls. Images were acquired on a 3T Siemens Skyra MRI scanner. We evaluated the rate of successful detection and segmentation quality, as well as the difference between automated and manually measured UCCA.

Results: Computation time per case is approx. 30 sec on a modern laptop. Spinal cord detection succeeded in 54 out of 55 cases. For each of these cases, the spinal cord sections C1-C4 were successfully segmented. The mean difference between automatically and manually measured UCCA was 1.53% (min: 0.02%, median 1.12%, max 6.1%), which is well within the range of inter-opera-
tor variability of the manual measurement.

Conclusion: We presented a fully automatic method for quantification of spinal cord atrophy, which is computationally fast, completely robust to operator variability and yields highly accurate results with no significant difference from established semi-auto-
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P385
Decreased articulation rate in multiple sclerosis and its relationship to overall disease disability and cognitive function
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Background: Influence of multiple sclerosis (MS) on speech is not fully recognized. The most common dysarthria in patients with MS are spastic, ataxic and mixed type. Slow articulation rate represents a typical sign of all of them. However, systematic assessment is limited and the relation of articulation rate to overall disease severity and cognitive function in MS remains unclear.

Objective:
(i) To verify whether the articulation rate is affected in MS based upon a large sample of patients.
(ii) To investigate if the decreased articulation rate reflects the overall disease disability in MS.
(iii) To determine if the oral motor slowing in MS may influence neuropsychological tasks requiring oral response.

Methods: Short passages of standardized 80-words text were acquired from 141 MS subjects and 70 age- and sex-matched healthy control individuals. The articulation rate was calculated from audio recordings as the number of words produced per sec-
tond (after removing the pauses lasting for more than 60 ms). In addition, all MS subjects underwent clinical evaluation including Expanded Disability Status Scale (EDSS), the oral form of Symbol Digit Modalities Test (SDMT) and 25-Foot Walk (25FWT).

Results: Our results confirmed slower articulation rate of MS subjects (mean 3.0, SD 0.5 words/s) compared to healthy controls (mean 3.3, SD 0.5 words/s) (t-test: p < 0.001). Articulation rate in MS correlated to the overall disability measured using EDSS (Spearman: r = -0.44, p < 0.001) including both pyramidal (r = -0.46, p < 0.001) and cerebellar (r = -0.47, p < 0.001) EDSS functional system scores as well as to gait deficits evaluated by 25FWT (r = -0.44, p < 0.001). Moreover, we observed a relationship between articulation rate and the value of SDMT (r = -0.58, p < 0.001).

Conclusion: Slow articulation rate represents a distinct sign of MS. Our findings suggest that this is related to the overall disease disability, mainly due to the involvement of both pyramidal and cerebellar tracts. Interestingly, our results indicate that slower articulation rate may bias neuropsychological assessment requiring an oral response.

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Phonatory dysfunction in multiple sclerosis
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Background: Phonatory dysfunction represents common but unspecific manifestation of many neurodegenerative diseases. Although dysphonia is also frequently reported by patients suffering from multiple sclerosis (MS), the prominent signs of voice dysfunction and their severity in MS have been poorly investigated.

Objective: The aim of this study was to explore specific changes in phonatory function in a large number of patients with MS.

Methods: Voice recordings were acquired from 141 MS subjects and 70 age- and sex-matched healthy control individuals. All subjects were instructed to take a deep breath and produce phonation of vowel /a/ at a comfortable pitch and loudness, as constant and long as possible. Quantitative acoustic analyses were designed using five traditional parameters including

(i) maximum phonation time (MPT), aerodynamic efficiency of the vocal tract measured as the maxim duration of prolonged vowel;
(ii) standard deviation of fundamental frequency (F0 SD), the variation in frequency of vocal fold vibration;
(iii) frequency perturbation (Jitter), the extent of variation of the voice range measured as the variability of pitch from one cycle to the next;
(iv) harmonics-to-noise ratio (HNR), the amount of noise in the voice signal, defined as the amplitude of noise relative to tonal components of speech; and
(v) degree of unvoiced segments (DUV), representing strained-strangled voice quality, defined as the fraction of

Results: Our results showed prominent phonatory dysfunction in MS. Four from five investigated acoustic parameters were significantly affected in MS when compared to controls including F0 SD (t-test: p < 0.001), Jitter (p = 0.03), HNR (p < 0.001) and DUV (p = 0.005). However, we observed only weak correlations between severity of MS represented by EDSS and different aspects of voice dysfunction including F0 SD (Pearson: r = 0.20, p = 0.02), Jitter (r = 0.28, p < 0.001), and HNR (r = −0.22, p = 0.008).

Conclusion: Our findings confirmed impaired phonatory function in MS patients. As the extent of phonatory dysfunction was found to partially parallel increasing motor involvement, a qualitative description of dysphonia symptoms may have a potential to provide functional biomarkers of MS.

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Assessing upper extremity function and mobility with multiple clinical tests of the Assess MS system
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Background: Accurate assessment of disease activity and disability progression is challenging in multiple sclerosis (MS) due to the heterogeneous nature of the disease. This includes assessment of upper extremity function (UEF) and mobility. The Assess MS system is currently being developed to improve this with automatic quantification of motor functions.

Objective: To determine how well several clinical ratings of the tests considered to be implemented in the Assess MS system explain UEF and mobility.

Methods: Patients diagnosed with MS according to the revised McDonald criteria 2010 were included and recruited from four European MS centres participating in the Assess MS project. Ratings of clinical tests covering UEF (i.e. Finger-to-Nose Test (FNT), Pronator Drift Test (PDT), drinking from CUP (CUP)) and mobility (i.e. Sit-To-Stand (STS), Romberg test (ROM), Turning-On-the-Spot (TOS), Tight-Rope-Walking (TRW), 25-foot walking (GAT)) were performed. After checking for co-linearity with partial regression (collinearity present if r ≥0.9), these tests were used in a multivariate linear regression model to determine how much they contribute to the variance of established measures for hand function (i.e. 9-Hole-Peg Test (9-HPT) and Arm Function in Multiple Sclerosis Questionnaire (AMSQ)) and ambulation (Timed-25 Foot Walk test (T25-FW)).

Results: In total 213 patients were included. No significant collinearity was found between variables of the models. We found that FNT and CUP explained 40.8 and 47.6% of the variance of the right and left 9-HPT respectively. For the average value of the 9-HPT of the left and right hand, FNT, CUP and PDT explained 58.3% of the variance. The movements for UEF explained only 28.8% of the AMSQ variance. The CUP test contributed most in the model of 9-HPT and AMSQ. The tests for mobility explained 74.5% of variance of the T25-FW. The TOS test influenced the variance of T25-FW most strongly.

Conclusion: Combinations of ratings of clinical tests considered for the Assess MS system explained T25-FW fairly well. For 9-HPT and AMSQ this was found to a lesser extent. Therefore, other factors not captured with the Assess MS system appear to play a role in assessment of these functions by the current established measures.

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S. Steinheimer has no conflict of interest.

C.P. Kamm has received honoraria for lectures as well as research support from Biogen-Idec, Novartis Pharma AG, Almirall, Bayer Schweiz AG, Teva Pharmaceuticals, Merck Serono, Sanofi Genzyme and the Swiss MS Society.

J. Burggraaff has no conflict of interest.

J. Dorn is an employee of Novartis Pharma AG.

L. Walsh is an employee of Novartis Pharma AG.

J. Boisvert has no conflict of interest.

M. Diederich has no conflict of interest.

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Poster Session 1, 23(S3)

Disability measures used in multiple sclerosis patients: correlations with MRI-derived global and microstructural damage

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Background: Over their disease course, large portion of multiple sclerosis (MS) patients develop walking disabilities. Currently the Expanded Disability Status Scale (EDSS) is the gold standard among tests used in assessing MS-related disability. There is a pressing need to understand how clinical measures portray the underlying global and microstructural neuronal integrity.

Objective: To assess the correlations between tests used to measure disability and MRI-derived global and microstructural damage.

Methods: The study consisted of 81 MS patients recruited in this prospective study. An experienced neurologist applied EDSS, expanded timed get-up and go (ETGUG) test, and timed 25-foot walk (T25FW) test as part of the clinical examination. Lesion volumes were calculated using a reproducible, semiautomatic thresholding and contouring technique. The SIENAX cross-sectional software tool was used to estimate gray matter volume (GMV), white matter volume (WMV), whole brain volume (WBV) and normalized cortical volume (NCV). To segment subcortical deep gray matter (DGM) structures, the FIRST tool was used. DTI processing was performed using FMRIB’s Diffusion Toolbox (FDT) and scalar maps of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were calculated. Spearman rank correlation analyses were performed.

Results: EDSS, T25FW test, and all ETGUG components were associated with all MRI-derived inflammatory measures (T2 lesion volume, p< 0.001; T1 lesion volume, p< 0.01), global (GMV and NCV, p< 0.001; WBV, p< 0.01; and WMV p< 0.05) and regional (DGM p< 0.001; thalamus < 0.001; and basal ganglia nuclei, p< 0.05) volumes. Specifically, the T2 lesion volume correlated with ETGUG (r=0.452, p< 0.001), EDSS (r=0.552, p< 0.001), and T25FW (r=0.393, p< 0.001). The highest volumetric

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correlations were noted for the EDSS and “turn around” segment of the ETGUG with GMV (r=-0.617, p< 0.001; r=-0.559, p< 0.001, respectively) and thalamic volumes (r=-0.553, p< 0.001; r=-0.580, p< 0.001, respectively). From the DTI measures, FA of the WM correlated with total ETGUG (r=-0.346, p=0.002), T25FW (r=-0.307, p=0.006) and EDSS (r=-0.363, p=0.002).

Conclusion: All three employed disability measures showed good association with MRI-derived global and microstructural pathology markers. This study also confirmed the association of global and subcortical gray matter pathology with respect to greater walking disability.

Disclosures of conflict of interest:
None

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A Comparison of participant supplied EDSS scores and clinically submitted data via the UK MS Register
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Background: The United Kingdom Multiple Sclerosis Register (UKMSR) has the largest amount of accessible Patient Reported outcome Measures (PrRoMS) of any UK study. Data is collected via dedicated web portal and linked with NHS patient data where possible. The UKMSR has always sought EDSS scores from its clinical cohort but has only recently started collecting self-reported scores from the online component via a webEDSS tool developed by Ledi et al [0.1007/s00415-013-7004-1].

Goals: To assess the performance of the webEDSS against scores supplied by clinical sites.

Method: The webEDSS tool was developed by a design firm and deployed in an iframe on the UKMSR. Collected data is stored in SQL Server 2016 and analysis carried out using R.

Clinical EDSS scores were supplied by NHS clinical system.

Results: Via the portal 1665 participants completed the online instrument with valid demographic data
Female: male 1165:500
MSType Other:PPMS:RRMS:SPMS 154:271:1097:133
Age: Min 18, Median : 54.0, Max 84
Age at Diagnosis: Min 13, Median : 41.0, Max 77
EDSS: Min 0, Median 6.0, Max 8.5
Clinically 1608 patients were analysed with valid demographics
Gender: Female:Male 1170:438
MSType: Other:PPMS:RRMS:SPMS 77:90:1351:90
Age: Min 19, Median 49.0, Max 85
AOD: Min 8, Median 36.0, Max 72
EDSS: Min 10, Median 3.0, Max 10
81 Patients overlapped for self-supplying an EDSS score and having a clinical score sent within the last year.
Gender M:F 62:19
MSType: Other:PPMS:RRMS:SPMS 3:12:65:1
Age Min 22, Median 46, Max 67
AOD Min, 17, Median 39, Max 63
EDSSClinical Min, 0, Median 3, Max 8
WebEDSS Min 0, Median 5, Max 8
When matched scores were considered 17.3% of clinical and self-scores matched exactly, with a total of 64.2% of the self-scores being within a range of 2 of the clinical. 35.8% of the scores were more than 2 scores different from the scores reported by clinicians.

Conclusion: For the majority of patients, the webEDSS score appears to score within a range of 2 compared to EDSS reported by clinicians. Whilst the webEDSS has some utility, mismatch with clinically reported scores warrants further investigation. We hypothesize the model is more focused on patients with less disability than observed in the portal cohort; timeliness of reporting may also be an issue. Future work will focus on exploring these confounders further combined with a correlation analysis with scores greater than 6.

Disclosure
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Information processing speed on the SDMT is predicted by saccadic eye movement dysfunction in patients with multiple sclerosis

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Background: The King Devick (K-D) test is a brief measure that requires rapid timed number naming, saccadic eye movements, and goal-oriented attention to assess underlying deficits in oculomotor functioning. The K-D test has been validated as a useful measure of visual performance in patients with multiple sclerosis (MS). However, the overlap between oculomotor pathways with major domains of cognitive functioning, the K-D test can also be used to determine neurologic disability associated with oculomotor dysfunction. The Symbol Digit Modalities Test (SDMT) is a widely used screening tool that measures information processing speed and is clinically useful for tracking cognitive deficits in patients with MS.

Methods: Adult and pediatric participants (n=51) with clinically definite MS were consecutively recruited at the NYU Langone MS Comprehensive Care Center and completed the K-D and SDMT during a single clinic visit. During the K-D, participants read three test cards twice; each card is read and timed separately, and the total time is obtained by adding the times for all three cards in each trial. For the SDMT, participants are required to orally relay the number corresponding to each symbol in several rows of 15 symbols each, according to the test’s key; the sum of all correct responses during the 90 second test period constitutes the participant’s score. The fastest total time of the K-D test for each participant was then correlated with SDMT scores to determine the impact of oculomotor functioning on information processing speed.

Results: Relative to normative data, more participants met criteria for cognitive impairment on the K-D than the SDMT (31% vs. 25%, respectively). Controlling for age, K-D test scores were significantly correlated with the SDMT scores (r = -0.43, p = 0.002), indicating a strong contribution of oculomotor function to SDMT performance.

Conclusions: The association between K-D and SDMT scores suggests that cognitive processing speed as measured by the SDMT may be influenced in part by impaired oculomotor functioning in MS, a variable that the K-D detects more readily than the SDMT. Thus, the K-D, previously thought to be isolated to the domain of eye movements, may also be used as a sensitive and rapid screening tool for cognitive impairment in MS. Investigating the data from both tests in the clinic yields a more comprehensive model for evaluating potential cognitive deficits in patients with MS.

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Leigh Charvet has nothing to disclose.
calculated to evaluate the performance of the tool. Reproducibility in scan-rescan was evaluated through a Bland-Altman plot.

**Results:** The automatic in-house software achieved a median DR of 73.2% (range: 21-96%) and a median FPR of 34.8% (range: 3-70%), with the worst performance achieved in patients with extremely low lesion load (<10 mL). The method showed a mean difference in lesion volume of 1.8 mL between the first and the second acquisition.

**Discussion:** The optimized method detected 73% of cortical and subcortical MS lesions. The performance of our method is limited in cortical and juxta-cortical lesions due to their inherently small size, poor contrast, and random locations. The presented method shows a moderate reproducibility compared to what is currently available in literature for automated tools developed for 3T images [Jain, NeuroImage:Clinical 2015].

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**P392**
**Validity of routine administration of Neuro-QoL in multiple sclerosis partners advancing technology and health solutions (MS PATHS)**
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**Background:** MS PATHS is a collaborative network of 10 health-care institutions in the United States and Europe, with a goal of enrolling over 10,000 MS patients. With high participation rates (>90%), it is likely the MS PATHS cohort is representative of MS patients seeking care at these institutions. At each clinic visit, patients completed a computer adaptive version of the Quality of Life in Neurologic Disorders (Neuro-QoL) instrument. MS PATHS represents the first attempt to capture QoL on all MS patients during routine care across 10 institutions in 3 countries.

**Objectives:** To establish the validity of Neuro-QoL captured during routine care in a large, cross-sectional sample of MS patients.

**Methods:** During routine clinic visits, patients used an iPad-based device, the Multiple Sclerosis Performance Test (MSPT), to complete an MS history, including disease progression using the patient determined disease steps (PDDS), 12 scales of Neuro-QoL, and electronic adaptations of the Multiple Sclerosis Functional Composite (MSFC). Concurrent validity of Neuro-QoL was assessed using Spearman’s correlations (r) between Neuro-QoL scales and the PDDS and functional composite. Known groups validity was assessed using ANOVA to compare Neuro-QoL t-scores in patients grouped by living situation and employment.

**Results:** The patient sample comprised 1353 patients. The mean (SD) age was 48.9 years (12.0), mean (SD) disease duration 12.2 years (9.4), 72% were female and 85% were white. Correlations between Neuro-QoL and PDDS were statistically significant for all scales (p< 0.001), except emotional behavioral dyscontrol. Each Neuro-QoL scale showed lower QoL with increasing disease progression. Correlations between Neuro-QoL and the functional composite were statistically significant for all scales (p< 0.001), with the strongest associations found for lower extremity function (r = -0.65), upper extremity function (r = -0.55), and satisfaction with social roles (r = -0.47). Neuro-QoL depression, anxiety, fatigue and sleep disturbance scales were significantly worse in patients living with assistance or in nursing homes (all p< 0.05) and in patients who were unemployed or disabled (all p< 0.0001).

**Conclusions:** Lower Neuro-QoL scores were associated with disease progression, functional performance and patient demographic groups reflecting increased disability. This supports the validity of Neuro-QoL administration during routine clinical care in a real world MS patient sample.

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**P393**
**Reliability of BICAMS (Arabic version) in Egyptian multiple sclerosis patients**
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**Background:** Multiple sclerosis (MS) is a common neurological disease that causes physical, psychological and cognitive disabilities. Prevalence of MS in Egypt is about 60/100,000. Cognitive impairment in MS occurs irrelative to disease course or duration. Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) is a validated test for detection of cognitive impairment in MS patients that can be done by the neurologist. Egyptian Arabic dialect is the most recognized, widely understood dialect by Arabic speakers around the world. Although there are several neuropsychological tests in classical Arabic language, lack of tests in Egyptian dialect is an obstacle in neuropsychological assessment in Egypt.

**Disclosure**

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Objective: To Assess the Reliability of Arabic version of the BICAMS (Egyptian dialect).

Methods: Fifty-Eight Egyptian MS patients and 43 healthy controls underwent neuropsychological testing using the BICAMS Arabic version (Egyptian dialect) battery including Symbol Multiple Digit Modality Test (SMDT), California Verbal Learning Test 2nd edition (CVLT2) & Brief visuospatial retention test (BVRT). Test-retest data were obtained from MS patients two weeks after the initial assessment. Mean differences between both groups were assessed controlling for age, gender and educational level.

Results: 84.7% of MS patients were relapsing remitting MS (RRMS), 11.9% were secondary progressive MS (SPMS), 1.7% were primary progressive MS (PPMS) & 1.7% were clinically isolated syndrome (CIS). The MS scores significantly lower on the SDMT, CVLT, BVRT tests compared to healthy controls with p values of < 0.001, < 0.001 and 0.001 respectively. For MS patients group, intra-observer (test retest) reliability was satisfactory for SDMT, CVLT total & BVRT total with r value of 0.85, 0.81, 0.98 respectively.

Conclusion: BICAMS Arabic version (Egyptian dialect) is a reliable tool for cognitive assessment of Arabic speaking MS patients.

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P394
Timed up and go and brain atrophy: a preliminary MRI study to assess functional mobility performance in multiple sclerosis

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Background: Mobility impairment is one of the most disabling problems and cause of comorbidity (eg. falls and bone injuries) in MS. Timed up and go (TUG) is a widely used measure of functional mobility and an instrumented TUG which make use of inertial sensors has been recently tested in MS (Pau et al., 2017). This approach allows obtaining time, acceleration and velocities of each TUG sub-phase (i.e. sit-to-stand, intermediate and final turning, stand-to-sit). In addition, as it is based on open-task, TUG evaluate also programming, planning, navigation and other executive functions. Since clinical disabilities, especially motor and cognitive impairment, are highly related to brain atrophy (Charil, A., et al., 2006), and TUG is able to combine these abilities in a single task, the purpose of this study was to evaluate relationship between brain volumes and instrumented TUG (iTUG) performances.

Methods: Inclusion criteria for enrollment were a diagnosis of MS according to McDonald criteria and been able to walk at least 20m. iTUG was performed using a wearable inertial sensor as previously reported by Pau et al. Times and velocities of TUG sub-phases were calculated by processing the trunk acceleration data.

All patients underwent to a brain MRI and volumes of whole brain (WB), white matter (WM), grey matter (GM) and cortical GM (C) were estimated with SIENAX (Smith et al., 2002). Relationship between brain volumes and TUG parameters were assessed by means of Spearman correlation.

Results: Sixty patients were enrolled (19 male); mean age was 41.5±11.6 years and mean EDSS was 2.3±1.2. The following significant correlations were found: total TUG duration with WB (Rho=0.270 p=0.038), WM (Rho=0.358 p=0.005), GM (Rho=0.309 p=0.017), C (Rho=0.317 p=0.014); for intermediate turning: mean velocity with WB (Rho=0.365 p=0.004), WM (Rho=0.331 p=0.10), GM (Rho=0.427 p=0.001), C (Rho=0.380 p=0.003), and maximal velocity with WB (Rho=0.274 p=0.035), GM (Rho=0.377 p=0.003), C (Rho=0.351 p=0.006). For the final turning: mean velocity with WM (Rho=0.256 p=0.042), GM (Rho=0.350 p=0.007), C (Rho=0.304 p=0.019) and maximal velocity with WB (Rho=0.265 p=0.043), GM (Rho=0.390 p=0.002), C (Rho=0.400 p=0.002).

Conclusions: iTUG is a very useful tool in clinical setting as it can not only evaluate patients’ disability in terms of impaired functional mobility, but also estimate pathological features such as cortical atrophy.

Disclosure

Dr. Lorefice received speaker fee from Teva and serves on scientific advisory boards for Biogen.
Dr. Fenu received honoraria for consultancy from Novartis and for speaking from Merck Serono and Teva.
Dr. Frau serves on scientific advisory boards for Biogen, received honoraria for speaking from Merck Serono and Teva.
Dr. Coghe and Prof Pau received speaker fee from Teva and Almirall.
Professor Cocchi and Marrosu have received honoraria for consultancy or speaking from Bayer, Biogen-Ideec, Novartis, Sanofi-Genzyme, Serono and Teva.
Mrs Porta M., Pilloni G., and Corona F., have nothing to disclose.

Economic burden

P395
An investigation into the cognitive impact on physical disability in the community in people with multiple sclerosis (PwMS)

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Objective: To examine interaction of self-reported physical and cognitive disability on fall risk in a population of PwMS.

Background: Falls are common in PwMS. Falling/injuries in PwMS increase costs. Increasing fear of falling (FOF) restricts activities, independence, and adversely impacts quality of life
Multivariable logistic regression analyses were undertaken to identify the HRQoL attributes associated with work productivity loss and greater caregiver burden.

**Results:** Our analysis included 530 PwMS, nearly half of whom reported receiving informal care and/or stopped working due to MS. Work productivity loss among PwMS was associated with impaired cognition (adjusted odds ratio [aOR]=1.97; 95% confidence interval [CI] 1.46-2.65), pain/discomfort (aOR=1.57; 95% CI 1.23-2.05), and impaired mobility (aOR=2.45; 95% CI 1.84-3.25) adjusting for sex, age, education, years living with MS, and comorbidity. Caregiver burden was associated with pain/discomfort (aOR=1.34; 95% CI 1.01-1.77), impaired mobility (aOR=1.36; 95% CI 1.10-1.68) and dexterity (aOR=1.77, 95% CI 1.02-3.06) adjusting for PwMS’ sex, age, education, years living with MS, and comorbidity.

**Conclusion:** People living with MS who report having pain and impaired mobility and dexterity are more likely to require greater informal care; while those who report impaired cognition and mobility and pain are more likely to incur productivity loss. Interventions targeting these HRQoL attributes could contribute to improving overall quality of life of PwMS and also keeping them in the workforce and reducing caregiver burden.

**Disclosure**

All authors: nothing to disclose

**P396**

Health-related quality of life attributes associated with work productivity loss and caregiver burden in multiple sclerosis

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**Background:** Multiple sclerosis (MS) is the leading neurological disorder affecting young adults during the primary productive time of their life, and exerts a significant burden not only on people living with the disease but also on their families, friends, healthcare systems and society as a whole. The objective of this study was to identify the health-related quality of life (HRQoL) attributes associated with work productivity loss and caregiver burden in MS.

**Methods:** Data were compiled from the national representative cross-sectional Survey on Living with Neurological Conditions in Canada (SLNCC) 2011/12. HRQoL was measured using Health Utilities Index Mark 3 (HUI-3). Work productivity loss was derived from two variables: not currently working because of MS and permanently unable to work because of MS. The frequency of informal care that people living with MS (PwMS) received was used as a surrogate of caregiver burden.

Multivariable logistic regression analyses were undertaken to identify the HRQoL attributes associated with work productivity loss and greater caregiver burden.

**Results:** 602 PwMS; average age=48.9±11.8, 74.6% female. Significant relationships were identified: MSIS-29 global scores and MFES (r=0.57, p<0.01), ADL-S (r=0.62, p<0.01), and ADL-C (r=0.64, p<0.01). MSIS-29 physical scores and MFES (r=0.64, p<0.01), ADL-S (r=0.69, p<0.01), and ADL-C (r=0.71, p<0.01). MSIS-29 cognitive scores and MFES (r=0.33, p<0.01), ADL-S (r=0.31, p<0.01), and ADL-C (r=0.32, p<0.01).

**Conclusions:** Global and physical disability scores were strongly associated with fall risk for both simple and complex ADL. However, cognitive disability scores consistently accounted for 30-35% of the change in all three disability outcomes. Not only is cognitive impairment an under-measured and underreported symptom in PwMS, its impact on ADL in this population is under-recognized.

**Disclosure**

All authors: nothing to disclose

**P397**

The burden of relapsing remitting multiple sclerosis on workers in the United States

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**Background:** Real-world studies that assess the impact of Relapsing Remitting Multiple Sclerosis (RRMS) on individual’s ability to maintain employment and work productivity are limited.

**Goals:** Quantify the burden of lost work productivity among adult RRMS patients in the United States (US) and describe the relationship between work impairment levels and patient-reported outcomes.

**Methods:** Data were drawn from the 2015-2016 US National Health and Wellness Survey. Individuals who reported a diagnosis of RRMS were propensity matched to individuals...
Conclusions: increasing work impairment and worsening of outcomes with (67.5 vs. 56.4%); all ps < 0.05. Employed RRMS patients report vs. 52.1%), difficulty remembering (85.8 vs. 75.8%), and fatigue more depression (52.7 vs. 43.1%), difficulty concentrating (65.7 physical summary scores (39.0 vs. 48.5) and EQ5D scores (0.69 vs. 0.80); all ps < 0.05. RRMS patients also reported less work productivity and greater activity impairment in past 7 days: absenteeism=12.3 vs. 6.0%; presenteeism=33.4 vs. 19.7%; activity impairment=50.2 vs. 28.7%; all ps < 0.05. Compared to non-LFP patients, LFP patients (n=211) were younger (45.6 vs. 52.7 years), reported less severe MS, less activity impairment (39.7 vs. 56.8%); p< 0.05) and higher physical QoL (43.9 vs. 35.9) and EQ5D scores (0.73 vs. 0.67); both ps < 0.05. Non-LFP patients reported more depression (52.7 vs. 43.1%), difficulty concentrating (65.7 vs. 52.1%), difficulty remembering (85.8 vs. 75.8%), and fatigue (67.5 vs. 56.4%); all ps < 0.05. Employed RRMS patients report increasing work impairment and worsening of outcomes with increasing RRMS severity by tertile.

Conclusions: Among employed MS patients, there appears to be an association between increased MS severity, work impairment and humanistic burden. Improvements in work impairment should be an important treatment goal in this population.

Disclosure
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J. Nicholas is a paid consultant for Novartis Pharmaceuticals Corporation.
B. Electricwala is a post-doctoral fellow at Novartis Pharmaceuticals Corporation.
L. Lee is a paid consultant for Novartis Pharmaceuticals Corporation.
K.M. Johnson is an employee of Novartis Pharmaceuticals Corporation.

P398
Estimating MS-related work productivity loss and factors associated with labour force participation in a representative Australian sample of people with multiple sclerosis
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Objective: Many people with multiple sclerosis (MS) leave the workforce early due to their MS. Less is known about MS-related work productivity loss, including absenteeism and presenteeism. We aimed to quantify MS-related work productivity loss and examine factors associated with labour force participation and work productivity loss in people with MS.

Methods: Participants in the Australian MS Longitudinal Study (AMSLS) completed three surveys from December 2015 to July 2016. We included 1,471 respondents for the labour force participation analysis and 824 for the work productivity loss analysis. Total MS-related work productivity loss combined absenteeism (percentage of working time missed) with presenteeism (percentage of reduced productivity while working). Data were analysed using log-binomial and linear regression.

Results: Among those working, 20.2% reported any MS-related absenteeism, 53.3% any presenteeism, and 55.6% any total work productivity loss. The mean MS-related absenteeism, presenteeism and total work productivity loss were 3.4% (SD 10.9), 10.8% (SD 17.2) and 14.2% (SD 21.6). The annual cost of MS-related work productivity loss was 7,331 Australian dollars (AUD) per person with AUD$5,641 due to presenteeism and AUD$1,690 due to absenteeism. In multivariable analysis, older age, lower education level, and higher levels of “problems of walking, balance and spasticity” and “fatigue and cognitive symptoms” were associated with not being in the labour force. Factors associated with work productivity loss included “fatigue and cognitive symptoms”, “pain and sensory problems”, “problems of walking, balance and spasticity” as well as being self-employed.

Conclusions: The contribution of MS-related presenteeism to productivity loss is almost three times that of absenteeism. The strong dominance of symptom severity in multivariable models suggest that an improved management of symptoms such as fatigue, cognitive symptoms, problems of walking, balance and spasticity, pain and sensory problems is important for people with MS to work more productively and stay longer in the labour force.

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P399
Multiple sclerosis relapses: budget impact analysis of oral high-dose corticosteroids
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Background: Replacing intravenous (IV) therapy for multiple sclerosis (MS) relapses with per os (PO) treatment should improve accessibility and patients’ quality of life, and consistently minimize treatment-related costs. We conducted a prospective study (PO vs. IV high-dose methylprednisolone for treatment of relapsed inpatients with MS (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. Lancet 2015 Sep 5;386(9997):974-81) that simultaneously measured the clinical effectiveness and treatment strategy-related costs of PO versus IV corticosteroids.

Objectives: To analyse the budget impact of PO versus IV high-dose corticosteroids in MS relapse treatment over 3 months after treatment onset.

Methods:
- Patient inclusion and exclusion: see COPOUSEP trial
- Points of view: health insurance perspective
- Primary endpoint: mean avoided cost for relapse treated with PO high-dose corticosteroids
- Time horizon: 90 days after treatment onset
Data acquisition: direct costs (medical, nonmedical) measured by loading patients’ data from the French national health insurance database linked to the national hospital discharge database[1]
- Cost assessment: medical costs based on the health insurance reimbursement rate and patients’ financial contributions towards medical costs; nonmedical costs based on daily benefits allowed by health insurers, according to average cost of an equivalent resource on the market (replacement cost), taking frequency and duration into account.

Results: 146 patients were included in this analysis, out of an initial sample of 200 randomized patients. The IV and PO groups had similar characteristics at baseline (age: 35.5 vs. 33.7 years; mean time from MS onset: 7.1 vs. 7.4 years; mean EDSS increase: 1.36 to 3.4 vs. 1.32 to 3.41). The economic analysis is under review. The introduction of PO high-dose corticosteroids under the conditions of the COPOUSEP trial (PO patients treated as inpatients) was associated with a mean saving of €107.11 per relapse. Definitive results (total costs, breakdown of expenditure, average cost per patient in each treatment group and across groups; sensitivity analysis (PO patients treated as outpatients)) will be validated in September.

Conclusion: The introduction of PO treatment for MS relapses will be associated with significant savings, allowing for budget reallocation.

[1 http://www.ameli.fr/fileadmin/user_upload/documents/SNIIRAM_database_at_a_glance.pdf]

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P400
The changing landscape of disease modifying treatments: cost implications for healthcare systems
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Background: Disease modifying treatments (DMTs) for Multiple Sclerosis (MS) have greatly expanded in the last decade. The introduction of more efficacious immunotherapies, different modes of administration and revised diagnostic criteria have shaped the MS landscape. We reviewed the changing landscape of DMTs and subsequent cost implications in a regional centre of a nationally funded health-care system.

Methods: We retrospectively reviewed the records of all patients seen by the East Kent MS service from 2009-2017. All patients receiving DMT were included. Costs were derived by NICE Technology Appraisals.

Results: The East Kent Neurology Unit serves a large geographical area in the East of England with a catchment population of 750,000. The regional prevalence of MS is 210/100,000, with an average of 65 new referrals per year. A total of 1410 patients with MS are currently in our service, 598 (42%) have relapsing-remitting MS (RRMS). Of those, 389 (65.1%) are receiving DMTs; this represents an increase of 118.6% from 178 patients in 2009.

Over eight years, we have seen a significant decline in the use of interferons from 58.4% (104 patients) of total DMT use in 2009 to 18.5% (72 patients) in 2017. A similar but less steep decline was seen in the use of glatiramer acetate, from 42.8% (86 patients) in 2009 to 18.0% (70 patients) in 2017. In contrast, the use of monoclonal antibodies has significantly increased, from 9 patients (4.5%) in 2009 to 83 (21.3%) in 2017.

The changes in DMT-use has significant cost implications; the total yearly cost of treatment has more than tripled from €1.7 million in 2009 to €6.4 million in 2017. This reflects not only the increased number of RRMS patients eligible for treatment, as the cost per patient has also increased from €8,162 per patient per year in 2009 to €16,324 in 2017.

Conclusion: In our publicly funded neurology unit, treatment for RRMS has significantly changed within the last eight years; use of injectables has substantially reduced, and 1 in 5 patients are receiving monoclonal antibodies. The increased use of highly effective but highly expensive treatments has led to a 6-fold increase in total yearly budget with a yearly cost of €16,324 per patient. Changes in DMTs have significant implications for patients but also health care systems, and with increased DMT costs, judicious use and careful consideration of treatments becomes paramount.

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Neuro-ophthalmology

P401
Pattern ERG related to ganglion cell loss and impaired visual function in patients multiple sclerosis
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Purpose: The goal of this study was to determine the relations between pattern electroretinogram (PERG) with visual functions and ganglion cell layer thickness in patients with relapsing remitting multiple sclerosis (RRMS).

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Method: One hundred forty eight eyes of 74 subjects (46 RRMS patients and 28 healthy controls) were recruited. All patients underwent a complete ophthalmic exam including low contrast visual acuity test. Steady-state PERG (Jorvec Corp) was recorded simultaneously from both eyes using surface electrodes in response to horizontal square-wave gratings presented on a LED visual display (1.6 cycles/deg, 98% contrast, reversal rate 15.63 Hz, 25 degree square field; 800 cd/sqm mean luminance). Binocular low contrast sensitivity tests (2.5% and 1.25%) were conducted by the Sloan low contrast letter chart (Precision Vision, La Salle, IL). The ganglion cell-inner plexiform layer (GCIPL) thickness was measured using Zeiss Cirrus optical coherence tomography.

Results: No differences were observed in the demographic characteristics between RRMS patients and normal control subjects. There were no significant differences in PERG amplitude between RRMS and controls (P > 0.05). However, the PERG phase showed a significant increase in MS compared to control analyzed separately in both eyes (P < 0.05). The averaged phase of both eyes was significantly and negatively related to low contrast visual acuity at 1.25% (r = -0.37, P < 0.05) and GCIPL thickness (r = -0.43, P < 0.05).

Conclusions: Increased PERG phase which related to impaired visual function and thinning of GCIPL thickness may indicate abnormal and disease specific activity of the ganglion cells in patients with RRMS.

Disclosure
All the authors have nothing to disclose.

P402
Mapping focal loss of the ganglion cell-inner plexiform layer in patients multiple sclerosis
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Purpose: A detailed analysis of the tomographic thickness patterns of intraretinal layers may provide more sensitive information on neurodegeneration in patients with multiple sclerosis. The goal of this study was to map the ganglion cell-inner plexiform layer (GCIPL) by ultra-high-resolution optical coherence tomography (UHR-OCT).

Method: Forty-two eyes of 42 relapsing and remitting multiple sclerosis (RRMS) patients, and 42 eyes of 42 age- (~± 5 yrs) and gender-match healthy subjects were recruited. Custom made UHR-OCT (axial resolution ~3 µm) was used to acquire three dimensional volumes of the macula. Automated segmentation software (Orion, Voxelera LLC) was used to segment the thickness of GCIPL in a diameter of 6 mm centered on the fovea. To create the average thickness map of each group, the center of fovea was aligned and the thickness in each pixel of the 512 × 128 pixels was averaged in the group, resulting in the average thickness maps. The thickness differentiation maps were calculated by subtracting the thickness of the control group from the MS groups in each pixel and partition was done using the Early Treatment Diabetic Retinopathy Study (ETDRS).

Results: The GCIPL thickness maps showed focal thinning located in inner annulus (3 mm in diameter) and superior and nasal sectors within the outer annulus (3-6 mm in diameter), which were significantly thinner in MS compared to controls (post hoc test, P < 0.05). The most profound thinning was located in the inner inferior with a difference of 10 µm between groups.

Conclusions: Focal thinning of the GCIPL was evident in patients with RRMS and the characteristic thinning pattern may be developed as an image biomarker of retinal neurodegeneration in MS.

Disclosure
All the authors have nothing to disclose.

P403
Outer retinal function and structure in multiple sclerosis
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Background: Multiple sclerosis (MS) is known to affect the structure and function of the inner retina and optic nerves via MS-related optic neuritis (ON). However, recent evidence may be consistent with structural changes to the outer retina1, 2. The functional correlates of these proposed structural abnormalities remain unclear. We therefore aimed to measure outer retinal function and structure in MS patients using retinal electrophysiology (electroretinogram, ERG; multifocal ERG, MF-ERG) and optical coherence tomography (OCT).

Methods: ERG and MF-ERG response amplitudes and peak times were calculated for all conditions. Segmentation of macular and peripapillary OCT allowed quantification of the retinal layers. Analyses were performed using generalised estimating equation (GEE) models accounting for ON history, inter-eye dependencies and age: ERG and MF-ERG values in patients were compared to pre-existing normative data acquired at our site, as were OCT values in patients, and the relationships between ERG and MF-ERG parameters and their structural correlates in patients were calculated.

Results: 32 patients (22 female; median age 35 years; median Expanded Disability Status Scale (EDSS) score 1.0) were examined. The majority of ERG responses were significantly delayed in patients when compared to normative data; amplitudes ranged from normal to supranormal. MF-ERG responses were partly delayed but of normal amplitude. No significant differences between eyes with and without previous ON were recorded. OCT in our MS cohort was normal, however significant reductions in inner retinal thickness and volume were observed in eyes with previous ON. ERG a- and b-wave amplitudes were significantly correlated with outer- and inner nuclear layer (ONL; INL) volume, respectively, however ERG peak times and all MF-ERG parameters were unrelated to OCT findings.

Conclusion: We recorded electrophysiological abnormalities in our MS cohort independently of a history of ON and without detectable abnormalities in OCT. The results are suggestive of...
Temporal dynamics of structural and functional retinal damage in acute optic neuritis

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Background: Optic neuritis (ON) is an acute inflammatory attack of the optic nerve and a common clinical manifestation in multiple sclerosis (MS). It can affect patients throughout their entire disease course, whilst 20% present with acute ON as initial symptom. Outcomes are heterogeneous, including severe visual loss. The identification of factors associated with poor outcomes may be key to optimize future treatments. In this longitudinal study, we assessed structural and functional changes following acute ON episodes, using optical coherence tomography (OCT) and low-contrast visual acuity (LCVA) testing.

Methods: 41 patients (28 females; mean age 32.4 years) with a first-ever episode of ON were retrospectively assessed over 12 months. Macular and peripapillary OCT scans, as well as LCVA testing with SLOAN letter charts (2.5%) were acquired at baseline, 1, 3, 6 and 12 months after ON. Macular ganglion cell layer + inner plexiform layer (GCIP) and peripapillary retinal nerve fibre layer (pRNFL) were assessed by OCT. We accounted for timepoints, age, gender, disease duration, steroid treatment and disease-modifying therapies using a linear mixed effects model. Independent-sample t-tests were used to compare OCT variables of ON eyes (all timepoints) with the baseline of the unaffected (NON) eyes. The relationship between GCIP thickness and LCVA in ON eyes was assessed by Spearman correlations.

Results: Baseline GCIP thickness was similar in ON and NON eyes. GCIP thickness of ON eyes was significantly lower at 1, 3, 6 and 12 months (p<0.001) compared to baseline NON. At month 12, ON eyes showed a mean GCIP reduction of -13.7µm (SD:12.0µm), with nearly 90% of the change (mean:+12.2µm, SD:6.5µm) occurring within the first month. Males suffered from greater loss than females (month 12: f: mean:-9.2µm, SD:9.1 µm; m: mean:-19.7µm; SD:13.6µm). GCIP thickness at month 1 was negatively correlated with LCVA at month 3 (rho=-0.63, p=0.01) in ON eyes. pRNFL of ON eyes showed swelling at baseline (mean:+18.2µm, SD:26.8, p< 0.001), a seemingly “normal” thickness at month 1 (mean:+3.05µm, SD:10.5, p=0.13), followed by a significant decline until month 12 (mean:-11.5µm, SD:9.2, p=0.02).

Conclusion: Macular structural damage develops rapidly in acute ON and correlates with functional visual outcomes. Our results may help to identify patients at risk of severe functional sequelae and may assist in clinical trial planning in studies targeting tissue damage in acute ON.

Disclosure

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Conclusion: We present a new test with very good sensitivity for acute ON, good reproducibility and a dynamic response following the acute phase of ON. Further follow up of the ON patients, and a general MS population, may provide evidence of an accurate and easy to use tool in diagnosing acute ON, monitoring the course and assessing signs of demyelinating disease in the visual pathway.

Disclosure
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Comorbidity

P407
The impact of depression and anxiety symptoms on information processing speed in MS and other immune-mediated inflammatory diseases
C. Whitehouse, J. D. Fisk, C. N. Bernstein, C. Hitchen, R. Ann Marrie, for the CHIR Team “Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease”

Background: Visual disorders are frequently characterised by optic nerve and retinal dysfunction. One of the classic resulting signs are visual field defects. Careful clinical evaluation is essential to rule in the diagnosis, prognosis and monitoring of such disorders. Currently, the routine assessment consist of the Humphrey’s test, but it’s time consuming and not widely available outside of specialist ophthalmology clinic.

Objective: To develop a smartphone application capable of assessing the visual field in order to ultimately diagnose and monitor visual impairment in resource poor settings and be used as a self-monitoring tool for people with Multiple Sclerosis.

Method: This pilot study assessed 23 eyes from volunteer patient coming initially for a follow-up in the Royal London Hospital eye clinic. Once results collected, we divided the visual field in 54 zones and compared only the “black zone”, considered as non visualized zone, one after the other. Finally, results were displayed as percentage of match.

Results: Six eyes showed a perfect reliability with 100% match, three others presented 50% of reproducibility while three more showed results ranging from 20% to 35%. Finally, 11 obtained a result lower than 20%. The latter is due to an excess of fixation loss, as the reliability of the visual when fixation loss is < 50% is clearly improved (p=0.01).

Conclusion: We developed an easy to use smartphone application capable of assessing visual fields. The results showed a promising reliability between Humphrey’s tests and the visual App. However the rate of fixation loss still need to be reduced to increase their reliability.

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comorbidities in IMID; data were obtained from baseline assessments. Participants completed the Symbol Digit Modalities Test (SDMT), Weschler Test of Adult Reading (WTAR; IQ estimate) and Hospital Anxiety and Depression Scale (HADS; screening measure for anxiety and depression symptoms). SDMT scores were converted to z-scores adjusted for age, sex, and education. Participants were classified as “impaired” and “unimpaired” (z ≤ -1.5); rates of impairment were compared between groups using chi-squared tests. Multiple regression analyses determined whether depression and anxiety symptoms accounted for variability in information processing speed.

**Results:** The groups did not differ in estimated IQ but significantly more persons in the MS group were classified as impaired compared to other IMID groups (MS 24%; IBD 6%; RA 3%). In all groups, symptoms of depression and anxiety each moderated information processing speed (all p < 0.01). Using stepwise regression, for IBD and RA groups only current symptoms of anxiety explained a unique proportion of variance in SDMT scores (p < 0.001). For the MS group, only current symptoms of depression explained a unique proportion of SDMT score variance (p = 0.001). However, for the MS group, after controlling for Expanded Disability Status Scale scores (R² = 0.07; p < 0.001) depression was no longer significant, while symptoms of anxiety now accounted for significant variance in SDMT scores (R² = 0.09; p = 0.002).

**Conclusion:** Current symptoms of anxiety and depression influence information processing speed in MS and other IMID. Although disease-related effects on the brain and symptoms of depression are associated with information processing speed in MS, distinguishing between their effects is challenging. Regardless, symptoms of anxiety remain an important influence on information processing speed. Managing mood and anxiety symptoms in persons with MS, and other IMID, is important to mitigate their impact on cognitive functioning.

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**P408**
Movement disorders in demyelinating diseases
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**Background:** Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are the main acquired demyelinating diseases. Movement disorders are not rare among them and previous studies have estimated tremor prevalence in MS between 25-58%. Tonic spasms or paroxysmal dystonia might be common in NMOSD, but whether they are more prevalent in NMOSD or MS is uncertain.

**Purpose:** To describe the prevalence and characteristics of movement disorders in MS and NMOSD and investigate the association of tonic spasms and NMOSD.

**Methods:** From June 2015 to September 2016 patients aged 18 years or older, without dementia and with diagnosis of MS or NMOSD (with positive anti-aquaporin-4 antibody) were consecutively evaluated using standard questionnaire and scales for movement disorders diagnosis. Fahn-Tolosa-Marin (FTM) scale was used for tremor evaluation. Patients with others defined or possible causes of movement disorders were excluded. Data from personal interview, neurological examination and medical files were collected. We used a logistic regression model to investigate whether tonic spasms or tremor was predicted by NMOSD (having MS as reference), controlling for sex, age, and disease duration.

**Results:** Two hundred and fifty-three patients were evaluated (MS=208; NMOSD=45). Sixty-six patients (26%) have reported or presented with movement disorders. Paroxysmal dystonia (n=32) was the most common movement disorder, followed by tremor (n=27). Overall, the prevalence of tremor in MS was 12.5% while intention tremor was the most common type of tremor (82%). MS was the most prevalent among patients with tremor (26 out of 27). We found a positive linear correlation between scores of the FTM scale (parts A, B, C) and the cerebellar functional system score of the Expanded Disability Status Scale (EDSS) (p=0.73-0.83 p-value<0.01). The prevalence of paroxysmal dystonia was 35.5% in NMOSD and 7.7% in MS. Having NMOSD (as compared to MS) increases 22 times the chance of tonic spasms (OR=22.07, 95%CI=2.56 to 189.78; p-value=0.005).

**Conclusions:** Our findings suggest that paroxysmal dystonia is strongly associated with NMOSD and tremor with MS. Intention tremor is the most common type of tremor in MS patients and the greater the cerebellar impairment the more severe the tremor.

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**P409**
A change in multiple sclerosis morbidity spectrum

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Background: Multiple sclerosis (MS) is associated with an increased risk of morbidity due to complications of the disease itself and to treatments. Typically, the most common cause of morbidity and mortality has been complicated infections in patients with a more severe disability but, in the last decade, other causes associated to new therapies have increased.

Objectives: To compare the morbidity spectrum and mortality in MS patients between two different periods of nine years.

Methods: Retrospective study that includes all MS patients treated at the MS Unit of the Virgen de la Arrixaca Hospital, in Spain, from 1998 to 2016. We have analyzed their demographic and MS characteristics, and we have compared morbidity causes in two nine-year periods: 1998-2007 and 2007-2016.

Results: In the first period there were 313 MS patients with an average age of 39 (SD 6.8) and EDSS 4.3 (SD 2.5); 450 MS patients in the second group with an average age of 45 (SD 9.8) and EDSS 4 (SD 2). The mean duration of the MS was longer in the second group. In the first group, the main cause of morbidity related with MS was urinary infection followed by respiratory infection. There were three patients with epileptic seizures and one with posterior reversible encephalopathy related to interferon. There were two women with breast cancer.

In the second group, the main cause was urinary infection followed by alterations in red and white blood count, hepatic damage, herpetic reactivation, autoimmune disease (idiopathic thrombocytopenic purpura, thyroiditis) and opportunistic infection (leishmaniasis, pneumocystis and herpetic encephalitis). In this group there were two breast-, one ovarian- and one testicular tumour.

Conclusions: MS patients are suffering a change in the main causes of morbidity due to the complications arising from new and emergent therapies. Opportunistic infections and hematological complications are emerging in the last years as frequent side effects in MS patients, which forces the neurologist to a deeper knowledge of this pathologies.

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P410
Self-reported smoking status associated with clinical disease worsening in CombiRx

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Background: Smoking history may increase risk of MS development and there is increasing evidence that smoking can increase risk of disease worsening.

Objective: We explored if self-report smoking status was associated with relapse, measures of disease progression, and MSFC in relapsing-remitting MS patients in the CombiRx clinical trial.

Methods: This analysis was carried out using the clinical data from 1008 RRMS subjects enrolled in the CombiRx trial, a multicenter, phase-III investigation of combination therapy of interferon and glatiramer acetate, followed for up to 7 years. Of the 1008 randomized participants, 840 completed the self-report smoking questions: Never, Past, or Current; analyzes as Non Current (NC, Past and Never) and Current Smokers (CS). Relapse required a confirmed change in EDSS, progression was a 6 month confirmed 1-point worsening of EDSS, MSFC was measured quarterly. Models were adjusted for baseline EDSS, race, gender, age, treatment, and time on study.

Results: Randomized between 2005-2009, the majority of participants reported never having smoked (49.2%), with 24.6% past and 26.2% current smokers. Age at baseline 37.9 (SD 9.6), 70.1% Female. CS were more likely to experience a relapse compared to NC (OR 1.39, p=0.037). CS had worse MSFC scores overtime compared to NC (0.59 lower, p=0.040). There was no statistical difference in the proportion experiencing 6-month progression (31.3% CS vs 28.4% NC, p=0.41). However NC were more likely to remain clinically disease free (no progression and no relapse) compared to CS (OR 1.6, p=0.004).

Conclusion: Self-report smoking is associated with clinical worsening in terms of MSFC While there was no difference in those with confirmed progression, current smokers experienced worse accumulation of clinical disease.

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P411
Neuropsychological impairment in newly diagnosed early multiple sclerosis: clinical and neuropsychological characterization of a German cohort of 1124 patients

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Background: Neuropsychological symptoms affect a large proportion of multiple sclerosis (MS) patients but standardized surveys are widely lacking, not only in Germany. The German competence network MS (KKNMS) has initiated a multi-center cohort study with more than 1000 early MS patients to answer clinical, paraclinical and epidemiological questions.

Objectives: To investigate baseline clinical characteristics and early neuropsychological findings in a large cohort of MS and clinically isolated syndrome (CIS).

Methods: The German MS cohort study (NationMS) is a prospective observational long-term study recruiting patients in 22 centres. Adult patients are eligible with a diagnosis of CIS within 6 months or relapsing remitting MS (RRMS) within 24 months (McDonald criteria 2005) when naïve for disease-modifying treatment (DMT). Standardized clinical, paraclinical (including MRI) and neuropsychological data and biomaterial are collected.

Results: Between 2010 and 2014, 1124 evaluable patients were enrolled, including 44.6% CIS and 55.3% RRMS patients with a 2.2:1 female to male ratio and a median age of 31.71 years (IQR 26.06-40.33) at first manifestation. At baseline, median EDSS was 1.5 (IQR 1.0-2.0). Nevertheless, the cohort comprises single severely disabled patients (max. EDSS 6.0). After inclusion, 763 (67.8%) patients started DMT treatment, splitting up in injectables (interferon-beta, glatiramer acetate), oral DMT (dimethyl fumarate, fingolimod, teriflunomide), less frequently natalizumab and single cases with alemtuzumab, mitoxantrone, rituximab, study medications and azathioprine. At least mild fatigue (Fatigue Scale for Motor and Cognitive Functions, FSMC) was detected in 36.5%, depressive symptoms (Beck Depression Inventory II, BDI II) were present in 33.5% and cognitive dysfunction (Multiple Sclerosis Inventory Cognition, MUSIC) was detectable in 14.7% of patients. Explorative correlation analyses indicated weak correlations between EDSS and FSMC (Kendall’s tau b (rb) 0.24; CI 0.20-0.29), MUSIC (rb -0.13; CI -0.17;-0.08) or BDI II (rb 0.20; CI 0.16-0.25).

Conclusion: This large cohort depicts baseline characteristics of CIS and early MS and DMT distribution in Germany. A significant proportion of patients experiences neuropsychological symptoms with putative impact on quality of life despite low EDSS in these early disease stages. These symptoms are not detected with routine neurological examination and argue for early implementation of screening batteries.

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P412
Altered grey matter networks in young patients with MS at genetic risk for Alzheimer’s disease


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Background: The Apolipoprotein E (APOE) ε4 is the major susceptibility factor for cognitive impairment and Alzheimer’s disease. Cognitive decline is also a concern in patients with multiple sclerosis (MS). Whether APOE ε4 exerts an effect on brain structure and grey matter (GM) networks in MS patients that could potentiate the long-term cognitive disabilities is unclear. Moreover the description of the exact link between genetic markers and MR driven measures of brain integrity are of essential importance to study cognition in patients with MS and for interventions to prevent longitudinal deterioration.

Methods: MS Patients with no immunomodulatory treatment were enrolled in the “Krankheitsbezogene Kompetenznetz Multiple Sclerosis (KKNMS)”. From this multicenter dataset 37 heterozygous APOE ε4 carriers (i.e. having the genotype ε3/ε4) and 37 non-carriers (ε3/ε3) were matched for demographics (mean age: 38.4±9.2 yrs, mean EDSS 1.23±0.99) from one site. A replication study was performed in a cohort (n=46) from a second site.

Cortical thickness (CT) was derived from 3T MRI using FreeSurfer. GM connectivity networks were reconstructed from the CT correlation between the 68 regions of the Desikan-Killiany atlas. Cortical integrity and network connectivity derived from graph theoretical approaches were compared between the groups in both cohorts. Results corrected for multiple comparisons were considered (p< 0.05 FDR).

Results: No regional or global cortical atrophy differences were attested between the two groups in both cohorts. In the network connectivity analysis a decreased local connectivity pattern (reduced transitivity, t=-3.24 p=0.008) was evident in APOE ε4 carriers. Regions with decreased connectivity were consistently seen in the medial part of the left temporal lobe. APOE ε4 status was further associated with raised whole brain connectivity, reflected by increased global efficiency (t=4.34 p=0.005) and reduced modularity (t=2.84 p=0.02). This network pattern was shown in the frontal, parietal and lateral temporal associative cortices. The results were entirely replicated in the second cohort.

Conclusion: We found that MS patients at genetic risk for cognitive decline have significant abnormalities of local GM networks and possibly compensatory increased long-range connectivity patterns. Chronic or focal neuroinflammation could lead to behaviourally relevant memory impairments in these patients through a specific break-down of the long-range paths.

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P413
Prevalence of restless legs syndrome/Willis-Ekbom disease in multiple sclerosis: a case-control study in Argentina
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Background: Restless leg syndrome (RLS) is often seen in patients with multiple sclerosis (MS). However, prevalence of RLS in MS patients and its association with sleep quality, anxiety, depression and fatigue has not been studied in Argentina yet. We aimed to assess RLS prevalence and to investigate its association with MS, as well as to identify possible associated risk factors in an Argentinian population.

Methods: A population-based case-control study was carried out via online interview using an anonymous self-assessment questionnaire (RLSQ), including the criteria of the International RLG Study Group. Prevalence of RLS in MS patients vs. control subjects (CS) was estimated. The Hospital Anxiety and Depression Scale and Fatigue Severity Scale (FSS) were used to evaluate all participants. In addition, insomnia, excessive daytime somnolence (EDS) and other risk factors associated with RLS in MS patients were assessed via regression analysis in a multivariate model.

Results: The study included 189 patients with definite MS and 238 CS. The prevalence of RLS was 29.10% in MS patients vs. 13.02% in CS (OR 2.74, 95%CI 1.67-4.47, p=0.00005). However, “clinically significant” RLS (CSRLS) prevalence, cases in which symptoms were present at least two days per week, was observed in 19.4% of MS patients vs. 4.20% in CS (p < 0.00001). Anxiety, depression, insomnia, smoking habit were significantly associated with RLS in MS patients. Moreover, the following risk factors for MS-CSRLS in multivariate analysis were significant: older age, longer MS duration, depression and there was a trend in FSS (p=0.056).

Conclusion: RLS was observed 2.74 times more frequently in MS patients than in the CS, especially in patients of older age, with depression and longer MS duration. RLS related to MS has a significant impact on sleep quality.

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Prevalence of sleep apnea in multiple sclerosis patients meeting clinical eligibility criteria for the Sleep Apnea in Multiple Sclerosis Positive Airway Pressure (SAMSPAP) trial
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Background: We have previously described a relationship between severe fatigue and obstructive sleep apnea (OSA) in MS patients (Mult. Scler. J. Vol 18; 1159 - 1169). SAMSPAP (NCT01746342) is a randomized, controlled trial evaluating the effects of PAP treatment of OSA on fatigue in MS patients. The objective of the present analysis was to assess the prevalence of OSA among MS patients meeting the clinical eligibility criteria for this study.

Methods: Patients with confirmed MS on stable immunomodulating medication were recruited from the MS clinics at our institutions. Clinical eligibility criteria included: Expanded Disability Status Scale score (EDSS) ≤7, severe fatigue (Fatigue Severity Scale (FSS) score ≥ 4), poor subjective sleep quality (Pittsburgh Sleep Quality Index (PSQI) >5) and no more than minimal cognitive impairment (Montreal Cognitive Assessment (MoCA) ≥26). OSA was defined by an Apnea-Hypopnea Index (AHI) ≥ 15 events/h on complete overnight polysomnography (PSG) scoring using American academy of sleep medicine research (Chicago) criteria.

Results: 87 subjects (35% male) were evaluated in an initial screening visit. Of these, 74 (83%) met the clinical eligibility criteria and underwent PSG. Reasons for exclusion included (n); withdrawal before completing screening (4); low FSS (5); low MoCA (5); and low PSQI (1). Subjects undergoing PSG had mean±SD age=49±9 y, BMI=28±6 kg/m², EDSS=4±2, MoCA=28±1, FSS=6±1 and PSQI=11±4, and on PSG had total sleep time=5.5±1.1h, AHI=30±22/h, 4% Oxygen Desaturation Index (ODI)=5±8/h and Central apnea index =1±2/h. 54 of 74 subjects had OSA (mean AHI = 37±21/h, ODI 6.4 ±8.5, respiratory arousal index =34±20/h), of whom 9 surpassed our pre-specified OSA safety threshold for randomization to this 6-month, sham PAP-controlled trial (AHI > 30 with either 4% ODI=15/h (n=8) or Epworth Sleepiness score ≥ 15 (n=1)). The positive predictive value for OSA of our clinical eligibility criteria was 73% (95% CI 61-83%), and for severe OSA (AHI >30/h) was 40% (95% CI 29-53%).

Conclusion: These findings suggest that a diagnosis of OSA should be considered among ambulatory MS patients presenting with severe fatigue and poor subjective sleep quality. The results of the ongoing SAMSPAP trial will provide new insights into the impact of OSA treatment on severe fatigue in MS patients.

Disclosure
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Prevalence of epilepsy in the MS population was 1.96%, 1.41%, and 2.45%, respectively.

Results:

Objective: To compare the prevalence of selected neurologic and psychiatric disorders in MS patients as compared with the general population of Catalonia, Spain.

Methods: Using population-based administrative health data from Catalonia, we identified adult patients with MS and age-, sex-, and geographically matched controls (1:5). We estimated the prevalence of neurologic (epilepsy, stroke, and migraine) and psychiatric (depression, anxiety and bipolar disease) conditions in cases and controls using information from the primary healthcare database that covers 5.8 million people. We determined the crude and sex-specific prevalence for each of the selected comorbidities using population figures from the Catalan Institute of Health. Rate ratios and 95% confidence intervals were calculated to compare the MS and general population.

Results: We identified 5,548 prevalent MS cases and 27,740 matched controls. From the MS cases, 69.7% were female, mean age was 48.26 years (SD 12.73) and mean disease evolution was 10 years (SD 7.6). The prevalence of epilepsy, stroke and migraine in the MS population was 1.96%, 1.41% and 2.45%, respectively. Relative to the matched population, the prevalence of epilepsy was more than two-fold higher in MS patients (RR 2.53 IC 95% 1.99-3.21) and this difference was specially marked for women.

Conclusions: This study provides further evidence of an increased prevalence of epilepsy, stroke, depression and bipolar disorder in MS patients as compared with the general population.

Background: Previous studies suggest an increased frequency of comorbid neurologic and psychiatric disorders in patients with multiple sclerosis (MS) as compared with the general population. These studies were conducted in few geographic regions, mainly North America, and data are lacking from other geographical areas.

Objective: To compare the prevalence of selected neurologic and psychiatric disorders in MS population and in the general population of Catalonia, Spain.

Methods: Using population-based administrative health data from Catalonia, we identified adult patients with MS and age-, sex-, and geographically matched controls (1:5). We estimated the prevalence of neurologic (epilepsy, stroke, and migraine) and psychiatric (depression, anxiety and bipolar disease) conditions in cases and controls using information from the primary healthcare database that covers 5.8 million people (80% of Catalonia’s population). We determined the crude and sex-specific prevalence for each of the selected comorbidities using population figures from the Catalan Institute of Health. Rate ratios and 95% confidence intervals were calculated to compare the MS and general population.

Results: We identified 5,548 prevalent MS cases and 27,740 matched controls. From the MS cases, 69.7% were female, mean age was 48.26 years (SD 12.73) and mean disease evolution was 10 years (SD 7.6). The prevalence of epilepsy, stroke and migraine in the MS population was 1.96%, 1.41% and 2.45%, respectively. Relative to the matched population, the prevalence of epilepsy was more than two-fold higher in MS patients (RR 2.53 IC 95% 1.99-3.21) and this difference was specially marked for women.

The prevalence of stroke was also significantly increased in MS patients (RR 1.51 IC 95% 1.15-1.95). There were no differences for migraine between cases and controls (RR 0.87 IC 95% 0.72-1.04). The prevalence of depression, anxiety and bipolar disorder in the MS population was 23.6%, 19% and 0.81%. When compared with the general population, both depression and bipolar disorder where significantly higher in MS patients (RR 1.99 IC 95% 1.9-2.1 and RR 1.87 IC 95% 1.3-2.7).

Conclusions: This study provides further evidence of an increased prevalence of epilepsy, stroke, depression and bipolar disorder in MS patients as compared with the general population.

Disclosure

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MAP, EB, TL, JD report no conflicts of interest.

Pathology

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Blockade of MCAM on TH17 cells impedes their CNS infiltration over the choroid plexus

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Very late antigen 4 (VLA-4; integrin α4β1) is critical in the transmigration of T_H17 cells into the central nervous system (CNS) under inflammatory conditions such as multiple sclerosis (MS). Here, we investigated the pathogenic relevance of VLA-4 and melanoma cell adhesion molecule (MCAM), which we have previously shown to be important for trans-endothelial T_H17 cell infiltration over the choroid plexus.
migration in vitro, in CNS inflammation by using murine models of MS in combination with antibody-mediated blocking of VLA-4 and/or MCAM and a system of CD4+ T cell conditional ablation of α4-integrin potential. VLA-4 blockade abrogated the encephalitogenic potential of T cells in a wide-ranging way by blocking migration over endothelial barriers, whereas MCAM targeting exclusively restricted CNS migration across the choroid plexus (CP). Upon blockade of MCAM lymphocytes were either already stopped from crossing the endothelial CP layer or were trapped between the endothelial and epithelial membranes of the CP. Importantly, this finding could be translated into the human system: during in vitro transmigration over primary human CP epithelium, blockade of MCAM on MCAM-expressing leukocytes trapped these cells within the epithelial layer. Furthermore, laminin α4, the major ligand of MCAM, was detected in the CP endo-, as well as epithelial basement laminas in tissue specimens from MS patients. Therefore, our findings suggest that MCAM - laminin α4 interactions specifically facilitate the enhanced trans-endothelial and trans-epithelial migration of MCAM-expressing T-cells through the CP into the CNS during neuro-inflammation.

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P417
Paraneoplastic neuromyelitis optica: an update on a single center cohort with cases of histological validation
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Background: Neuromyelitis optica (NMO) is an autoimmune central nervous system syndrome associated with aquaporin-4 (AQP4) antibodies, which are found in 60-70% of patients. Paraneoplastic syndromes are remote effects of cancer caused by an autoimmune response triggered by tumor cells. The co-occurrence of NMO and cancer has been previously described, but the underlying mechanism for these rare cases is not well characterized.

As available tissue does not enable detection of AQP4 expression, we hypothesize that AQP4 antibodies can bind cancer cells in some patients and be involved in a paraneoplastic response.

Objectives:
1) Describe the largest case series of paraneoplastic NMO cases.
2) Confirm that AQP-4 antibodies can bind tumor cells.

Methods: 11 patients with NMO and cancer were identified from a database of 155 NMO patients followed at the UBC NMO Clinic. A retrospective chart review assessed demographics, NMO history, AQP4 status and cancer histology. The pathology reports were used to confirm the cancer diagnosis. Solid tumor biopsies, available for 3 cases, were stained with AQP4-IgG.

Results: The mean age of patients at NMO diagnosis was 55 years (range 35-68; SD 10). 82% were female. Five patients presented with longitudinally extensive transverse myelitis (LETM), 2 with severe unilateral optic neuritis (ON), 1 with bilateral ON, 1 with simultaneous LETM and bilateral ON, 1 with an area postrema syndrome and 1 with a partial TM followed by recurrent ON. AQP4 sero-positivity was found in 45% (5/11).

One patient had Lynch syndrome with multiple cancers (endometrium, colon and bladder). The other cancer types were breast carcinoma(3), lung adenocarcinoma(1), non-Hodgkin lymphoma(1), thymoma(1), adrenocortical carcinoma(1), multiple myeloma(1), melanoma(1) and ovarian adenocarcinoma associated with BRCA1 mutation(1).

Positive staining for AQP4 was found on 2/3 tumor samples. An ovarian adenocarcinoma and a teratoma, found in patients with serological evidence of AQP4, showed a positive reactivity to AQP4 immunostaining. A melanoma from an AQP4-negative patient did not have positive AQP4 staining.

Conclusion: We report a series of 11 cases of paraneoplastic NMO. Ovarian adenocarcinoma and adrenocortical carcinoma are histological subtypes not previously described with NMO.

We showed in 2 of 3 cases that tumor cells can bind AQP4 antibodies. Produced as an immune response to cancer, AQP4 antibodies can lead to a clinical presentation of NMO.

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P418
Inflammation effectively eliminates JC virus during progressive multifocal leukoencephalopathy
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Progressive multifocal leukoencephalopathy (PML) is an opportunistic brain infection caused by the JC virus (JCV) in immunosuppressed patients, e.g. in natalizumab treated MS patients. When the immune system recovers, an immune reconstitution inflammatory syndrome (IRIS) may occur, accompanied by a profound inflammatory reaction. A sufficient immune response is necessary for viral clearance, but can also cause life-threatening brain damage.

The aim of our study was to characterize non-inflammatory (n=7) and inflammatory PML lesions (n=13; >500 lymphoid cells/mm²) histologically to identify the role different immune cell populations play in viral elimination.

Up to 2000 lymphoid cells/mm² were found in inflammatory PML lesions; these were mainly CD8+ cytotoxic T cells (44%), followed by CD138+ plasma cells (24%), CD4+ T cells (24%) and B cells (8%). The lymphoid infiltrate correlated negatively with the number of virally infected cells, suggesting an effective viral clearance (r=-0.5; p=0.01). The strongest correlation was found for plasma cells (r=-0.7; p=0.0001) and CD8+ T cells (r=-0.5; p=0.01), but not for CD4+ T cells. Patients who survived the PML clearance (r=-0.5; p=0.01). The strongest correlation was found inflammatory reaction. A sufficient immune response is necessary for viral clearance, but can also cause life-threatening brain damage.

In conclusion, our results suggest that a strong immune response is necessary for viral clearance, but can also cause life-threatening brain damage.

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P419
Alterations of minicolumnar cytoarchitecture and axonal loss in multiple sclerosis cortex
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Cortical pathology is now recognized as an important feature of MS and as an important contributor to physical and cognitive disability. Diffuse neuronal loss, synaptic loss, atrophy and focal demyelination have all been described in MS cortex. The cerebral cortex is organized in a complex modular architecture based on minicolumnar aggregates of neurons with associated dendrite and axon bundles, with afferent and efferent connections to other brain regions (Opris, 2014). Minicolumns constitute a fundamental computational unit of the cerebral cortex (Mountcastle, 1997; Buxhoeveden, 2002; Casanova, 2008). Abnormalities or disruption of minicolumnar organization has been described in aging and in pathological conditions, such as autism (Casanova, 2003; Buxhoeveden, 2006; Mc Kavanagh, 2015), schizophrenia (Casanova, 2007; Di Rosa, 2009), Alzheimer’s disease (Buldyrev, 2000; Esiri, 2006; Chance, 2011; van Veluw 2012), Lewy body dementia (Buldyrev, 2000), mild cognitive impairment (Chance, 2011), drug addiction (Opris, 2015).

The aim of the present study was to assess the presence of abnormalities of minicolumnar organization in MS cortex. The study was performed on an autopsic series of 8 MS and 5 control brains, using a modification of a previously described density map method (Buldyrev, 2000; Cruz, 2009), applied to digital images of Nissl-stained sections of the posterior cingulate cortex and the superior temporal gyrus. Axonal density was also estimated in the cortex, using a software-assisted procedure on digital images of Bielschowsky-stained sections. Neuronal density was reduced in MS cortex, by a mean of -23.6% if compared to control cortex. Axonal density was similarly reduced in MS cortex, by a mean of -27.4% if compared to control cortex, with the highest degree of axonal loss (-37.8%) in the most superficial layers (I-II) of the cerebral cortex. A variable disruption of minicolumnar ensemble architecture was observed in MS cortex, up to a nearly complete loss in cases of secondary progressive MS, apparently independently from the presence of focal cortical demyelinating lesions.

Alterations of minicolumnar organization represent a novel feature of cortical pathology in progressive MS. The exact mechanisms underlying these alterations of minicolumnar organization remain to be determined. The loss of a significant number of minicolumns may disrupt information processing among distributed networks thus contributing to neurological dysfunction.

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P420
The impact of high level of perivenular inflammation on active white matter lesions and disease progression in multiple sclerosis

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Introduction: Neuropathological studies have demonstrated a strong association between leptomeningeal immune cell infiltration within the subarachnoid space and subpial cortical lesions, B-cell related intrathecal immunity and MS rapid disease progression. It remains still poorly understood whether the presence of perivenular immune infiltration may be similarly associated with different levels of lesion activity and disease outcome.

Aims: In order to identify the potential association between perivenular inflammation, early active white matter plaques and clinical outcome, a systematic neuropathological analysis was performed.

Methods: Using immunohistochemistry, 20 different cerebral sites from 269 post-mortem MS brains collected by the UK MS Society Tissue Bank (MSSTB) were studied. A subset had previously had detailed assessment of the presence of meningeal inflammation. The presence of early active lesions and the extent of perivenular inflammation (high/low) were examined with particular attention to the presence of the CD20+ and CD3+ cells in perivenular infiltrates.

Results: A shorter time from progression to death was associated with increased prevalence of early active lesions and high levels of perivenular inflammation (both p<.0001) in the SPMS cases examined. Independently, earlier age of onset and shorter time from onset to progression further increased the prevalence of these features. A shorter time from onset of progression to wheelchair use was associated with a higher prevalence of early active lesions (OR 0.921, 95% CI (0.858, 0.989), p=0.0230) and a higher level of perivenular inflammation (OR 0.932, 95% CI (0.886, 0.981), p=0.0071). Early active lesions were present in 35% (48/136) of cases with high levels of perivenular inflammation, but were less frequent in (11/127) in the absence of perivenular inflammation. Elevated levels of meningeal inflammation were associated with a high degree of perivenular inflammation (29/34) and significantly higher levels of B cells within perivenular infiltrates.

Conclusions: The association of early active lesions and high levels of perivenular inflammation with a rapid progressive phase and higher levels of both meningeal and perivascular B-cell infiltrates is consistent with the hypothesis that chronic inflammation drives the progressive MS phase in some way. Predicting their presence in the progressive phase before a wheelchair is required will help to extend the window of therapeutic opportunity.

P421
Neuromyelitis optica: distinct staining patterns of sera containing AQP4- and MOG-antibodies in the murine visual system

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Background: Neuromyelitis optica (NMO) is an autoimmune-inflammatory CNS disease, mostly affecting spinal cord and optic nerve (ON). Disability in NMO can be severe and loss of visual function has major consequences for patients. Besides autoantibodies (abs) directed against aquaporin-4 (AQP4), abs targeting myelin-oligodendrocyte-glycoprotein (MOG) have been discovered. Knowledge about pathogenic effects of these abs on retina and ON is sparse.

Objective: To investigate binding characteristics of sera with AQP4- and MOG-abs to retina and ON as well as potential pathogenic effects on the visual pathway.

Methods: We incubated cryo-slices of murine retina and ON with sera of AQP4-ab (age 40.1 ± 10.8) or MOG-ab (age 31.5 ± 13.2) positive NMO patients. The sera’s binding behavior was compared to sera from matched healthy controls. Serum staining was evaluated by three independent examiners in masked fashion using a non-parametric scoring system, ranging from 0 to 4 depending on signal intensity and specificity. To evaluate potential binding sites, we performed double stainings of sera and commercial antibodies against murine AQP4 or GFAP.

Results: 2/8 sera from AQP4-ab positive, and 3/8 sera from MOG-ab positive patients depicted distinct staining patterns in the retina or ON. In the retina, quantification did not show significant differences between sera containing AQP4- or MOG-ab (1.86±0.54; p=0.85) in comparison to control sera (1.55±0.36). In the ON, again no significant differences were found, however with a tendency of AQP4-ab-positive sera to show a stronger signal (2.11±0.52; p=0.25) than MOG-ab-positive sera (0.96±0.38; p=0.85) in comparison to controls (1.23±0.22). One serum from three distinct MOG-ab positive sera exclusively stained ON while the other two only stained retina. Two AQP4-ab positive sera displayed a specific signal against retina and ON, one with co-localization with AQP4- and one with GFAP-staining.

Conclusion: Sera from NMO patients with AQP4- or MOG-ABS show distinct and within each group different binding patterns against murine retina and ON, indicating that various epitopes are targeted. Co-staining of NMO sera with AQP4 but also GFAP was shown previously. This points towards existence of anti-GFAP-abs in NMO. Their role in the disease still needs to be

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investigated. In further studies, we will examine the mechanisms of ab-mediated damage to retina and ON.

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P422
Focal cortical astrocytopathy lesions with demyelination and inflammatory cell infiltrates in neuromyelitis optica spectrum disorder: a neuropathological study of eleven autopsied cases
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Background: Cortical lesions on magnetic resonance images have rarely been reported in neuromyelitis optica spectrum disorder (NMOSD), although aquaporin-4 (AQP4) is abundantly expressed in the cerebral cortex. Recent neuropathological studies have revealed cortical neurodegeneration without demyelination or inflammation in NMOSD.

Objective: To elucidate the distribution and extension patterns of brain lesions in NMOSD, focusing on inflammatory cortical lesions.

Methods: We immunohistochemically examined cerebral and cerebellar lesions from eleven autopsied NMOSD cases, including three anti-AQP4 antibody-positive cases, for astrocytic and oligodendrocytic/myelin markers, deposition of activated complements, and macrophage infiltration. Subsequently we evaluated the distribution patterns of grey and white matter lesions in the cerebrum and cerebellum.

Results: Pathological analysis revealed 96 cerebral and five cerebellar lesions. The cerebral cortex was involved in 20/96 (20.8%) lesions from three cases, including an anti-AQP4 antibody-positive case. The cortical lesions were 45.0% intracortical, 30.0% subpial, and 25.0% leukocortical. These lesions were focally present and characterised by loss of AQP4, presence of degenerated astrocytes and demyelination, lack of complement deposition, and infiltration of lymphocytes and macrophages around blood vessels, with or without glia limitans disruption. Other cerebral lesions were found in subcortical white matter (25/96, 26.0%), periventricular white matter (14/96, 14.6%), the corpus callosum (18/96, 18.8%), deep white matter (16/96, 16.7%), and deep grey matter (3/96, 3.1%). All cerebellar lesions were in white matter. In the cerebrum, isolated perivascular lesions were identified in both white (7/96, 7.3%) and cortical grey matter (2/96, 2.1%), while in the cerebellum, such lesions only occurred in white matter (1/5, 20.0%).

Conclusion: This comprehensive neuropathological study indicates that focal cerebral cortical lesions occasionally exist in NMOSD, featuring astrocytopathy with demyelination and inflammatory cell infiltrates. Isolated perivascular lesions are also present in cerebral and cerebellar white matter and the cortex. We propose that vasculocentric lesion formation may also occur in brain tissue in NMOSD, as pathologically demonstrated in the spinal cord.

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Experimental models
P423
In vivo modeling of the nascent multiple sclerosis lesion: epsilon toxin induced mechanisms of blood brain barrier permeability
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Background: Clostridium perfringens epsilon toxin (ETX) has been proposed as a candidate environmental factor responsible for

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Focal overexpression of FGF9 in rat cortex induces de- and dysmyelination

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Previous studies showed a correlation between actively demyelinating lesions in patients with multiple sclerosis and increased glial expression of Fibroblast growth factor 9 (FGF9). Furthermore, myelinating cultures treated with FGF9 revealed an increase in oligodendrocyte progenitor cell (OPC) numbers. However, these oligodendrocytes failed to myelinate axons (Lindner et al., 2015). Here, we examine the influence of FGF9 in vivo. Therefore, we stereotactically injected adult Lewis rats with either an adenovirus- or myelin basic protein (MBP)-expressing AAV vector encoding FGF9 (AAV-FGF9) or EGFP (AAV-EGFP) into the motor cortex. This system facilitates a stable protein production under the astrocytic glial fibrillary acidic protein (GFAP) promoter. The brain tissue was collected after 3 days, 10 days, 1 month, 3 months and 9 months and processed for immunocytochemistry and electron microscopy.

Already 10 days after injection astrocytes were activated and showed extremely enlarged processes. These morphological changes persisted over time and were not visible in the controls. Additionally, the numbers of OPC and mature oligodendrocytes continuously increased over time. Already one month after AAV-FGF9 injection, de-myelination started and was prominent after 3 and 9 months, as indicated by loss of the myelin proteins 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), proteolipid protein (PLP), myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and myelin-associated glycoprotein (MAG). At the lesion edge we found activated oligodendrocytes expressing MOG, MAG and CNP in the cytoplasm but failing to build "functional" myelin sheaths. Findings were confirmed by high resolution images showing unfolded myelin sheaths around axons.

These observations reveal a novel model for studying demyelinating disorders, and illustrates alternate mechanisms leading to myelin dysfunction and loss.

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P425
Neutrophils mediate blood-brain barrier disruption in a rat model of neuromyelitis optica

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Neuromyelitis optica (NMO) is a demyelinating autoimmune disease of the central nervous system (CNS), in which a fast accumulation of disability is observed. The antigenic target in about 70% of patients is the water channel aquaporin 4 (AQP4) located on astrocytic end-feet, resulting in complement- and cell-mediated astrocyte depletion. Magnetic resonance imaging (MRI) indicates a prolonged and severe blood-brain barrier (BBB) disruption allowing additional pathogenic antibodies (Ab) and possibly neurotoxic serum components to enter the CNS, aggravating lesion development. To investigate the relative contribution of cellular and molecular mediators to BBB disruption we took advantage of a well established focal NMO-model in rats which is based on intracerebral injection of a human recombinant NMO-Ab directed against AQP4, and human complement. Performing time course experiments we observed an opening of the BBB to vascular tracer molecules early after lesion induction, coinciding with the development of astrocyte depleted lesions. Interestingly, BBB integrity to vascular tracers was rapidly restored, even in the absence of astrocytes. Immune cells infiltrating the CNS are

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thought to be main mediators of BBB disruption under inflammatory conditions. We found that in early lesions, neutrophils are the most abundant infiltrating leukocytes and that the number of neutrophils in the lesions correlates with the extent of tracer extravasation. Depletion of neutrophils prevented not only the breakdown of the BBB, but interestingly also the loss of astrocytes. Moreover, pharmacological inhibition of neutrophil attraction, as well as inhibition of proteases released by neutrophils resulted in a reduction of astrocyte lesion size. To conclude, this study affirms the importance of neutrophils in the development of focal NMO lesions and is the first to show that infiltrating neutrophils mediate the breakdown of the BBB. These findings, together with the detection of neutrophils in early human NMO lesions, identify the neutrophil mediated breakdown of the BBB as a promising target for future therapeutic approaches.

Disclosure

Funding

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P426

Critical role of GM-CSF, not IL-17, in relapsing experimental autoimmune encephalomyelitis

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The pathogenic contributions of IL-17 and GM-CSF have been extensively studied in experimental auto-immune encephalomyelitis (EAE) but not in induced chronic EAE relapses (Cr-EAE). Here, we used proteolipid protein peptide (PLP) to induce relapses in SJL mice that had recovered from an initial EAE episode. This resulted in severe and irreversible disease that, contrary to primary EAE, was not abolished by treatment with a monoclonal anti-IL-17 antibody (mAb), even in mice protected during the first PLP vaccination by IL-17 blockade. In contrast, anti-GM-CSF mAb prevented both primary EAE and Cr-EAE. This was particularly striking in mice treated continuously with anti-GM-CSF during both EAE episodes, as these animals remained completely disease-free. Lymph node cells from anti-GM-CSF-treated mice showed impaired IL-17 responses while proliferation and IFNg production were normal. However, it completely silenced the central nervous system inflammatory response, since IL-17, GM-CSF, IFNg, TNFa and chemokines MCP1/CCL2, MIP1a/ CCL3, MIP2/CXCL2 and RANTES/CCL5 mRNAs were strongly inhibited in the spinal cord of mice. Interestingly, the expression of the anti-inflammatory mediators IL-10, IL-27p28 or TGFb in the CNS of the mice treated with the anti-GM-CSF mAb during both EAE episodes was also down-regulated. In the group not treated during the initial disease, the anti-GM-CSF mAb did not completely prevent relapses but ultimately resulted in complete recovery. Anti-GM-CSF treatment also strongly impaired and ultimately resolved the monophasic and normally permanent EAE induced by MOG35-55 peptide in C57Bl/6 mice. In such protected mice, a relapse could be induced by MOG revaccination but only when anti-GM-CSF treatment was interrupted, demonstrating that GM-CSF is also required to induce a relapse in this model. These results underscore the critical role of GM-CSF in the emergence of encephalitogenic Th17 cells and the production of inflammatory mediators during EAE induction and relapses.

Disclosure

Vincent Van Pesch received travel grants from Biogen, Bayer Schering, Genzyme, Merck, Teva, Sanofi and Roche. His institution receives honoraria for consultancy and lectures from Biogen, Bayer Schering, Sanofi, Merck, Roche, Teva and Novartis Pharma as well as research grants from Novartis Pharma, Bayer Schering, Sanofi and Roche.

P427

Subtle biochemical myelin pathology triggers secondary inflammatory demyelination in mouse brain

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Objective: The etiology of inflammatory demyelination in multiple sclerosis (MS) remains unresolved. On the one hand, the ‘outside-in’ model of MS suggests that demyelinating lesions reflect peripheral, immune attacks on central targets, a concept recapitulated in the EAE animal model. Unlike EAE, however, the identity and target of pathological self-antigens in MS has proven stubbornly elusive. An alternative, ‘inside-out’ model posits that autoimmunity follows rather than causes CNS tissue damage. We sought to test whether myelin changes in particular can secondarily generate pathological auto-antigens and cause inflammatory lesions.

Methodology: To generate endogenous myelin auto-antigens, mice were fed 0.2% cuprizone for two weeks, an exposure brief enough that no overt demyelination occurs. This was then followed by immune adjuvant (identical to standard EAE but without myelin peptides) and a two-week interval on normal chow. In parallel experiments, to test whether MS-relevant protein-arginine deiminases (PAD) contributed to pathology in this inside-out model, small molecule PAD inhibitors were systemically delivered daily.

Results: Cuprizone-altered myelin in an immune-stimulated host elicited focal lesions of robust inflammatory demyelination mainly in the medial corpus callosum. Brains were gadolinium MRI-enhancing prior to lesion formation, correlating with infiltrating CD3+ T cells. Shorter or longer cuprizone feeding abrogated inflammatory lesion formation, demonstrating that myelin immunogenicity depended not only on a stimulated immune system but also on the extent and timing of biochemical myelin modification. PAD inhibitors virtually eliminated Gd enhancement and subsequent inflammatory demyelination.

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Disclosures

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P426

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C. Uyttenhove1, M. Gaignage,1 L. D’auria2, Z. Nasr2, D. Donckers1, J. Van Snick1, V. van Pesch3

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The pathogenic contributions of IL-17 and GM-CSF have been extensively studied in experimental auto-immune encephalomyelitis (EAE) but not in induced chronic EAE relapses (Cr-EAE). Here, we used proteolipid protein peptide (PLP) to induce relapses in SJL mice that had recovered from an initial EAE episode. This resulted in severe and irreversible disease that, contrary to primary EAE, was not abolished by treatment with a monoclonal anti-IL-17 antibody (mAb), even in mice protected during the first PLP vaccination by IL-17 blockade. In contrast, anti-GM-CSF mAb prevented both primary EAE and Cr-EAE. This was particularly striking in mice treated continuously with anti-GM-CSF during both EAE episodes, as these animals remained completely disease-free. Lymph node cells from anti-GM-CSF-treated mice showed impaired IL-17 responses while proliferation and IFNg production were normal. However, it completely silenced the central nervous system inflammatory response, since IL-17, GM-CSF, IFNg, TNFa and chemokines MCP1/CCL2, MIP1a/ CCL3, MIP2/CXCL2 and RANTES/CCL5 mRNAs were strongly inhibited in the spinal cord of mice. Interestingly, the expression of the anti-inflammatory mediators IL-10, IL-27p28 or TGFb in the CNS of the mice treated with the anti-GM-CSF mAb during both EAE episodes was also down-regulated. In the group not treated during the initial disease, the anti-GM-CSF mAb did not completely prevent relapses but ultimately resulted in complete recovery. Anti-GM-CSF treatment also strongly impaired and ultimately resolved the monophasic and normally permanent EAE induced by MOG35-55 peptide in C57Bl/6 mice. In such protected mice, a relapse could be induced by MOG revaccination but only when anti-GM-CSF treatment was interrupted, demonstrating that GM-CSF is also required to induce a relapse in this model. These results underscore the critical role of GM-CSF in the emergence of encephalitogenic Th17 cells and the production of inflammatory mediators during EAE induction and relapses.

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Conclusions: Our Cuprizone Autoimmune Encephalitis (CAE) model provides proof-of-concept showing that primary endogenous myelin changes can secondarily elicit inflammatory demyelination in an immune-primed host. It also identifies PAD as a potential molecular mechanism through which inside-out inflammation occurs. These results may impact MS treatment regardless of its underlying pathogenesis: cytodegeneration may be the initiating event in MS or it may represent a mechanism through which outside-in pathology is exacerbated. Comprising both inflammatory and degenerative components, the CAE model is an ideal preclinical model to uniquely inform MS pathogenesis and to guide future therapeutic development.

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P428
Visual evoked potentials reflect optic nerve demyelination in EAE
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Experimental autoimmune encephalomyelitis (EAE) to immunization with myelin oligodendrocyte glycoprotein (MOG) is a widely used disease model of multiple sclerosis (MS). Although visual evoked potentials (VEPs) allow to monitor demyelination and remyelination in the clinical setting, their pathological correlate in the chronic phase of EAE still needs to be exploited. We aimed at investigating VEPs and ON histology in MOG-EAE induced in Dark Agouti (DA) rats.

Twenty-six DA rats were immunized with MOG and VEPs and histology were performed after EAE onset (day 10-12) at day 21 (n=3), 47 (n=5), 54 (n=10) and 68 (n=8) days post injection (dpi) with quantification of demyelination percentage, axonal loss percentage and number microglial activated cells in both optic nerves. A healthy control group (n=8) was monitored over the same time points and histology was performed in 2 rats. T-test for independent samples was performed for group comparisons and Pearson’s coefficient for correlation analysis. At 21 dpi, VEPs were delayed for 83% of EAE eyes, while at 47 dpi all VEPs were delayed (50%) or absent (50%), with lower frequency of absent VEPs at later time points (54 dpi: 25% absent, 45% delayed; 68 dpi: 25% absent, 75% delayed). VEPs latency was significantly correlated with demyelination (Pearson’s r=0.565, p<0.0001), axonal loss (r=0.482, p=0.0003) and activated microglia (r=0.488, p=0.0002).

VEPs latencies were best correlated with the extent of demyelination rather than axonal loss or inflammation. This finding is consistent with the view that VEPs latency can be considered as an in vivo, repeatable measure to monitor demyelination in EAE for validating new models and testing drugs acting on demyelination and remyelination.

Disclosure
The authors declare no competing financial interest

P429
Amelioration of secondary progressive experimental autoimmune encephalomyelitis by restoring mitochondrial energy production in a GOT2-dependent manner
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Background: Oxidative stress and mitochondrial dysfunction are important determinants of axonal degeneration in secondary progressive multiple sclerosis (SPMS). We previously showed that febuxostat, a xanthine oxidase inhibitor, ameliorated both relapsing-remitting and secondary progressive experimental autoimmune encephalomyelitis (EAE) by preventing axonal loss in mice. In this study, we investigated how febuxostat preserves axons in secondary progressive EAE.

Methods and Results: A DNA microarray analysis revealed that febuxostat treatment increased the CNS expression of several mitochondria-related genes in EAE mice, most notably including GOT2, which encodes glutamate oxaloacetate transaminase 2 (GOT2). GOT2 is a mitochondrial enzyme that oxidizes glutamate to produce α-ketoglutarate for the Krebs cycle, eventually leading to the production of adenosine triphosphate (ATP). Whereas GOT2 expression was decreased in the spinal cord during the chronic progressive phase of EAE, febuxostat-treated EAE mice showed increased GOT2 expression. A detailed morphological assessment of GOT2 distribution suggested that GOT2 was predominantly expressed in neuronal somata within gray matter of the spinal cord. Double immunofluorescence staining of GOT2 with neuronal marker Microtuble Associated Proteins 2 (MAP2) and mitochondrial marker TOM20 demonstrated that GOT2 was predominantly expressed in neuronal mitochondria. Reflecting the ability of febuxostat to rescue mitochondrial dysfunction in neurons, febuxostat treatment of Neuro2a cells in vitro ameliorated ATP exhaustion induced by rotenone application. By contrast, febuxostat alone did not affect steady-state ATP levels. The ability of febuxostat to preserve ATP production in the presence of rotenone was significantly reduced by GOT2 siRNA.

Conclusions: GOT2-mediated ATP synthesis may be a pivotal mechanism underlying the protective effect of febuxostat against axonal damage in EAE. Accordingly, febuxostat may also have clinical utility as a disease-modifying drug in SPMS.

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Makoto Kinoshita: nothing to disclose, Josephe A. Honorat: nothing to disclose, Tatsusada Okuno: nothing to disclose, Yuji
**P430**

**Immunomodulatory therapy in genetic mouse models of progressive multiple sclerosis**

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**Background:** Progressive forms of multiple sclerosis (PMS) are characterized by consistently increasing disability and often respond poorly to established immunomodulatory therapies, although histopathological features indicative of inflammation are usually detectable (Ontaneda et al., 2017; Lancet. 389:1357-1366). Consequently, the pathogenic relevance of inflammation and the reason for failure of immune therapies in PMS are unclear.

**Objectives:** We previously generated novel mouse models carrying point mutations in the PLP1 gene that have been described in PMS patients. The PLPmut mice reflect important aspects of PMS and we could unequivocally demonstrate a detrimental pathogenic impact of chronic secondary neuroinflammation in the models by cross-breeding them with distinct knockout mouse models to abolished or enhance adaptive immune reactions (Groh et al., 2016; Human Molecular Genetics. 25:4686-4702). Here we tested the efficacy of the clinically approved immunomodulatory compound teriflunomide to attenuate or prevent neuroinflammation-related neural damage in the mouse models.

**Methods:** PLPmut mice were treated for several months with teriflunomide (10mg/kg/day) ad libitum in drinking water and monitored with non–invasive methods like optical coherence tomography (OCT). Subsequently, the respective treatment and control groups were analysed by flow cytometry, immunohistochemistry, histology and electron microscopy.

**Results:** The long-term treatment with teriflunomide significantly attenuated neuroinflammation in PLPmut mice. This resulted in reduced axonal perturbation, neuron loss and - in case of the OCT analysis - reduced retinal thinning. Early treatment in young and mildly affected mutants was more effective than later treatment at advanced disease stages. The treatment did not cause obvious deleterious side effects and treatment termination did not result in a rebound effect.

**Conclusions:** Our data corroborate the pathogenic relevance of secondary neuroinflammation in the PMS-related mouse models with primary oligodendroglial myelin defects. They also show that specific immunomodulatory compounds like teriflunomide can significantly ameliorate disease progression, especially when applied in early stages. These findings might be of high relevance regarding putative treatment approaches for PMS and other chronic progressive disorders of the CNS accompanied by secondary neuroinflammation.

**Disclosure**

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**P431**

**Transcriptomic analysis of disease reversal in EAE: comparison of laquinimod and FTY-720**

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**Background:** Laquinimod is currently in clinical development for the treatment of multiple sclerosis (MS) and Huntington disease. Previously, we reported that laquinimod reverses the gene expression profile associated with EAE and induces genes associated with the AhR pathway. Furthermore, we showed that AhR is required for the effect of laquinimod in EAE.

**Objectives:** In the present study, we have expanded transcriptomic analysis to identify 1) Pathways associated with the disease reversal that are unique to Laquinimod versus FTY-720, and 2) AhR-independent effects of laquinimod in EAE.

**Methods:** MOG35/58 EAE was induced in Wild Type (WT) C57BL/6 or AhR KO (C57BL/6-Ahrtm1.2Arte) mice and animals were treated daily with vehicle, 25mg/kg laquinimod or 1mg/kg FTY-720 via oral gavage. Brains and spinal cords were removed on day 15 post immunization, and processed for RNA-Sequencing.

**Results:** Transcriptome analysis revealed that EAE induced similar patterns of differentially modulated genes in brain and spinal cord (FDR< 0.05) of WT and AhR KO mice. Specifically, pathway analysis revealed that immune-related pathways (cytokine–cytokine receptor interaction; NOD-like receptor & NFκB signaling) were upregulated and neuronal-related pathways (glutamatergic synapse, calcium signaling pathway and axon guidance) were down-regulated in EAE. Laquinimod and FTY-720 reversed the expression pattern in WT EAE mice and shared much of the reversal of immune response, whilst each displayed some unique differentially expressed pathways, especially in the spinal cord. In AhR KO mice, FTY-720 reversed the disease pattern as seen in WT mice. In contrast, there was only a single gene differentially expressed in AhR KO mice treated with laquinimod.

**Conclusion:** These data indicate that the gene expression pattern for reversal of EAE is largely common to laquinimod & FTY-720. However, the data show that AhR is the predominant driver of the effect of laquinimod in EAE.

**Disclosure**

Haim Belinson, Steve Barash, Joel Kaye, Emanuel Raymond, Daphna Laienfeld, & Ralph Laufer are all employees of Teva Pharmaceutical Industries Ltd.

**P432**

**Potential beneficial effect of neuroinflammation on experimental stroke**

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**Background:** Experimental data indicate similar molecular mechanisms in cerebral hypoxia and autoimmune neuroinflammation. Consequently, potential effects of immunomodulatory MS therapeutics on secondary stroke-associated inflammatory damage were investigated in clinical trials. Mutual interactions of autoimmune, antigen-specific inflammatory reactions and cerebral ischemia have not been extensively investigated thus far.

**Objective:** To investigate the effects of autoimmune antigen-specific CNS inflammation on cerebral ischemia.

**Methods:** Active MOG<sub>35-55</sub> experimental autoimmune encephalomyelitis (EAE) vs. sham control (CFA-immunized animals) was induced in male C57Bl/6 mice. Transient middle cerebral artery occlusion (tMCAO, 60 minutes) was performed in the acute phase of EAE or in sham-immunized mice. Brain tissue was collected after 24h. Infarct and edema size and immune cell infiltration were analyzed histopathologically.

**Results:** Actively immunized mice showed gradually smaller infarct sizes inversely correlating with EAE score (p<0.005, t<0.38, n=43). This held similarly true for edema size (p=0.006, t=0.32) and combined damaged tissue (infarct+edema size; p<0.001, t=-0.408). Group comparisons of severely diseased mice (score 5-7, n=6) versus both non-diseased immunized (n=21) and control mice (n=34) demonstrated significantly smaller infarct sizes (p=0.003 and p=0.005) and smaller areas of combined tissue damage (p=0.004 and p=0.008). In addition, we detected a shift in immune cell infiltration in favor of both diffuse and partially rim-like configuration of CD45<sup>+</sup> cells 24h after tMCAO in the ipsilateral hemisphere. This is now being analyzed for the different groups.

**Conclusions:** Our data indicate a positive influence of antigen-specific CNS autoimmunity on both infarct size as primary tissue damage and edema as an early consequence of the ischemic insult. This hints at a very early involvement of immune mechanisms in this experimental model of stroke. As this is not detected in both control (CFA) and MOG-immunized mice which did not develop clinical signs, this effect appears to be linked to active CNS involvement of an antigen-specific inflammatory reaction. This ongoing work will contribute to a better understanding of interactions between CNS autoimmunity and cerebral ischemia.

**Disclosure**

KG: former employee of Biogen, not related to this work.

NH: nothing to declare.

LS: received travel grant from Genzyme, not related to this work.

AS: received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche and Sanofi Genzyme, none related to this work.

RH: received research and travel grants from Novartis and Biogen, not related to this work.

DMH: received speaker honoraria and consulting fees from Servier, not related to this work.

AC: received consulting fees from Bayer, Biogen, Genzyme, Merck, Novartis, Roche, Sanofi-Aventis, Teva Neuroscience, UCB and research grants from Biogen, Genzyme, Novartis, and UCB, none related to this work.

**P433**

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**Optical coherence tomography identifies structural retinal damage in experimental autoimmune encephalomyelitis**

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**Background:** Neuro-axonal injury is a key contributor to non-reversible long-term disability in multiple sclerosis (MS). However, underlying mechanisms are not yet fully understood. Visual impairment is common among MS patients, in which episodes of optic neuritis (ON) are often followed by structural retinal damage. Optical coherence tomography (OCT) can be used to quantify retinal injury in vivo. Alterations in the optic nerve and retina have also been described in experimental autoimmune encephalomyelitis (EAE). Investigating structural damage in the anterior visual pathway therefore provides a potential model to assess mechanisms of neurodegeneration in MS. We used a multimodal imaging approach to explore the basic mechanisms and temporal sequence of visual pathway damage in EAE.

**Methods:** 7 EAE-MOG<sub>35-55</sub> and 5 healthy female C57BL/6J mice were used in this study. Ganglion cell complex (GCC) thickness was obtained from a volume scan centred over the optic nerve head using the Spectralis OCT-2 Plus device. Diffusion tensor imaging (DTI) parameters were obtained from the optic nerve on a 7T Bruker MRI unit. Data was acquired at baseline, disease onset, peak and remission. Generalized linear mixed model was used to account for intra-subject, inter-eye dependencies, group and endpoint. Correlation analyses assessed the relationship between GCC thickness, EAE disability scores and DTI parameters (corrected for multiple comparisons).

**Results:** In EAE mice, a significant increase in GCC thickness was observed at onset (p<0.001) and a significant decrease at remission (p<0.001) compared to healthy controls. The EAE group had significant GCC thinning at remission compared to all other timepoints (p<0.001 for each). GCC at remission was positively correlated with DTI-derived fractional anisotropy (rho=0.81, p=0.03) and axial diffusivity (rho=0.91, p=0.001) and negatively correlated with radial diffusivity (rho=-0.81, p=0.02). GCC thickness was also negatively correlated with EAE scores at remission (rho=-0.80, p<0.001).

**Conclusion:** GCC changes in EAE may be reflective of what is observed in MS-related ON: an initial phase of swelling followed by decreased thickness (representative of neuro-axonal degeneration) over time. OCT together with DTI can characterise retinal and optic nerve damage and the temporal sequence of neurodegeneration in MOG induced EAE in vivo. The underlying cause for those alterations will be further investigated by immunohistochemical analyses.

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Diffusion tensor imaging of the afferent visual pathway as an in vivo tool to assess neurodegeneration in experimental autoimmune encephalomyelitis

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Introduction: Multiple sclerosis (MS) is a neurodegenerative disorder in which inflammatory mechanisms lead to neuro-axonal damage. Visual impairment is a common feature of MS. Alterations in the optic nerve and retina have also been described in a mouse model of MS (experimental autoimmune encephalomyelitis; EAE). Investigating structural damage in the afferent visual pathway might constitute a translational model for assessing neurodegenerative changes and may increase our understanding of basic mechanisms underlying tissue damage in MS. Therefore, we used diffusion tensor imaging (DTI) of the visual pathway to obtain measurements of axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) in the optic nerves and tract of EAE mice.

Methods: 7 MOG35-55 induced EAE and 5 healthy female C57BL/6J mice have been used for this study. DTI (TE 26.5ms, TR 2500ms, 60 diffusion directions, 75mm2) as well as a co-registered T2-weighted sequence (TE 33ms, TR 2500ms, 75mm2), were performed on a 7T scanner (Pharmascan 70/16, Bruker, Germany) equipped with a CryoProbe. MRI data was acquired at baseline, disease onset, peak, and remission. Region of interest based analysis was used to calculate FA, AD, and RD in the optic nerves and tract. Linear mixed effect model was used to account for intra-subject dependencies, groups and time points. Spearman’s rank correlation assessed the relationship between DTI measures and EAE disability scores.

Results: Signal increase on T2-weighted images around the optic nerves indicative of inflammation was seen in most of the EAE mice but none of the healthy controls. A significant decrease in FA, AD and increase in RD values in EAE optic nerves (FA: p=0.003, AD: p=0.0008, RD: p=0.003) and tract (FA: p=0.00005, AD: p=0.02, RD: p=0.004) was observed compared to controls at all time points. DTI measures at peak (optic nerve: FA [rho=−0.61], AD [rho=−0.86]; optic tract: FA [rho=−0.81], AD [rho=−0.86], RD [rho=−0.66]) and remission (optic nerve: FA [rho=−0.75], AD [rho=−0.67], RD [rho=−0.76]; optic tract: FA [rho=−0.62], AD [rho=−0.59], RD [rho=−0.73]) were significantly correlated with EAE scores (all p-values < 0.01).

Conclusion: DTI of the visual pathway in mice identifies EAE-induced pathology (decreased fractional anisotropy, axial diffusivity, and increased radial diffusivity) in vivo. The underlying cause for those alterations will be further investigated using histological and immunohistochemical analyses.

Disclosure
Christine Egger has received travel support from Merck and Praveena Manogaran received travel support from Sanofi Genzyme. Conny Waschkies and Markus Rudin have no conflict of interest to disclose.

Sven Schippling has received research grants from Novartis and Sanofi Genzyme, and consultancy and speaking fees from Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, and Teva.

Diffusion tensor imaging of the afferent visual pathway as an in vivo tool to assess neurodegeneration in experimental autoimmune encephalomyelitis

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Introduction: Multiple sclerosis (MS) is a neurodegenerative disorder in which inflammatory mechanisms lead to neuro-axonal damage. Visual impairment is a common feature of MS. Alterations in the optic nerve and retina have also been described in a mouse model of MS (experimental autoimmune encephalomyelitis; EAE). Investigating structural damage in the afferent visual pathway might constitute a translational model for assessing neurodegenerative changes and may increase our understanding of basic mechanisms underlying tissue damage in MS. Therefore, we used diffusion tensor imaging (DTI) of the visual pathway to obtain measurements of axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) in the optic nerves and tract of EAE mice.

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Discourse

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P436
Investigating blood-brain barrier integrity, immune cell infiltration and disease-related gender differences in a spontaneous transgenic mouse model for multiple sclerosis

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Background & Objectives: The TCR1640 transgenic mice carry a T cell receptor (TCR) specific for myelin oligodendrocyte glycoprotein (MOG) peptide 92-106 and develop spontaneous experimental autoimmune encephalomyelitis (EAE). The disease is more prevalent in female mice and most of them develop an EAE with a relapsing-remitting (RR) disease course whereas the majority of the males present a primary progressive (PP)-EAE. Our objective is to use this model to study different MS disease courses and distinct disease phases and to assess disease-related gender differences.

Methodology and Results: The blood-brain barrier (BBB) permeability and integrity of central nervous (CNS) tissues from TCR1640 mice at different phases in their disease (pro-symptomatic, acute relapse, remission, primary progressive chronic phase), based on their clinical score, was investigated using immunohistochemistry and in vivo tracer. A downregulation of adhesion and junctional molecules, together with increase in leakage (ZO-1, JAM-A, laminin and fibrinogen) in active phases of the disease, accompanied with CD4+ T cell infiltration that remains through remission phase was found. Moreover, intravenously (IV) injected fluorescent-labeled dextran particles indicated that the BBB permeability differs in the various disease stages.

To investigate disease related gender differences observed in these mice adoptive transfer experiments were performed. Immune cells from TCR1640 were injected IV in wildtype SJL/J mice in different combination of genders. Preliminary results shows that the disease course seems to be driven by the gender of the recipients that is: male recipients develop PP disease independently of the gender of the immune cell injected, whereas female recipients develop a RR passive EAE.

Conclusion: The BBB integrity and permeability is affected during the course of EAE in the spontaneous TCR1640 mice, emphasizing the relevance of this model in the study of MS. Moreover, the study of gender difference in this model seems to show that the gender of the recipient dictates the disease course inflicted by the injected cell.

Disclosure

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P437
IL-15 enhances pro-inflammatory T cell responses in multiple sclerosis and experimental autoimmune encephalomyelitis

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Background & Objective: Although it is well established that the immune system participates in the tissue destruction in multiple sclerosis (MS), the contribution of immune mediators to injury remains to be defined. Our group has identified interleukin-15 (IL-15) as a key factor in MS pathobiology. Notably, we have shown that IL-15 levels are elevated in both central nervous system (CNS) and peripheral blood of MS patients compared to controls. Therefore, we hypothesize that IL-15 contributes to the immune-mediated damage in MS and constitutes a valid target for the development of new therapeutics.

Methodology: We have evaluated the consequences of peripheral IL-15 administration in EAE pathology. We have evaluated the impact of IL-15 on CD4/CD8 T cell polarisation (Th1/Th17) and intracellular signalling (pSTAT3/pNFkB) in human immune cells isolated from MS patients and healthy donors using flow cytometry. We have assessed the expression of IL-15 and its receptors during the progression of the experimental autoimmune encephalomyelitis (EAE), the most common animal model of MS. We have evaluated the consequences of peripheral IL-15 administration on EAE pathology.

Results: Our data suggest that IL-15 enhances the Th1 polarisation in human CD8 T cells (elevated IFNγ/TNFα/GMCSF production). Moreover, IL-15 triggers a stronger pSTAT5 signalling in human memory CD4/CD8 T cells than in their naive counterparts, without any change in MS patients. In addition, a higher level of IL-15 mRNA expression in the CNS of EAE mice is measured at disease peak. The proportion of T-cells expressing IL-15 receptors chains is increased during EAE pathology. We found that CD4/CD8 T-cells bearing IL-15R display a pro-inflammatory profile as illustrated by higher expression of CD44, GMCSF or KLRG1 markers. Finally, the administration of IL-15 from disease onset in EAE mice aggravates clinical scores and increases the number of CNS-infiltrating T cells.

Conclusions: Altogether, our results indicate that IL-15 enhances pro-inflammatory T cell responses in human and augments murine EAE severity. Therefore, this cytokine represents a potential valid target in MS pathobiology.

Disclosure

Nothing to disclose
P438
Preferential axonal accumulation of mitochondria during cuprizone-induced demyelination

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Background and purpose: Axonal damage is the main factor contributing to permanent disability in Multiple sclerosis (MS). Organelle and vesicle transport is vital for the maintenance of axonal health, in which the distances between sites of organelle biogenesis, function, and recycling or degradation can be vast. There is evidence that focal accumulation of axonal mitochondria may be an essential requisite for degeneration of axons in MS. The purpose of this study was to investigate the kinetics and distribution of mitochondrial versus vesicle axonal transport deficits during the course of central nervous system demyelination.

Materials and Methods: Toxic demyelination was induced in C57BL/6J mice by cuprizone intoxication. Controls received normal chow. 3D-Electron Microscopy was performed to study mitochondrial transport deficits on the ultrastructural level. Anti-amyloid-precursor protein (APP) stains were performed to study vesicle-specific axonal transport deficits. Mitochondria-specific axonal transport deficits were visualized using anti-VDAC1 (voltage dependent anion channel 1; located in the outer mitochondrial membrane) and anti-COX IV (cytochrome-c-oxidase; located in the inner mitochondrial membrane) immunohistochemistry. Double-labeling experiments were performed for in-depth mitochondrial characterization.

Results: Ultrastructural 3D-reconstruction of the corpus callosum clearly showed an axonal mitochondrial as well as vesicle transport deficit early during cuprizone-induced demyelination. In some cases, mitochondrial and vesicle accumulation preceded axonal demyelination. After 5 weeks of cuprizone treatment, widespread accumulation of VDAC1- and COX IV-positive spheroids was present. Of note, COX IV-positive spheroids clearly outnumbered APP-positive spheroids. Just a minor number of spheroids (20%) were COX IV/APP double-positive.

Conclusion: Our results confirm previous observations that mitochondria and neuronal vesicles accumulate during the course of cuprizone-induced demyelination. It appears that there is a predominate impairment of the mitochondrial axonal-transport machinery. Further studies are now needed to understand the consequence of selective axonal transport deficits in MS.

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Kipp: nothing to disclose
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Hochstrasser: nothing to disclose

P439
Development of an in vitro myelination assay using mouse oligodendrocytes and a 3D scaffold of engineered nanofibers

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Background: Oligodendrocytes (OLs) are the only cells capable of generating myelin in vertebrate central nervous system (CNS). Myelinated axons are crucial for efficient and rapid conduction of action potential throughout the CNS. In multiple sclerosis (MS), pathological insults cause a loss of OLs, which in turn leads to demyelination, axon degeneration and ultimately irreversible neurological disability. Remyelinating therapies are the key for changing the long-term course of MS progression. One of the limiting steps in identifying potential remyelination therapies is a reliable and sensitive in vitro myelination system.

Objective: To develop a reliable in vitro myelination assay to evaluate the potential of remyelinating therapies using mouse oligodendrocytes.

Methods: Mouse oligodendrocyte progenitor cells (OPCs) were immunopurified from the cortex of postnatal mouse (P3-4) and cultured on a 3D matrix of PLL-coated engineered nanofibers in a 24-well plate. Mature myelinating OLs were identified by immunostaining with PLP and MBP antibodies. The number of myelinating OLs, the number of myelinated fibers and the length of the myelin sheath were quantified.

Results: There was a significant increase in the number of myelinating OLs in cultures treated with T3 compared to control (P<0.001 ). Moreover, there were significant increases in the total number of myelinated fibers and total length of myelin sheath in T3-treated wells compared to control (P<0.05). In the 3D nanofiber culture system, each OL myelinates multiple fibers, similar to what has been observed in vivo. Electron microscope analyses reveal that the myelin processes wrap around the nanofibers. Other agents have also been tested for myelination in this system as positive control.

Conclusion: Our data demonstrate a viable 3D in vitro system to differentiate mouse OPCs into OLs forming a multi-level layer of myelin wraps on nanofibers without axonal signaling. This system can be used effectively to evaluate the potential of remyelinating therapies. In addition, the use of mouse OLs in this culture system could provide a new avenue to investigate the mechanism of action of therapeutics by taking advantage of the mouse genetic system.

Disclosure
Conflict of Interest: Yan Yang, Brain Bai, Emily Berson, Simon Lunn and Vivek Shenoy, are full time employees of Renovo Neural, Inc. Jed Johnson and Nolan Kleinhennes are employee of Nanofiber Solution LLC. Grahame Kidd is a part time employee of Renovo neural, Inc. Bruce Trapp is an employee of Cleveland Clinic and a consulting Chief Scientific Officer of Renovo Neural. Bruce Trapp received compensation as a speaker or consultant for EMD Serono, Novartis and Biogen.

P440
Effect of ozanimod (RPC1063) on action potential parameters in adult human Purkinje fibres

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Background: Ozanimod (RPC1063) is an oral, once-daily immunomodulator that selectively targets sphingosine-1-phosphate

**Methods:** At pacing rates of 1 and 2 Hz (mimicking normal and elevated heart rates, respectively), human Purkinje fibres (PFs) from female hearts were used to evaluate the effects of ozanimod and fingolimod on AP duration (APD) at 30, 50, and 90% repolarization (APD₃₀, APD₅₀, and APD₉₀); and recognized pro-arrhythmia predictors (triangulation (ADP₉₀ - APD₃₀), shortterm variability (STV) of APD₉₀, and incidence of early afterdepolarizations (EAD)). Vehicle control (DMSO 0.3%) and flecainide (10 μM) were used to determine the stability and responsiveness, respectively, of the PFs.

**Results:** Ozanimod, up to a physiological concentration of 150 nM, had no significant effects on APD and did not increase the manifestation of pro-arrhythmia markers or induce beat escape (BE; electrical stimulus does not trigger an AP after full repolarization). Although fingolimod, up to a concentration of 500 nM, also had no significant effects on APD, triangulation, or EADS, it did elicit an increase in STV (APD₉₀). Moreover, 50 nM fingolimod showed BE, which was more pronounced at 500 nM, and flecainide (10 μM) were used to determine the stability and responsiveness, respectively, of the PFs.

**Disclosure**

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P. Frohna, Shareholder: Celgene.
G. J. Opiteck, Shareholder: Celgene.

**P441**

**Differential effects of primary and secondary progressive MS cerebrospinal fluid on motor function and spinal cord pathology**

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**Background:** Primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS) patients all experience neurological decline over time. However, there are differences in their lesion distribution and extent of inflammation. It remains unclear whether the pathophysiological mechanisms contributing to clinical progression in PPMS and SPMS are the same.

**Objectives:** To establish an experimental model to investigate disease pathogenesis underlying PPMS and SPMS.

**Methods:** Mice underwent laminectomies at cervical levels 4 and 5 to expose the underlying spinal cord and cerebrospinal fluid (CSF) was injected under the dura mater into the subarachnoid space. Control animals were injected with saline or CSF from healthy donors. Functional deficits were assessed by evaluating forelimb reaching, gripping and tail rigidity at 1 day post injection (DPI), 3 DPI, and 7 DPI. Mice were perfused at these same time points following CSF delivery. Spinal cords were post-fixed overnight in 4% paraformaldehyde, cryoprotected in 30% sucrose, then cryosectioned for histological analyses. RNA was extracted from cervical spinal cords at 1 DPI for qPCR analyses.

**Results:** Mice injected with PPMS CSF displayed significantly higher behavioral deficit scores in comparison to mice injected with SPMS and control CSF. Mice injected with SPMS CSF did not show functional impairments and scores were not statistically different from controls. Spinal cords from mice injected with PPMS CSF exhibited evidence of astrogliaosis at all time points examined, as revealed by significantly increased GFAP immunostaining in the dorsal white matter. However, astrogliaosis was not observed in mice injected with SPMS CSF. Similarly, a significant increase in immunostaining intensity for SMI-32, a marker of axonal damage, was observed in mice injected with PPMS CSF, but not SPMS CSF. In contrast, db1 immunostaining was similar in all groups, suggesting that microglia do not play a major role in contributing to deficits and pathology observed in PPMS CSF-injected mice. Preliminary qPCR data show that PPMS CSF-injected mice have greater changes in GFAP mRNA expression than other groups.

**Conclusions:** Motor deficits and spinal cord pathology are induced by PPMS CSF, but not SPMS CSF, suggesting that pathophysiological mechanisms underlying PPMS and SPMS may be different and merit further investigation.

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Jamie K. Wong: Nothing to disclose
Nathan J. Kung: Nothing to disclose
Jessie Z. Huang: Nothing to disclose
Saud A. Sadiq: Nothing to disclose

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**Genetics/Epigenetics**

**P442**

**NINJ2 as a novel protein involved in response to Interferon-β in multiple sclerosis**

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**Background:** NINJ2 is a novel protein involved in response to Interferon-β in multiple sclerosis.

**Objectives:** To establish an experimental model to investigate disease pathogenesis underlying PPMS and SPMS.

**Methods:** Mice underwent laminectomies at cervical levels 4 and 5 to expose the underlying spinal cord and cerebrospinal fluid (CSF) was injected under the dura mater into the subarachnoid space. Control animals were injected with saline or CSF from healthy donors. Functional deficits were assessed by evaluating forelimb reaching, gripping and tail rigidity at 1 day post injection (DPI), 3 DPI, and 7 DPI. Mice were perfused at these same time points following CSF delivery. Spinal cords were post-fixed overnight in 4% paraformaldehyde, cryoprotected in 30% sucrose, then cryosectioned for histological analyses. RNA was extracted from cervical spinal cords at 1 DPI for qPCR analyses.

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**Disclosure**

Jamie K. Wong: Nothing to disclose
Nathan J. Kung: Nothing to disclose
Jessie Z. Huang: Nothing to disclose
Saud A. Sadiq: Nothing to disclose

Funding source: Tisch MS Research Center of New York (private funds)
Introduction: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration. Several therapies are available for MS treatment, however clinical response is heterogeneous and a more personalized approach is needed to maximize treatment efficacy. In this context, using a genome-wide association approach on 337 Interferon-β (IFNβ) treated Italian MS patients, we previously identified rs7298096 as genetic marker of the long-term clinical response to treatment. In the present study, we aim to understand the role of rs7298096 in influencing the response to IFNβ treatment.

Methods: A total of 616 IFNβ-treated MS patients have been recruited across 4 centers (discovery cohort: n=456 Italian patients, replication cohort: n=160 patients from Spain and Australia). The association between rs7298096 and the time to first relapse (TTFR) after treatment start was evaluated using a survival analysis on 4-years follow-up. We also run eQTL analysis between rs7298096 and NINJ2 expression using the GTEx repository and in vitro effects of IFNβ on peripheral blood mononuclear cells were also evaluated.

Results: An association between rs7298096 and TTFR was observed in the Italian cohort (P=0.032) and confirmed in the replication cohort (P=0.03), with rs7298096, associated with a longer TTFR (meta-analysis: HR=1.54, P=0.003). This SNP is located ~3.3kb upstream the NINJ2 gene in a putative enhancer region. Follow-up analyses confirmed a significant eQTL association between the SNP and NINJ2 gene expression in whole blood (P=2.6x10^-6; β=0.18), with the G allele associated with a lower expression. Moreover, we observed that IFNβ stimulation downregulates NINJ2 expression both in vitro (p=3.1x10^-8) and ex vivo (P< 0.05), and that an increase of NINJ2 expression after 1 month of treatment is associated with a shorter TTFR (HR=0.22, P=0.021).

Conclusions: Results suggest that rs7298096 and NINJ2 are associated with disease activity during IFNβ treatment in MS patients. We can speculate that NINJ2, an adhesion molecule, is implicated in the transmigration of immune cells to the CNS and that rs7298096 represents a genetic variant that modulates this process. These data support further studies aimed to characterize the role of NINJ2 in multiple sclerosis inflammatory processes.

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P443
An alternatively spliced isoform of HLA-DRA may be implicated in multiple sclerosis

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Background: The strongest disease association signal genome-wide in MS maps within the major histocompatibility complex (MHC). This multi-genic and multi-allelic association has been

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observed across all populations studied, but has not been fully decoded yet. The lower linkage disequilibrium in African Americans compared to Europeans provides an opportunity to further fine-map this key disease risk locus and better describe the allelic heterogeneity driving susceptibility.

**Goals:** Fine-map HLA in an African American MS cohort.

**Methods:** 1,305 African American MS cases and 1,155 controls were genotyped on the custom MS Chip. The MHC region is densely covered with ~7,000 SNPs allowing for a deep analysis of the locus and robust imputation of classical HLA alleles. 651 samples with existing two-field HLA-A, B, C, DRB1 and DQB1 genotyping were used to train HLA imputation models for the remaining 1,809 individuals. HLA association with MS was tested using a logistic regression model, and SNPs outside classical HLA loci were examined to fine-map extended HLA haplotypes. We used data from the 1KG RNA-seq project to assess allelic-specific expression variance.

**Results:** We replicated the association of A*02:01 (p=1.7x10^-4, OR=0.71) and DRB1*15:01 (p=1.2x10^-4, OR=1.84). We also identified a previously unrecognized class I protective allele B*53:01 (p=8.5x10^-4, OR=0.7), a private African allele. Despite differing in a single amino acid at position 30 with DRB1*15:01, the African DRB1*15:03 allele is not associated with MS in this dataset. Interestingly, 15:01 or 15:03 were found to segregate exclusively with a seven SNPs haplotype, and it includes rs8084 [A/C], a splice acceptor variant for HLA-DRA. Alternative splicing has been previously shown to result in expression of a short (-25 amino acids) DRA transcript. Our analysis of the 1KG RNA-seq dataset shows significantly higher relative abundance of the short transcript associated with the DRB1*15:01-linked SNP (A) (p=2.8x10^-11).

**Conclusions:** We identified a new class I protective allele, B*53:01, which is found at high frequency in African but not European populations. We show that a DRB1*15:01-linked SNP leads to expression of an alternative DRA transcript with a predicted functional protein and important implications for the HLA class II heterodimer in MS susceptibility. Analysis of public tissue specific protein databases suggests the alternate transcript may be preferentially expressed in the brain.

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**P444**

**Association of smoking but not HLA-DRB1*15:01, APOE, or body mass index with brain atrophy in early multiple sclerosis**

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**Background:** The course of multiple sclerosis (MS) shows substantial inter-individual variability. The underlying determinants of disease severity likely involve genetic and environmental factors. Previous studies have reported a role of APOE, HLA, body mass index (BMI), and smoking in the long-term course of MS.

**Objective:** The aim of this study was to assess the impact of APOE and HLA polymorphisms as well as smoking and BMI in the very early MS course.

**Methods:** The study was based on 263 untreated patients with a diagnosis of relapsing-remitting (RR)MS within two years and patients with a diagnosis of clinically isolated syndrome within six months prior to study enrollment. All patients were recruited in a multicenter effort in Germany from the German Competence Network Multiple Sclerosis (KKNMS) and underwent standardized 3 Tesla MRI protocols. Genotyping was performed for the single-nucleotide polymorphisms (SNPs) rs3135388 tagging the HLA-DRB1*15:01 haplotype as well as for rs7412 (e2) and rs429358 (e4) in APOE. Linear regression analyses were applied based on the three SNPs, smoking and BMI as exposures and MRI surrogate markers for disease severity, i.e. gray matter fraction and brain parenchymal fraction, as outcomes.

**Results:** Current smoking was significantly associated with reduced gray matter fraction in comparison to non-smoking. Smoking was also nominally significantly associated with reduction in brain parenchymal fraction; however, the latter result did not withstand multiple testing correction. BMI and the SNPs in HLA and APOE were not associated with structural MRI parameters.

**Conclusions:** Smoking has an unfavorable effect on the gray matter fraction already in early MS as a potential measure of MS severity. These findings may impact patients’ counseling upon initial diagnosis of MS.
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RG serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, and Novartis; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Novartis; serves as editor for Therapeutic Advances in Neurological Diseases and on the editorial boards of Experimental Neurology and the Journal of Neuroimmunology; and receives research support from Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, Genzyme, Merck Serono, and Novartis, none related to this work.

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CL holds an endowed professorship supported by the Novartis foundation, has received consulting and speaker’s honoraria from Biogen-Idec, Bayer Schering, Novartis, Sanofi, Genzyme and TEVA, and has received research scientific grant support from Merck-Serono and Novartis.

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P445
A whole-genome sequencing study associates GRAMD1B with multiple sclerosis risk and disease activity
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Background: While the role of common genetic variants in multiple sclerosis (MS) has been identified in large GWAS studies, the contribution of rare variants to MS remains unclear.

Objectives: To identify low frequency and rare genetic variants contributing to MS susceptibility in an Italian multiplex family.

Methods: SNP microarray genotyping and whole-genome sequencing in 4 affected and 4 unaffected relatives of a consanguinous Italian multiplex family was performed. The Merlin software was used for linkage analyses and in-silico predictive tools (GATK, SNPeff, GERP++RS and Polyphen 2 HDIV software) were applied to filter rare variants. To deeply screen the GRAMD1B locus, a target sequencing approach was applied in 91 unrelated MS patients with at least one first or second-degree MS-affected relative. GRAMD1B gene expression in rat cells and tissues and in human peripheral blood immune cells were evaluated by qRT-PCR, while the protein expression was evaluated in immune and brain cells and brain tissues by immunofluorescence.

Results: Filtering criteria identified a missense c.1801T>C (p.S601P) variant in GRAMD1B gene located under a linkage peak (LOD: 2.194) and segregating according to a recessive model (p=0.02). Interestingly, using target sequencing we identified 2 additional variants only in cases, located very close to S601P (rs755488531 and rs769527838). Burden test analysis identified an excess of alternative alleles of p.S601P (rs755488531 and rs769527838). Burden test analysis identified an excess of alternative alleles of p.S601P (rs755488531 and rs769527838). Burden test analysis identified an excess of alternative alleles of p.S601P (rs755488531 and rs769527838). Burden test analysis identified an excess of alternative alleles of p.S601P (rs755488531 and rs769527838).

Peak (LOD: 2.194) and segregating according to a recessive (p=S601P) variant in GRAMD1B gene located under a linkage

Conclusions: These findings suggest a role of GRAMD1B in inflammation and disease pathophysiology and open new avenues of investigation.

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P446
Genotype is predicting multiple sclerosis lesion activity in autopsy cohort of the Netherlands Brain Bank
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Background: Multiple Sclerosis (MS) is both clinical and pathological a heterogeneous disease. We hypothesize SNPs contribute to differences in pathogenic mechanisms in subgroups of MS macrophages. Notably, GRAMD1B protein was significantly downregulated by vessel-associated astrocytes in active MS lesions (p<0.05) and by inflammatory stimuli in primary astrocytes (p=0.007) and peripheral monocytes (p=0.002), and the down-regulation was paralleled at mRNA level (p=0.029) suggesting a possible role of the gene in the modulation of inflammatory responses and disease pathophysiology.

Conclusions: These findings suggest a role of GRAMD1B in inflammation and disease pathophysiology and open new avenues of investigation.
patients leading to differences in MS lesion pathology, clinical disease course and response to immunomodulatory therapy.

**Methods:** 183 MS patients were included, all archived tissue (n=3615 tissue blocks) was characterized with HLA-PLP immunohistochemistry. Reactive sites, active-, chronic active-, inactive- MS lesions, remyelinated regions, and cortical grey matter lesions were quantified. 105 SNPs were selected based on association with clinical disease severity or MRI measures in GWAS (Baranzini 2009, Brynedal 2010, IMSGC 2011). SNPs were included with minor allele frequency (MAF)>0.02 and linkage disequilibrium (LD)<0.8 with other SNP in the selection. DNA was isolated from leukocytes or frozen cerebellum tissue. Competitive allele specific polymerase chain reaction (PCR) was performed by LGC genomics for 105 SNPs. SNPs were related with total white matter lesion load, proportions of lesion subtypes, cortical grey matter lesion presence/absence using generalized linear models including sex. Multiple testing correction was performed using Benjamini-Hochberg. SNPs that showed a significant relation with MS pathology were tested for an effect on mRNA expression with qPCR on RNA isolated from superior temporal gyrus (n=40 patients).

**Results:** All SNPs are in Hardy Weinberg Equilibrium in our cohort (HWE). 10 SNPs show a significant relation with MS pathology after multiple testing correction. 4 SNPs show a relation with proportion of active lesions, 3 SNPs with proportion of lesions with foamy microglia/macrophages and 3 SNPs with either reactive site load, cortical grey matter lesion presence or proportion of remyelinated regions. The most significant SNP relating to the proportion of active lesions also shows a significant relation with mRNA expression in superior temporal gyrus.

**Discussion:** This analysis shows that SNPs, that were previously related to clinical disease severity or MRI measures, can now be related to histologically determined MS lesion pathology in the Netherlands Brain Bank MS autopsy cohort. Relating SNPs to MS pathology helps to better understand MS lesion pathogenesis in subgroups of MS patients. Most importantly, these SNPs are a potentially useful prognostic marker in clinical practice.

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**P447**

Investigating the role of the major histocompatibility complex on multiple sclerosis in an admixed Hispanic population

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The Major Histocompatibility Complex (MHC), located on chromosome 6p21.3, has long been known to demonstrate the strongest genetic association with multiple sclerosis (MS) risk, on its own explaining ~10% of the sibling recurrence risk. The most extensively studied and replicated association has been seen with HLA-DRB1*15:01, demonstrating the strongest genetic effect in Europeans and African Americans. However, the complex genomic structure of the region has made it difficult to comprehensively identify risk alleles across populations. The region has been most studied in individuals of Northern European ancestry, with additive and dominant effects for at least 13 different alleles. However, MHC variation across populations is high, with various population-specific alleles and allele frequency differences noted, and so those alleles may not be the most relevant in all populations. To assess MHC variation in Hispanic populations, we performed association analyses using genotype data from a custom Illumina array which were available on 1222 Hispanic MS cases and 1339 controls from sites across Puerto Rico and both the east and west coasts of the United States. Single Nucleotide Polymorphisms (SNPs) which tag (R^2>0.2) 9 of the 13 published alleles were available. Association with MS was confirmed for 5 of the 9 in this Hispanic sample (p ≤ 0.05) including HLA-DRB1*15:01, HLA-DOA1*01:01, HLA-DQB1*03:02, HLA-A*02:01, and rs9277565 (correlated with HLA-DPB1). However, association was not confirmed (p > 0.05) for HLA-DRB1*08:01, HLA-B*55:01, HLA-B*44:02, and rs2229092 (missense in LTA).

Utilizing conditional linear modeling (p ≤ 1.0E-05) within the extended MHC on chromosome 6 from 27 to 34 Mb, the three most strongly associated independent signals observed were HLA-DRB1*1501 (OR = 2.45, p = 1.06E-22), rs9277565 (OR = 1.55, p = 5.80E-08), HLA-A*02:01 (OR = 0.75, p = 9.42E-07), and an intronic SNP in NFKB inhibitor like 1 (NFKB1) which serves as an eQTL for both DEXD-box helicase 39B (DDX39B) and natural cytotoxicity triggering receptor 3 (NCR3) in lymphoblastoid cell lines (OR = 0.66, p = 5.80E-06). Further work is being done to characterize the local ancestry across each of these loci. This detailed investigation of the MHC provides a first step towards uncovering the MHC risk for MS in admixed Hispanic populations and chronicling the ancestral lineage of MHC risk haplotypes.

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P448
A genetic risk variant for multiple sclerosis modulates the processing of CD58 mRNA and microRNA-548ac from the same transcript

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More than a hundred genetic risk loci for multiple sclerosis (MS) have been identified. Functional analyses of these variants are needed to better understand the biological processes related to disease pathogenesis. We explored whether MS-associated single nucleotide polymorphisms (SNPs) within the first intron of the CD58 gene influence the expression of the intronic primate-specific microRNA hsa-mir-548ac.

Expression quantitative trait locus (eQTL) analyses were performed using public microarray data of HapMap populations (n=726 individuals), public RNA-sequencing data of the Geuvadis project (n=465 individuals) and own real-time PCR data (n=32 MS patients). Analysis of variance (ANOVA) was used to test the relationship between CD58 gene expression, hsa-miR-548ac levels and the number of MS risk alleles (defined either by SNP rs1335532 or SNP rs1414273) carried by each individual. Welch t-tests were calculated for pairwise comparisons of genotype groups. Statistical significance was defined as p-value<0.05.

The genetic susceptibility variant for MS was associated with significantly lower CD58 mRNA levels in the HapMap cohort and in the Geuvadis cohort. On the other hand, significantly increased levels of hsa-miR-548ac were seen in risk allele carriers in the Geuvadis data. The inverse eQTL effect suggests a genotype-dependent processing of both mRNA and microRNA from the same primary transcript. Moreover, CD58 and hsa-miR-548ac were not strictly coexpressed across different immune cell populations, with elevated levels of the microRNA seen in CD4+ T helper cells.

To conclude, we provide evidence that the causal SNP of the CD58 gene locus is located in the hsa-miR-548ac stem-loop sequence. Further experiments are currently performed to quantify the effect of the respective alleles on the kinetics of Drosha processing and to screen for target genes of this microRNA. We postulate similar eQTL effects for other members of this microRNA family.

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P449
Expression profile of long non-coding RNAs (lncRNAs) in serum of patients with progressive multiple sclerosis

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The pathobiology of Multiple Sclerosis (MS) includes inflammatory and neurodegenerative mechanisms that affect both white and gray matter. The course of MS is heterogeneous and confident prediction of long-term individual prognosis is not yet possible. Thus, guiding research towards distinguishing reliable biomarkers for every independent MS pathogenic factor is of primary importance. There is now a growing interest in long non-coding RNA (lncRNAs) as potential biomarkers that could provide information predicting disease activity and progression.

In a previous study we showed specific over-expression of three circulating lncRNAs in the serum of relapsing-remitting MS (RR-MS) patients: nuclear paraspeckle assembly transcript 1 (NEAT1), taurine up-regulated 1 (TUG1) and 7SK small nuclear RNA (RN7SK RNA).

NEAT1 promotes the increase of CXCL8 expression of the gene encoding Interleukin 8 via relocation of SFPQ splicing factor, TUG1 is a component of the p53 regulatory network and RN7SK RNA is involved in regulation of CD4+ T lymphocytes. These lncRNAs play an important role in neurodegenerative processes.

In the present study we analyze expression profile of lncRNAs in the serum of secondary progressive MS (SP-MS) patients to identify any lncRNAs specifically expressed in progression phase of the disease.

Materials and Methods: We screened 84 lncRNAs, involved in autoimmunity and human inflammatory response, in the serum of SP-MS patients (n=12) and age-matched controls (n=12).

In order to evaluate lncRNAs expression levels, we used Real-Time PCR and validated PCR array of human inflammatory response/autoimmunity using as analysis criteria: fold change >2 and p<0.05.

Results: We identified two lncRNAs up-regulated in SP-MS patients compared to controls: TUG1, fold change = 7.00 (p = 0.02) and AC104820.2, fold change = 9.60 (p = 0.04).

Discussion: Unlike RR-MS, in SP-MS patients only TUG1 is significantly up-regulated. Instead AC104820.2 is only expressed in SP-MS. This lncRNA is strongly expressed in CD8 T-cells that are known to be involved in axon and myelin loss through a possible cytotoxic effect.

Conclusions: Different MS phenotypes seem to have a specific lncRNA expression profile. Altered epigenetic gene regulation involved in neurodegenerative mechanisms could have an important role in MS pathology. Additional data in larger cohort of MS patients at different stage of the disease are needed to better understand lncRNAs role in MS.

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P450
An integrated candidate gene study of response to fingolimod in relapsing remitting multiple sclerosis patients

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Background: Fingolimod (FTY) is the first oral drug approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Despite its confirmed effectiveness, treatment response is heterogeneous and may be suboptimal, enhancing the need for biological markers of response.

Aim: To investigate genetic determinants of response to FTY adopting an extensive candidate-gene strategy according to data-driven and knowledge-driven approaches, in a cohort of RRMS patients followed for 2 years at San Raffaele Hospital.

Methods: 255 RRMS subjects were genotyped on the Illumina Human OmniExpress BeadChip. We selected genes to be tested for association as following:

1. genes belonging to the Sphingolipid signaling pathway in the KEGG database;
2. genes modulated by FTY in B-cells, T-cells and monocytes in an RNA-seq experiment conducted internally on 24 RRMS patients;
3. genes encoding for transcription factors drawn from co-expression and promoter analyses of the selected differentially expressed genes, as possible key regulators of the observed transcriptional changes. Association analyses were carried out at the gene level using VEGAS and SKAT tools. Patients were classified in responders (R) and non-responders (NR) according to the clinical and MRI activity recorded during the 2-year follow-up. Time to first relapse (TFR) for also considered as additional outcome response.

Results: The cohort was composed of 135 R and 70 NR. For the TFR analyses, 51 relapses were recorded during the follow-up. The final constructed panel of candidates included 1,480 genes, with 43k mapping SNPs. Gene-level analyses revealed ARNTL (p=1.6x10^{-5}, adjusted-p=0.024) as being associated to response when comparing R vs NR. ARNTL is an essential component of the mammalian clock gene regulatory network, and it is known that the disruption of the internal clock may be associated to inflammatory diseases. MCTP1 (p=3.3x10^{-5}, adjusted-p=0.025) appeared to be associated to TFR outcome. MCTP1 contains calcium-binding domains found in proteins involved in signal transduction and membrane trafficking and is expressed in neurons where it seems to regulate cellular vesicle retrieval and oxidative stress.

Conclusions: Our strategy contributed to the identification of genes that appear to be associated to response. These results need to be replicated in independent cohorts, but could provide hints for the heterogeneity in FTY response, towards a more personalized treatment choice and management.

Disclosure

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L. Moiola received honoraria for speaking at meetings or for attending to advisory board from Sanofi-Genzyme, Biogen-Idec, Novartis and TEVA.
these 123 genes and 2200 differentially methylated probes (obtained using NPC, between RRandHC and SPandRR) and identified a novel candidate gene associated to motility and migration of cells.

Conclusions: The results of this study emphasize the benefits of using omics integration approaches in studying complex autoimmune diseases such as MS. These findings provide additional evidence for the diminished role for T cells in SP along with new insights into the immune and molecular mechanisms underlying MS progression in T cells.

Keywords: Multiple Sclerosis, Non-Parametric Combination, T Cells, RNA Seq, DNA Methylation, Omics Integration.

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Immunology

P452
DICAM: a new player in multiple sclerosis pathogenesis
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The earliest cellular and molecular events that lead to lesion formation in multiple sclerosis (MS) include a disruption of the blood-brain barrier (BBB) and migration of leukocytes from the periphery into the central nervous system (CNS). Pathogenic TH17 lymphocytes are important contributors of (MS) lesion formation. They express pro-inflammatory cytokines and factors, and are known to migrate more readily across CNS barrier, including the blood-brain barrier (BBB). Using proteomic and RNA sequencing techniques, we identified a new member of the immunoglobulin superfamily Dual Ig domain containing Cell Adhesion Molecule (DICAM) on a subset of human TH17 lymphocytes and human BBB endothelial cells. DICAM is known to interact with itself and with avb3 integrin, expressed by endothelial cells (ECs). While expression and function of DICAM in MS remains unexplored. The current study aims to evaluate the role of DICAM in the migration of encephalitogenic TH17 lymphocytes to the CNS and it inflammation. To do that we used primary cultures of human BBB-endothelial cells (BBB-ECs), ex-vivo and in situ studies on MS samples as well as in vivo experiments using animal models of MS.

Our results show that DICAM expression is strongly associated with expression of ROR-γ, IL-23R, IL-17, IL-22, GM-CSF and GZMB. These unprecedented data demonstrate that DICAM is specifically expressed on the surface of potentially encephalitogenic TH17 lymphocytes and that expression of DICAM is regulated by IL-23, IL-1b and IL-6, cytokines which are involved in CNS autoimmune diseases. Furthermore, the proportion of DICAM+ CD4+ lymphocytes is significantly increased in the blood and CNS of MS patients compared with healthy controls. Same is observed in experimental autoimmune encephalomyelitis (EAE) animals. Also DICAM expression is upregulated at the blood-brain barrier within inflammatory lesions. Moreover, blockade of DICAM restrict the migration of TH17 lymphocytes across blood-brain barrier endothelial cells and decrease the severity of EAE.

This work aims to characterize the interaction between aggressive TH17 lymphocytes and BBB, via this new identified cell surface protein DICAM. This interaction might be involved in the pathology of MS and therefore, this work may lead to the identification of a new therapeutic target for MS treatment.

Disclosure
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P453
Non-canonical autophagy drives CD4+ T cell reactivation during autoimmune CNS inflammation
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Reactivation and expansion of autoreactive CD4+ T cells within the central nervous system (CNS) are considered to play a key role in the pathogenesis of multiple sclerosis and its animal model experimental autoimmune encephalomyelitis (EAE). Autophagy-related proteins (ATGs) deliver antigens into MHC class II-containing compartments (MHCs) for recognition by CD4+ T cells. The autophagy protein ATG5 is essential in recruiting intracellular substrates for lysosomal degradation during canonical macroautophagy. In addition, ATG5 is required for LC3-associated phagocytosis, a non-canonical autophagy pathway which delivers extracellular, endocytosed material to lysosomes and MHCs and can be induced upon recognition of phosphatidylserine (Ptd-L-Ser)+ dying cells. Here, we report that mice deficient in the autophagy protein ATG5 in CD11c+ cells (DC-ATG5−/−) are resistant to EAE development following adoptive transfer (AT-EAE) of
myelin-specific CD4+ T cells. DC-Atg5-/- mice showed substantially lower frequencies of activated CNS-infiltrating CD4+ T cells while the frequency of CNS-infiltrating CD8+ T cells were similar. Although limited in expansion, effector cytokine production by CNS-infiltrating CD4+ T cells was unaltered in DC-Atg5-/- mice as compared to control littermates (DC-Atg5+/-). Loading of DCs with surface Ptd-L-Ser-expressing oligodendroglial cells (ODGs) resulted in higher myelin-specific CD4+ T cell activation as compared to low surface Ptd-L-Ser-expressing ODGs. Increased T cell activation upon loading with Ptd-L-Ser-expressed ODGs was abrogated in ATG5-deficient DCs. Our data demonstrate a requirement for ATG5 in CD11c+ APCs in driving the re-activation of myelin-specific CD4+ T cells during the effector phase of EAE and suggest that LC3-associated phagocytosis of dying ODGs augments T cell-mediated CNS injury during autoimmune neuroinflammation.

**Disclosure**

All authors have declared that no conflict of interest exists.

**P454**

**The T<sub>H</sub>17-associated cytokine IL-26 enhances BBB integrity: implications for MS**

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Pathogenic T helper (T<sub>H</sub>17) cells play a major role in multiple sclerosis (MS). Cytokines expressed by these cells, IL-17 and IL-22, have been shown to compromise the blood-brain-barrier (BBB). BBB disruption is an important early event in MS, which allows recruitment and migration of peripheral immune cells into the central nervous system. IL-26 is a T<sub>H</sub>17 cell associated cytokine, which signals through its heterodimeric receptor, IL-26R. This receptor was also found in MS brain tissue on choroid plexus in patients with multiple sclerosis.

**Results:** Our results showed that IL-26 is mainly expressed by T<sub>H</sub>17 differentiated cells in HC and MS patients. Moreover, we found CD4+IL-26+ cells in perivascular infiltrates in MS brain tissue. Next, we showed that HBEC express the heterodimer IL-26R. This receptor was also found in MS brain tissue on endothelial cells. Treatment of an HBEC single cell layer with rhIL-26 showed a reduced permeability and an increased resistance. Finally, our in vivo data in mice with EAE showed that rhIL-26 treatment started before disease onset resulted in a reduced extravasation of IgG and fibrinogen into the spinal cord at peak of disease compared to HBSS treated mice. Moreover, there was a significant reduction in disease severity in the IL-26 treated group.

**Conclusion:** Although IL-26 is mainly a T<sub>H</sub>17 associated cytokine, it promotes BBB integrity in vitro and in vivo. Moreover, it reduces disease severity in EAE.

**Disclosure**

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**P455**

**CNS-transmigration of distinct B-cell subsets through the choroid plexus in patients with multiple sclerosis**

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**Background:** The role of B lymphocytes in MS immunopathogenesis is increasingly recognized. B cells undergo compartmentalized redistribution in blood and cerebrospinal fluid (CSF) during active MS, whereby antigen-experienced memory B-cells accumulate in the CSF. While trafficking of B cells across the blood-brain barrier has been intensively investigated, cellular dispersion through the blood-CSF barrier (BCSFB) is incompletely understood.

**Goals and objectives:** To investigate the interaction of B cells with the choroid plexus to transmigrate into the CSF.

**Methods:** We isolated B cells and B-cell subsets from peripheral blood samples of healthy donors (HC) and MS patients, utilized an inverted transwell culture system of human choroid plexus papilloma (HIBCPP) cells to determine transmigration rates of distinct B-cell subsets, and immunofluorescence microscopy to analyze their migration route through the epithelial barrier. Experiments were completed by cytokine assays and RT-PCR to determine cytokines/chemokines mediating B-cell transmigration.

**Results:** Transmigration rates of both HC- and MS-derived B cells across HIBCPP were initially low, significantly increased in response to B-cell specific chemokines (including CXCL-12, -13), and were further enhanced following pre-activation (CPEG-ODN, CD40/IgM). Migrated cells predominantly exhibited a CD27+ memory phenotype. Interestingly, chemotactic activities of MS-derived memory B cells were higher when compared with HC-derived cells. Exposure of HIBCPP to pro-inflammatory cytokines cytokine assays and RT-PCR to determine cytokines/chemokines mediating B-cell transmigration.

**Conclusion:** Further investigations are necessary to determine the role of B cells in MS immunopathogenesis.
stimuli induced distinct changes in their cytokine/chemokine profiles and permeability during B-cell transmigration.

**Conclusions:** Our findings provide new information on how antigen-experienced B-cell phenotypes and the BCSFB act together to facilitate aberrant B-cell accumulation in the CSF of MS patients.

**Disclosure**

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**P456**

Gene-expression analysis of blood memory CD8+ T cells at the single-cell level reveals a specific pattern of clonally expanded cells in multiple sclerosis patients

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**Background:** A body of evidence highlights the involvement of CD8+ T cells in Multiple sclerosis (MS). We have recently demonstrated that overrepresented (oligoclonal) CD8+ T cells found at lesion sites, thought to be driven by local cognate antigens, are the same overrepresented T cells found in the CSF of the same patients and represent up to 47% of the overrepresented blood CD8+ T cells. Based on these previous results, the CSF and the blood can be used as a source of T cells involved in the disease process. However, to date we have not identified yet, in the periphery, the culprit CD8+ T cells driving autoimmune inflammation nor their phenotype and/or function. Our working hypothesis is that the cells able to provoke damages in the CNS may have a specific phenotypic or functional pattern.

**Methods:** To analyze single-cells molecular signatures, we isolate single memory CD8+ T cells from the blood and CSF from MS patients, Healthy Controls (HC) and patients with other neurological diseases (OND) and performed amplifications of 96 well-chosen genes together with their TCR Vβ chain. In parallel, we performed a TRBV deep immunosequencing on a pool of memory CD8+ T cells to identify the expanded clones in the samples.

**Results:** We observed a clear clustering of MS single-cells highly different from HC and OND with numerous genes involved in T cell activation, effector function, cytotoxicity, and cell migration.

Moreover, when analyzing the molecular profile of oligoclonally expanded CD8+ T cells, we observed that they harbor a specific pattern with an increased expression of activation genes. Finally, we also found only in MS patients and not in OND that the CSF CD8+ T cells and those from the blood have a similar profile with expression of migration markers allowing blood CD8+ T cells to migrate to the central nervous system (CNS).

**Interpretation:** Our data are the first to describe a specific molecular pattern of memory CD8+ T cells from blood and CSF in MS patients and to link this pattern to the cell clonality. We detect a specific signature of MS single cells orienting the cells toward an activated, effector and cytotoxic profile and allowing the cells to migrate to the CNS.

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cells were able to migrate freely within microglia and to escape from microglial engulfment. Our observations point towards a novel capacity of microglia to antagonize invading T lymphocytes during neuroinflammation, revealing a new target mechanism for the therapeutic treatment of neuroinflammatory diseases.

Disclosure

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P458

Persistent clonally related CSF B cells in multiple sclerosis: a longitudinal immune repertoire study

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Objective: Determine stability across time of clonally related cerebrospinal fluid (CSF) B cells in patients with multiple sclerosis (MS).

Background: Anti-CD20 therapy efficacy highlights the need to better understand the role B cells play in MS pathophysiology. We investigated whether related B cell clonotypes persist in the CSF over time.

Design and Methods: IgM and IgG B cell receptor (BCR) heavy chain variable region immune repertoires were generated on an Ion Torrent machine using RNA extracted from CSF and peripheral blood B cells of ten MS patients at an untreated time point (a) and at a later time point (b) (1.18 years later +/- 0.28). A custom bioinformatics pipeline based on MiXCR identified CDR3 sequences. Clonally related BCRs were identified by comparing CDR3 sequences using a distance metric approach.

Results: In five of the ten patients, related CSF B cell clonotypes were found at both time points. Persistent clonally related B cells were more often plasmablast/plasma cell (15/31) and switched memory (14/31) phenotype rather than unswitched memory (1/31) double negative (1/31) or naïve (0/31). Persistent CSF B cell relatives’ CDR3s were unique to each patient.

Conclusions: To our knowledge, this is the first longitudinal B cell immune repertoire study in the CSF compartment of MS patients. Persistent related CSF B cells are more likely to be found in patients with a recent relapse, suggesting that recurring recruitment or intrathecal persistence of disease-associated B cells may be a marker of active relapsing disease. These persistent B cell clonal relatives will also serve as a population to further investigate at a single cell level.


Disclosure

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P459

The nuclear receptor Nur77 restricts T cell responses and limits central nervous system autoimmunity

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The orphan nuclear receptor Nur77 is involved in various biological processes such as metabolism, apoptosis and inflammation. Nur77 is upregulated in T cells during T cell receptor (TCR)-mediated clonal deletion of immature thymocytes. Therefore, we investigated the role of Nur77 in modulation of human and murine T cell responses in vitro. Further, we characterised autoreactive T cell responses in vivo by using the animal model of Multiple Sclerosis (MS), i.e. experimental autoimmune encephalomyelitis (EAE). Nur77-deficiency in T cells resulted in either increased proliferation compared to wildtype T cells and an enhanced potential to differentiate into pathogenic Th1 and Th17 cells. This may be due to a metabolic advantage in Nur77 deficient T cells. In vivo, Nur77 knockout mice exhibited a significantly aggravated EAE disease course after active immunization with MOG35-55 peptide, when compared to wildtype controls. Importantly, transgenic Nur77 knockout 2D2 mice, where 90% of their T cell repertoire are MOG35-55-reactive T cells, develop spontaneous Central Nervous System (CNS) inflammation accompanied by neurological symptoms, which is only rarely seen in their Nur77 competent counterparts, hence illustrating the central role of Nur77 in control of autoreactive T cell responses. This increase in disease severity in both active and spontaneous EAE was accompanied by an enhanced presence of T\(_{h1}\) and T\(_{h17}\) cells within the CNS. Furthermore, adoptive transfer of MOG35-55-reactive T cells from Nur77 knockout mice into healthy wildtype recipient mice lead to an aggravated EAE disease course, which strongly supports the idea that Nur77 in T cells plays a role in limiting autoimmune T cell responses. In human T cells, Nur77 is also expressed after TCR-triggering and short interfering RNA-mediated knockdown of Nur77 in activated human T cells significantly enhanced their
capacity to differentiate into proinflammatory T<sub>H</sub>1 and T<sub>H</sub>17 cells. Interestingly, Nur77 expression was found to be altered in relapsing-remitting MS patients, which further underlines the potential relevance of Nur77 in the context of MS. In summary, Nur77 limits local activation of auto-reactive T cells in autoimmune diseases such as MS.

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HW: honoraria for acting as a member of Scientific Advisory Boards and as consultant for Biogen, Evgen, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertz-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, TEVA, and WebMD Global.

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**P460**

Anti-MOG antibodies from NMO-SD patients facilitate low dose antigen recognition promoting activation of peripheral auto-reactive T cells

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**Background:** In the majority of patients with neuromyelitis optica (NMO) or NMO-spectrum disorders (NMO-SD) peripheral antibodies (Ab) against central nervous system (CNS) antigens, such as astrocytic aquaporin-4 or myelin oligodendrocyte glycoprotein (MOG) can be detected. In an experimental setting, we recently observed that peripheral Ab against MOG can trigger expansion of MOG-reactive T cells, subsequently causing experimental autoimmune encephalomyelitis. In the present study, we examined how these peripheral Ab can activate auto-reactive T cells and whether human anti-MOG Ab may exert a similarly underestimated role in development of acute flares of inflammatory CNS demyelination.

**Methods:** Disease triggering mechanisms were investigated using phagocytosis assays and/or co-culture assays with murine or human antigen-presenting cells (APC), T cells and traces of MOG protein in the presence of murine or human anti-MOG antibodies.

**Results:** To elucidate how anti-MOG Ab facilitated T cell activation, murine MOG-specific T cells were co-cultured in vitro with APC at limiting low concentration of MOG. In this system, anti-mouse MOG Ab facilitated recognition, internalization and presentation of MOG to T cells triggering their encephalitogenic differentiation. This mechanism was strictly Fc-dependent, as inhibition of Fc signaling abolished the opsonogenetic effect. To exemplify that opsonization can also occur in NMO-SD patients, we used a similar in vitro approach challenging human CD14 positive monocytes with human MOG protein. We observed that patient-derived anti-MOG Ab enhanced similarly recognition of human myelin resulting in increased phagocytosis and activation of APC.

**Conclusion:** Our data indicates that peripheral CNS-specific Ab may activate CNS-reactive T cells by opsonization of otherwise unrecognized traces of CNS antigen in peripheral compartments. We propose that CNS draining lymph nodes may be the site where anti-CNS Ab confer specific antigen recognition via opsonization to myeloid APC. Thereby, Ab boost antigen uptake and generation of peripheral auto-reactive T cells triggering CNS infiltration in return. This process could be of particular relevance for disease initiation and development of acute relapses in the subgroup of NMO-SD patients containing MOG-specific Ab. Furthermore, these data highlight peripheral anti-CNS Ab responses as a promising target for future therapeutic interventions independent of controlling cellular B cell function.

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Silke Kinzel and Sebastian Torke have nothing to disclose.

**P461**

Progressive multiple sclerosis: selective involvement of the CD30/CD153 signalling pathway in innate immunity

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**Background:** The adaptive immune system is playing an important role in multiple sclerosis (MS) while the role of the innate immune system is less clear. Dendritic cells (DC) and Natural Killer (NK) cells are effectors of the innate immune system.

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The expression of some surface markers are associated with autoimmunity. Also known as TNF receptor supra family member 8, CD30 has been implicated in lymphoma and autoimmune diseases like MS. CD30 is exclusive to immune cells and CD153 is CD30 ligand.

We hypothesize that the CD30/CD153 expression on innate immune cells will be different in Primary Progressive MS (PPMS) and Relapsing-Remitting MS (RRMS), considering PPMS is a more degenerative phenotype and RRMS a more inflammatory one.

**Methods:** 20 MS patients (10 RRMS experiencing a relapse and 10 PPMS) and 26 healthy controls (HC) were included. RRMS patients were untreated (70%) or on a first-line therapy (30%). Whole blood was stained with antibodies to distinguish myeloid DC (MDC), plasmacytoid DC (PDC), monocytes and NK cells subtypes (CD56dim and CD56bright). Expression of CD30 and CD153 was assessed by flow cytometry. The group mean and its standard deviation are presented. Wilcoxon rank-sum test was used for group comparison.

**Results:** Compared to HC, PPMS had an increased number of MDC expressing CD30+/CD153+ (0.34±0.41 vs 0.17±0.61, p=0.037), PDC CD30+/CD153+ (1.33±1.64 vs 0.29±0.92, p=0.026), PDC CD30+/CD153− (0.45±0.53 vs 0.3±1.47, p=0.004), NK CD30+/CD153+ (0.17±0.27 vs 0.03±0.08, p=0.003) and NK CD30+/CD153− (0.85±1.1 vs 0.04±0.09, p=0.0003). Surprisingly, when compared to RRMS, PPMS had an increased number of NK CD30+/CD153+ (0.17±0.27 vs 0.01±0.01, p=0.005) and NK CD30+/CD153− (0.85±1.1 vs 0.07±0.2, p=0.007). NK cell subset analysis revealed that CD56bright and CD56dim NK cells expressing CD30+/CD153+ and CD30−/CD153− were increased in PPMS when compared to HC (p< 0.0001) and when compared to RRMS (p< 0.0001).

**Conclusion:** We demonstrated a higher expression of CD30/CD153 on DC and NK in PPMS compared to controls and on NK in PPMS compared to RRMS. In our sample, treatment and active relapse could explain why RRMS behaves differently. These preliminary results suggest a differential regulation of the innate immune system in PPMS and provide support for a role of the innate immune system in MS.

Effective treatments for PPMS are needed. If these findings are confirmed, CD30/CD153 may reasonably be targeted for the treatment of PPMS.

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**P462**

**Metabolic control of macrophage-mediated myelin phagocytosis: implications for multiple sclerosis**

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**Background:** The clearance of myelin debris by phagocytic monocyte-derived macrophages (MDMs) is essential for tissue repair in multiple sclerosis (MS). A selective defect in myelin phagocytosis but not in uptake of opsonized red blood cells by MS MDMs has been previously demonstrated (Natrajan 2015, Healy 2017). The metabolic state of MDMs, defined on the basis of oxidative phosphorylation (OXPHOS) and glycolysis, has been linked with the activation state of MDMs.

**Objective:** The aims of this study were to determine whether the metabolic activity of MDMs influences the rate of myelin phagocytosis, and then determine whether there was defect in metabolic activity of MS patient-derived MDMs.

**Methods:** MDMs were prepared by isolating monocytes from whole venous blood samples derived from control donors and untreated MS patients (1 relapsing and 4 secondary progressive) and culturing these cells for 1 week in macrophage colony stimulating factor (M-CSF)-supplemented media. Myelin phagocytosis was measured using pHrodo-labelled myelin in a flow cytometry assay as described (Healy 2016). A Seahorse bioanalyzer was used to measure oxygen consumptions rates that predominantly reflect OXPHOS, and extracellular acidification rates that mainly reflect glycolysis.

**Results:** Both OXPHOS and glycolytic metabolism were upregulated in control donor MDMs following myelin uptake. Blocking OXPHOS by addition of the ATP synthase inhibitor oligomycin significantly reduced myelin phagocytosis. Blocking glycolysis by addition of the competitive inhibitor 2-deoxyglucose (2DG) did not reduce phagocytosis but did modulate subsequent cytokine production following phagocytosis. MS patient-derived MDMs showed significant deficits in both basal OXPHOS and glycolytic metabolism.

**Conclusion:** Our data using control donor MDMs indicate a central role for OXPHOS in the control of myelin phagocytosis by healthy donor-derived MDMs. MDMs from MS patients display a deficit in both myelin phagocytosis and basal metabolic activity. The basis of this metabolic defect in MS MDMs remains to be defined.

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Activation of the aryl hydrocarbon receptor in dendritic cells is sufficient for the UV-B-induced amelioration of experimental autoimmune encephalomyelitis

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Besides genetic susceptibility factors, environmental and lifestyle stimuli, including the exposure to UV-B light, are known to play a role in the modulation of multiple sclerosis. In experimental autoimmune encephalomyelitis (EAE), we have shown that irradiation with UV-B ameliorated disease. The transcription factor aryl hydrocarbon receptor (AhR) that is expressed in the skin and the central nervous system (CNS) can be activated by environmental factors including UV-B-induced photoproducts of tryptophan. Thus, we investigated the role of AhR during the transmission of environmental stimuli, sensed in the skin and known to modulate CNS inflammation. Therefore, wild-type (wt) and AhR-deficient mice (AhR-/-) were irradiated with UV-B and immunized with myelin oligodendrocyte glycoprotein (MOG)-peptide and the UV-B-induced activation of AhR was confirmed by the up-regulation of AhR target genes like cytochrome P450 family member A1 (CYP1A1) and CYP1B1. Whereas irradiated wt mice showed a delayed onset and reduced severity of disease, EAE perpetuation was comparable in UV-B-irradiated and non-irradiated AhR-/- mice. Flow cytometry and immunofluorescence staining revealed reduced numbers of pathogenic Th17 and increased levels of regulatory T cells (Treg) in the CNS from irradiated wt but not AhR-/- mice, indicating that AhR activation by UV-B may play a role during the expansion of Treg. To characterize the underlying cellular and molecular mechanisms we deleted AhR in T cells and different subsets of dendritic cells (DC) that have been shown to mediate the expansion of Treg. Interestingly, in mice specifically lacking AhR in CD11c+ mature DC or CD207+ cutaneous DC UV-B-irradiation did neither ameliorate EAE perpetuation nor modulate Treg or Th17 numbers, whereas deletion of AhR in T cells had a less prominent effect. Worth mentioning, that the deletion of AhR in neurons had no impact on the UV-B-induced protection from EAE. Thus, our data indicate that AhR activation in DC might be required for transmitting the environmental factor UV-B into susceptible mice during MOG-induced EAE.

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Fingolimod-induced changes in the peripheral immune repertoire and their potential as biomarkers of treatment response in multiple sclerosis

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Background: There are presently no biomarkers predicting response to fingolimod treatment for relapsing-remitting multiple sclerosis (MS). Here, we prospectively examined fingolimod’s effects on a broad range of peripheral blood mononuclear cell (PBMC) subsets in treated patients, and tested for association with clinical and radiological disease activity while on treatment.

Methods: Thirty-six patients initiating fingolimod for MS were followed clinically and with co-registered serial MRI for up to 24 months (mean 23 months, range 8–24 months). Patients were classified as ‘active’ (n=18) or ‘stable’ (n=18) based on clinical (relapse) and radiological (new T2 hyperintense lesions) evidence on treatment. ‘Active’ and ‘stable’ groups were well matched, including for pre-fingolimod disease activity. Using standardised protocols, detailed multicolour flow cytometric analysis of T-cell subsets, B-cell subsets, NK cells, monocytes and dendritic cells were performed on rigorously collected and cryopreserved PBMC obtained pre-treatment and after at least 6 months on treatment.

Results: Decreased absolute counts of most B-cell and T-cell (CD4+ and CD8+) subsets were seen with fingolimod treatment, including naive, memory, regulatory and pro-inflammatory cytokine-expressing subsets. Senescent CD8+ T cells (CD8+CD28- and CD8+CD57+), CD56+ NK cells, monocytes and dendritic cells were not reduced in number and hence relatively increased in frequency with treatment. Lower pre-treatment frequencies of CD8+ central memory cells (TCM) (28% vs 37%, p=0.0133) and higher frequencies of CD8+ terminally differentiated effector memory (TEMRA) cells (22% vs 13%, p=0.038) were noted in patients who remained stable on fingolimod compared with the active cohort. Stable patients were also noted to have significantly lower B-cell counts pre-treatment (p=0.0066), mainly reflecting lower numbers of mature (p=0.0061) but not transitional B cells.

Conclusions: In this prospective and rigorously studied cohort, we document effects of fingolimod treatment on a broad range of peripheral immune cell subsets, including several not previously studied. Early analysis suggests pre-treatment mature B-cell counts, CD4+ TCM and CD8+ TEMRA cell frequencies may have value in predicting fingolimod treatment response and warrant further study. Multiparametric analysis exploring whether interplay between different immune cell types predicts treatment response will also be performed.

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Multiple sclerosis risk variants alter expression of co-stimulatory genes in B cells

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The increasing evidence supporting a role for B cells in the pathogenesis of multiple sclerosis prompted us to investigate the influence of known susceptibility variants on the surface expression of co-stimulatory molecules in these cells. Using flow cytometry we measured surface expression of CD40 and CD86 in B cells from 68 patients and 162 healthy controls that were genotyped for the multiple sclerosis associated single nucleotide polymorphisms (SNP) rs4810485, which maps within the CD40 gene, and rs9282641, which maps within the CD86 gene. We found that carrying the risk allele at rs4810485 increases the expression of CD40 (p < 5.10 x 10^{-5} in patients and ≤ 4.09 x 10^{-6} in controls), while carrying the risk allele at rs9282641 increases the expression of CD86 (p = 0.048 in patients and 5.38 x 10^{-5} in controls). In concordance with these results analysis of RNA expression demonstrated that the risk allele of rs4810485*G resulted in lower total CD40 expression (p = 0.057) but with an increased proportion of alternative splice-forms leading to decoy receptors (p = 4.00 x 10^{-7}). Finally, we also observed that the risk allele of rs4810485*T is associated with decreased levels of interleukin-10 (p = 0.020), which is considered to have an immunoregulatory function downstream of CD40. Given the importance of these co-stimulatory molecules in determining the immune reaction that appears in response to antigen our data suggest that B cells might have an important antigen presentation role in the pathogenesis of multiple sclerosis.

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Insulin and leptin impair regulatory T cell function in obese multiple sclerosis patients

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Background and goals: Obesity in childhood and adolescence increases the risk of developing multiple sclerosis (MS). Presence of hyperinsulinemia in obese MS patients points towards a potential link between metabolism and autoimmunity. We previously demonstrated that in the presence of elevated insulin levels, regulatory T cells (Treg cells) acquire a specific defect in IL-10 production, a pathway mediated by AKT. Leptin, which is a soluble factor secreted by adipocytes and different immune cells

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participating in a wide range of biological functions is elevated in obese individuals, and may play a role in this link. Our aim was to study how leptin in association with hyperinsulinemia affects Treg cell function.

**Design and Methods:** CD4+CD25-FoxP3- T cells and CD4+CD25-FoxP3+ T cells were purified from peripheral blood mononuclear cells of 30 obese MS patients, 30 non-obese MS subjects, and 30 healthy controls. Leptin receptor and FoxP3 expression were measured by RT-PCR and flow cytometry, and phosphorylation of AKT Ser473, ribosomal protein S6, mTORC1, p27kip, p21WAF, leptin levels, and IL-10, were assessed by ELISA.

**Results:** Obese MS patients showed higher serum levels of leptin compared to non-obese MS subjects. CD4+CD25-FoxP3- and CD4+CD25-FoxP3+ T cells expressed similar leptin receptor levels both ex vivo, and after activation. However, activation of mTORC1 signaling by leptin was significantly higher in CD4+CD25-FoxP3+ Treg cells from obese MS patients than from non-obese MS subjects, or in CD4+CD25-FoxP3+ T cells from either group. Increased activation of the leptin-mTORC1 pathway was associated with decreased expression of FoxP3 and with decreased Treg cell proliferation, as well as with increased expression of cell cycle inhibitors p27kip and p21WAF. Leptin receptor blockade or mTORC1 inhibition by rapamycin abolished these effects. Furthermore, mTORC1 activation by leptin increased AKT signaling pathway activity in CD4+CD25+FoxP3- cells, enhancing insulin-induced effects leading to IL-10 production suppression.

**Conclusions:** Both hyperinsulinemia and higher serum leptin levels present in obese MS patients may represent a link between metabolism and autoimmunity. Under these conditions, Treg cells acquire a specific defect in IL-10 production, as well as reduced proliferation capacity and decreased expression of FoxP3. These mechanisms may help explain Treg cell hyporesponsiveness observed in autoimmune diseases like MS.

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**Histone deacetylase SIRT1 mediates C5b-9-induced cell cycle in oligodendrocytes**

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**Background:** Oligodendrocytes (OLG) are the myelin-forming cells in the central nervous system and the main target of the inflammatory attack in multiple sclerosis (MS). They are susceptible to lytic complement attack mediated by the terminal complex C5b-9. However, sublytic levels of complement C5b-9 increased the survival of OLG and induced cell cycle. We have found that SIRT1 is co-localized with surviving OLG in MS plaques, but it is currently not known if SIRT1 is implicated in OLG survival after exposure to sublytic C5b-9.

**Objectives:** We investigated the role of SIRT1 in OLG differentiation and the effect of sublytic levels of C5b-9 on SIRT1 expression. We also investigated the downstream effects of SIRT1 by measuring histone H3 Lysine 9 trimethylation (H3K9me3) and expression of cyclin D1 as a marker of cell cycle activation.

**Materials and Methods:** OLG progenitor cells (OPC) purified from the brain of rat pups were differentiated in vitro and stimulated with sublytic C5b-9 or C5b6 (as control) for 3, 6 and 8 hours. The levels of SIRT1, myelin basic protein (MBP) and proteolipid protein (PLP) mRNA were measured using real-time PCR and SIRT1, MBP, cyclin D1 and H3K9me3 protein expression were measured using western blotting.

**Results:** Our data show a significant decrease of SIRT1 during OPC differentiation (p=0.01) associated with a decrease of H3K9me3 and an increase of cyclin D1 expression (p=0.001), MBP (p=0.01) and PLP. Stimulation of OLG with sublytic C5b-9 for 3 hours resulted in a further decrease in SIRT1 mRNA and protein levels (p=0.02) while stimulation with C5b6 had no effect. SIRT1 protein remained significantly decreased after 8 hours of exposure to C5b-9 as compared to C5b6 treatment (p=0.009). H3K9me3 levels also decreased significantly after stimulation with C5b-9 as compared to unstimulated (p=0.0004) or C5b6-treated OLG. Cyclin D1 expression increased after stimulation with C5b-9 (p=0.03), indicating cell cycle activation. In addition, MBP and PLP expression were significantly reduced after exposure to C5b-9 (p=0.009).

**Conclusions:** Our data suggest that SIRT1 participates in C5b-9-induced cell cycle activation by regulating the levels of repressive methylation of H3K9. In addition, C5b-9-mediated MBP and PLP reduction may play an important role in inflammatory demyelination by affecting the OLG ability to express myelin proteins.

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**CD70 expression defines a subset of pro-inflammatory and pathogenic T cells that are implicated in multiple sclerosis**

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Background and Objective: CD70, a cytokine that binds CD27, is upregulated on T cells after activation. CD27-CD70 signaling promotes T cell survival and cytokine production. CD70 was identified in a proteomic screen to be associated with MCAM+T H17 cells and could be involved in T H1 differentiation.

In multiple sclerosis (MS) autoimmune T H1 and T H17 cells are able to infiltrate the central nervous system; therefore our goal is to investigate if CD70 expression is important for this T cell pathogenicity and migration.

Methodology and Results: We confirmed by flow cytometry (FC) that CD70 is present, albeit low (0.5-1% of T cells), on ex vivo T cells from peripheral blood (PB) of healthy donors (HD). Next, we found that CD70+ T cells produce significantly higher amounts of IL17 and IFNγ compared to CD70- T cells. In addition, in vitro activation of T cells with various cytokines shows that CD70 is significantly upregulated in the presence of TGFβ1 and TGFβ3. This upregulation is accompanied by an increased amount of IFNγ, IL17, GMCSF producing and MCAM expressing CD70+ T cells. Furthermore, RT-PCR and FC showed that CD70 is significantly higher expressed on T H1 and T H17 cells compared to T H2 cells. When adding TGFβ to these polarization conditions the proportion of CD70+ cells increased together with an increase in pro-inflammatory cytokine (IFNγ, IL17 and GMCSF) producing CD70+ T H1 and T H17 cells.

In untreated MS patients, the percentage of ex vivo CD70+ T cells in the PB is significantly higher compared to HD. In addition, stimulation with TGFβ leads to a significantly higher increase of CD70 and a higher percentage of IFNγ and IL17 production compared to HD. When adding TGFβ to these polarization conditions the proportion of CD70+ cells increased together with an increase in pro-inflammatory cytokine (IFNγ, IL17 and GMCSF) producing CD70+ T H1 and T H17 cells.

Conclusions: CD70 expression, upregulated by TGFβ1 and TGFβ3, discriminates a highly active and pro-inflammatory subset of T H1 and T H17 cells. The expression and pro-inflammatory nature of CD70 in ex vivo, polarized or TGFβ stimulated T cells is much higher in MS patients compared to HD.

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P469 Amplified STAT phosphorylation signaling in peripheral blood mononuclear cells from MS patients in response to interferon alpha
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Background: Multiple sclerosis (MS) is characterized by increased immune activation of peripheral mononuclear cells, but little is known about the specific pathways that are dysregulated.

Abnormal levels of phosphorylated proteins and correlations with disease activity and treatment response have been reported in several autoimmune diseases. Phosphoflow is a flow cytometry-based technology that allows tracking multiple intracellular signaling molecules at the single-cell level in response to different stimuli. In this study we aimed to profile the levels of different phosphorylated proteins and phosphorylation response in treatment-naive MS patients.

Methods: We developed a phosphoflow protocol to quantify the levels of 11 phosphorylated proteins (Btk, Akt, PLCγ, Cbl, p38MAPK, ERK1/2, Stat1, Stat3, Stat4, Stat5 and Stat6), at baseline conditions and after cell activation, in distinct peripheral blood cell populations isolated from 41 treatment-naive relapsing remitting (RRMS) patients and 37 matched controls. Levels of HLA-ABC, HLA-E and HLA-DR were also assessed after stimulation with IFN-α and IFN-γ. A second independent sample set consisted of 9 RRMS and 10 secondary progressive (SP) MS patients.

Results: No significant differences were observed at baseline conditions between patients and controls. However, levels of phosphorylated STAT (p-STAT) proteins were highly upregulated across all cell types in MS patients compared to controls after stimulation with IFN-α. This difference was particularly significant for p-STAT1 and p-STAT6 in the NK cell population (p=2.5x10-6 and p=3.2x10-6 respectively), and for p-STAT1 in monocytes (p=1.2x10-4). Furthermore, levels of all p-STAT proteins correlated with the expression of HLA molecules in monocytes after stimulation with IFN-α, but especially levels of p-STAT1 correlated with expression of HLA-DR (cor=0.6; p=2.8x10-3). On the other hand, the levels of phosphorylated proteins did not differ between RRMS and SPMS patients either in baseline conditions or after stimulation.

Conclusions: We have shown that the response to IFN-α through STAT proteins signaling is strongly dysregulated in MS patients irrespective of disease stage. Furthermore, our findings suggest that the aberrant activation of this pathway could lead to changes in the expression of HLA molecules in NK and antigen presenting cells, which are known to play important roles in the immune response and regulation.

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P470 Role of intestinal IgA-producing cells at regulating neuroinflammation in EAE
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Antibody-secreting cells (ASC), including plasmablasts and plasma cells (PB/PC), play an important role in the pathophysiology of many disease states including Multiple Sclerosis, where PB/PC are found in the affected central nervous system (CNS). In the context of MS, the originating source of the ASC that ultimately
invasion of the CNS, and the role these cells play in disease pathogenesis is unclear. Examining the kinetics of ASC accumulation in the CNS during myelin oligodendrocyte peptide (MOG35-55)-induced Experimental Autoimmune Encephalomyelitis (EAE) in Aid -> YFPfl/fl and Prdm1yfp reporter mice, we found that PB/PC were absent from the CNS during the steady-state but gradually increase in the brain and spinal cord as disease progresses. Notably, a portion of CNS-resident PB/PC were IgA+, and IgA+ PB/PC were found to be concomitantly decreased in the small intestinal lamina propria (SILP) during the chronic phase of EAE. Using Rotavirus (RV) infection and EAE as a dual model, we found that RV specific IgA+ B cells primed in the gut could be mobilized out of the intestine into extra-intestinal sites including the bone marrow and the inflamed CNS. Removal of Blimp-dependent PB/PC by using conditional CD19Cre-Prdm1fl/fl mice resulted in exacerbated EAE that was normalized by the introduction of gut-derived IgA+ PC, and BAFF-Transgenic mice with an over-abundance of IgA+ PB/PC were resistant to EAE. These data generate new information regarding the source and function of ASC, particularly gut derived IgA+ B cells, during neuroinflammation.

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Single cell transcriptomics identifies multiple sclerosis-specific expression profiles of cerebrospinal fluid cells

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Background: The central nervous system is ensheathed by cerebrospinal fluid (CSF) that is constantly circulated by immune cells and provides one level of protection and immune surveillance to the brain. CSF provides the unique opportunity to study local immune reactions in multiple sclerosis (MS), but our understanding of cells in the CSF is rudimentary - partly because outdated techniques are employed to study them.

Aims: Here, we aimed to study the genome-wide expression profile of individual CSF cells and dissect local immune mechanisms in MS at unprecedented resolution.

Methods: We employed microfluidics-based single cell RNA-sequencing (scRNA-seq) to study CSF cells from human patients with multiple sclerosis and controls.

Results: We found unexpected transcriptional heterogeneity of CSF immune cells and identified subsets of CD4+ T and B lymphocytes in the CSF beyond the known enrichment of central memory effector T cells in the CSF. We also identified transcripts expressed preferentially in CSF cells compared to peripheral blood lymphocytes and enriched in cells derived from MS patients compared to controls.

Conclusion: In this unbiased high-throughput transcriptional profiling of CSF cells of MS patients we thus identify novel candidates potentially regulating influx into the CSF compartment and locally controlling MS-specific disease mechanisms. This study thus sets the stage for a deeper understanding of immune surveillance and auto-inflammation in the central nervous system.

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Novel anti-neuronal antibodies in multiple sclerosis

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Background: Grey matter pathology is extensive in relapsing-remitting and secondary progressive multiple sclerosis (MS) and has been shown to correlate with disability. Histopathological studies demonstrate neuronal loss in grey matter lesions and in some cases selective destruction of interneurons.

Objective: To identify whether anti-neuronal antibodies occur in MS.

Methods: Seventy-nine patients with relapsing-remitting MS and 61 healthy blood donors were analysed. Sera were applied to frozen cryostat sections of rat cortex, cerebellum, kidney and small intestine that had been fixed using in vitro 2% paraformaldehyde perfusion. Bound IgG was detected using a goat anti-human IgG (Alexa Fluor 488) and M1 Zeiss Axiocam Imager. Specimens were analysed by two raters in a blinded fashion for binding to neurons and other CNS structures and regarded as positive if fluorescence was greater than ++ which equivocated to an antibody dilution of more than 1:320. The frequencies of anti-neuronal antibodies were compared using chi-square statistics with Bonferroni corrections where appropriate.

Results: Anti-neuronal antibodies were more frequently detected in MS (35.4%, 28/79) than healthy controls (11.5%, 7/61, p < 0.05). Antibodies directed against neuronal cytoplasm were most frequent in MS (20.3%, 16/79) and healthy controls (9.8%, 6/61) but in MS, antibodies were also identified against synaptic vesicles, neurofilaments and neuronal nuclei. An antibody directed against a vesicular intracytoplasmic component of interneurons (bipolar cells, golgi and basket cells) was found in 10.1% of MS patients and 4.9% of healthy controls.

Discussion: Anti-neuronal antibodies are more frequently found in MS than healthy people and have a wider distribution of targets. The disability and clinical correlates of novel anti-neuronal antibodies will be discussed.

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P473
Concerted T cell response in experimental autoimmune encephalomyelitis and multiple sclerosis
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Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS). The role of T cells in MS is well established. Yet, whether there are key T cell antigen(s), which drive the initial inflammatory response is not known. Therefore, there is a need for comprehensive understanding of the T cell receptor (TCR) repertoire in MS with a focus on identifying and targeting dominant T cell clones. We have analyzed both recent onset MS patients and in mice with experimental autoimmune encephalomyelitis (EAE) with respect to their overall immune system and the specific T cell types. Surprisingly, upon EAE induction there is co-mobilization and oligoclonal expansion of CD4, CD8, and γδ T cells day 10 post-immunization both in blood and CNS as determined by single cell paired TCR sequencing. Moreover, these expanded T cell clones are similar and shared between mice and tissue, indicating shared specificities. Many of the expanded CD4 and CD8 T cell clones do not respond to myelin which suggests initiation of broad antigen specificities upon EAE immunization. By using yeast displayed mouse class I peptide-MHC (p-MHC) library which contains 5 X 10^8 peptide antigens, we have screened some of the yeast displayed p-HLA library, we have screened some of the expanded CD4 T cells from MS patients who are homozygous for HLA-DR*1501 and found ligands which are not myelin. Overall, our results strongly suggest that there is coordinated and focused antigen specificity of the T cell responses involving all T cell types to novel antigens, both in MS and in EAE.

Conclusion:
Our results suggest that derangement of γδ T cell subsets may contribute to MS severity through insufficient regulation of autoimmune CD4 T cells by a decreased Vδ2/Vγ9 γδ T cell population.

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A distinct repertoire of the γδ T cell population is associated with disease severity of multiple sclerosis
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Background: γδ T cells play an important role in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS), by producing interleukin (IL)-17 or suppressing the development of regulatory T (Treg) cells. We have recently shown that the deletion-type copy number variation at γδ T cell receptor locus regions is associated with MS susceptibility. However, the roles of γδ T cells remain to be elucidated in MS.

Objective: To clarify the roles of γδ T cells in MS patients by comprehensive immunophenotyping using flow cytometry.

Methods: Peripheral blood mononuclear cells were obtained from 33 untreated MS patients in remission and 23 age and gender-matched healthy controls (HCs), and stained for surface markers and intracellular cytokines after in vitro culture with phorbol 12-myristate 13-acetate and ionomycin. Stained cells were analysed by a FACSVerse flow cytometer.

Results: The frequencies of Treg cells (CD25+CD127low/-) among CD4 T cells, Vδ2+ γδ T cells, and Vδ2+Vγ9+ γδ T cells were significantly decreased in the γδ T cell population (p = 0.010, p = 0.001, and p = 0.002, respectively), while that of Vδ1+ γδ T cells and the Vδ1/Vδ2 ratio were significantly increased in MS patients compared with HCs (p = 0.005 and p = 0.002, respectively). Intracellular cytokine staining showed significant decreases of IL-17A, interferon (IFN)-γ, or IL-17A and IFN-γ-producing Vδ2+ γδ T cells in the γδ T cell population (p = 0.007, p < 0.001, and p < 0.001, respectively). The Vδ1/Vδ2 ratio was correlated negatively with the frequency of Treg cells in HCs, but this association was not observed in MS patients (r = -0.5927, p = 0.0037 and r = 0.1632, p = 0.4497, respectively). The Vδ1/Vδ2 ratio was correlated positively with disease severity defined by Expanded Disability Status Scale scores of Kurtzke in MS patients (r = 0.5219, p = 0.018).

Conclusion: Our results suggest that derangement of γδ T cell subsets may contribute to MS severity through insufficient regulation of autoimmune CD4 T cells by a decreased Vδ2+Vγ9+ γδ T cell population.

Disclosure:
Koji Shinoda has received speaking honoraria from Takeda Pharmaceutical Company. Takuya Matsushita has received honoraria from Bayer Schering Pharma, Biogen Idec Japan, Takeda Pharmaceutical Company, and Mitsubishi Tanabe Pharma. Jun-ichi Kira is a consultant for Biogen Idec Japan and Medical Review. He has received honoraria from Bayer Healthcare, Mitsubishi Tanabe Pharma, Nobelpharma, Otsuka Pharmaceutical, and Medical Review. He is funded by a research grant for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare of Japan and grants from the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology of Japan. Yuri Nakamura, Katshusa Masaki, and Yasunobu Yoshikai have nothing to declare.

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Inflammatory mediators regulate ARNT2 expression in CNS and peripheral immune populations and influence their pathogenic or protective properties in MS and in models of inflammatory neurodegeneration
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Background: ARNT2 is highly expressed in multiple immune cell populations and in the CNS. We have recently shown that increased ARNT2 expression in CNS and peripheral immune populations correlates significantly with disease severity defined by Expanded Disability Status Scale scores of Kurtzke in MS patients (r = 0.5219, p = 0.018).

Methods: A human peripheral blood mononuclear cell (PBMC) panel including HCs and patients with MS was used to determine the expression level of ARNT2 in different immune cell populations. The association of ARNT2 expression with disease severity was determined using Spearman’s rank correlation coefficient.

Results: We found that the frequency of Treg cells (CD25+CD127low/-) among CD4 T cells, Vδ2+ γδ T cells, and Vδ2+Vγ9+ γδ T cells was significantly decreased in the γδ T cell population (p = 0.010, p = 0.001, and p = 0.002, respectively), while that of Vδ1+ γδ T cells and the Vδ1/Vδ2 ratio were significantly increased in MS patients compared with HCs (p = 0.005 and p = 0.002, respectively). Intracellular cytokine staining showed significant decreases of IL-17A, interferon (IFN)-γ, or IL-17A and IFN-γ-producing Vδ2+ γδ T cells in the γδ T cell population (p = 0.007, p < 0.001, and p < 0.001, respectively). The Vδ1/Vδ2 ratio was correlated negatively with the frequency of Treg cells in HCs, but this association was not observed in MS patients (r = -0.5927, p = 0.0037 and r = 0.1632, p = 0.4497, respectively). The Vδ1/Vδ2 ratio was correlated positively with disease severity defined by Expanded Disability Status Scale scores of Kurtzke in MS patients (r = 0.5219, p = 0.018).

Conclusion: Our results suggest that derangement of γδ T cell subsets may contribute to MS severity through insufficient regulation of autoimmune CD4 T cells by a decreased Vδ2+Vγ9+ γδ T cell population.

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Background: The aryl-hydrocarbon receptor nuclear translocator 2 (ARNT2) is a basic-helix-loop-helix period-ARNT-single minded protein (bHLH/PAS) transcription factor which acts by heterodimerizing with other members and directing transcription of target genes in response to various environmental and physiological stimuli, including hypoxia, early cell determination/differentiation and environmental toxins. We have previously shown ARNT2 expression is altered over the course of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. After detecting ARNT2 expression in immune and glial populations, we examined the regulation of ARNT2 expression in CNS and peripheral immune cell populations.

Methods: ARNT2 expression in microglia, mouse spleen and human peripheral blood cell (PBMC) populations was characterized in response to inflammatory mediators in vitro and also examined in EAE compared to healthy immunized controls.

Results: ARNT2 is expressed at negligible levels in microglia examined in the healthy spinal cord as well as in primary cultures established from embryonic tissues cultured with or without granulocyte-macrophage colony-stimulating factor. Following exposure to the inflammatory mediators interferon-gamma (IFN-Υ) and lipopolysaccharide (LPS), ARNT2 protein increased 1.5-6.5 and 1.5-8 fold, respectively in microglia in vitro. Similarly, LPS, IFN-γ and to a lesser degree tumor necrosis factor alpha increased both message and protein for ARNT2 in bulk PBMC populations. Studies are ongoing to characterize the leukocyte subsets which are increasing ARNT2 expression in response to these mediators. A 78% decrease (n=5, p=0.025) in ARNT2 expression in the spleens of EAE immunized mice compared to healthy controls, and the appearance of ARNT2+ immune cells within CNS infiltrates of EAE mice suggest that ARNT2 expression may correlate with the effector phenotype of immune cells.

Conclusion: As key checkpoints in responses to environmental and physiological stressors, ARNT2 and its partners may link environment and immune cell characteristics in disorders such as MS. To characterize the functional relevance of ARNT2 to reparative or degenerative processes in MS, studies are ongoing to compare ARNT2 expression in specific immune subsets both in EAE and in MS patient populations undergoing relapses and remissions compared to stable patients or healthy individuals.

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Objective: We investigate whether CD4+CD28null T cells induce worse clinical outcomes in multiple sclerosis (MS) and evaluate the prognostic value of these cells.

Methods: CD4+CD28 null T cell percentages were measured in the blood of 176 MS patients with relapsing-remitting MS (=baseline). Multimodal evoked potentials (EP) combining information on motoric, visual and somatosensory EP and expanded disability status scale (EDSS) were used as outcome measurements at baseline and after 3 and 5 years.

Results: Baseline CD4+CD28null T cell percentages are associated with EP (P=0.003), indicating a link between these cells and disease severity. In addition, baseline CD4+CD28null T cell percentage have a prognostic value since they are associated with EP after 3 years (P=0.005) and with EP and EDSS after 5 years (P=0.008 and P=0.003).

Conclusion: This study provides a direct link between CD4+CD28null T cell percentages and MS disease severity. Moreover, CD4+CD28null T cell percentage is a predictor for worse prognosis. Investigating strategies to block or reverse pathways in the formation of these cells could result in new treatments that slow down MS disease progression.

Disclosure
LMP: nothing to disclosure,
MV: nothing to disclosure,
VS: nothing to disclosure,
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PS: nothing to disclosure,
BB: nothing to disclosure,
NH: nothing to disclosure.

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Oxysterols impair IL-10 secretion and induces cholesterol accumulation in regulatory T cells via LXR signalling to favour autoimmunity
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Background: The development and progression of multiple sclerosis (MS) and other autoimmune disorders, results in part from a dysbalance between pathogenicity of effector CD4+ T cells and negative regulation imposed by regulatory T cells. Oxysterols, cholesterol metabolites, have recently been assigned novel functions in modulating the immune response during MS and its animal model, the experimental autoimmune encephalomyelitis (EAE). However, neither their roles nor their mechanisms of action have been assessed in CD4+ T lymphocytes.

Objectives: We here proposed to assess oxysterol expression levels in subsets of CD4+ T helper cells and further examined their function and mechanisms of action during autoimmunity.

Methods: Subsets of CD4+ T helper cells were generated in vitro and in vivo and expression levels of oxysterol converting enzymes were examined by real-time PCR. Secretion of oxysterols was measured by mass-spectrometry in T cells obtained in vitro.

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Oxysterol functions and downstream signaling were assessed using oxysterols-deficient T cells.

**Results:** We showed that the oxysterol 25-hydroxycholesterol (25-OHC) and transcript levels of its synthesizing enzyme, cholesterol 25 hydroxylase (Ch25h), were specifically increased in IL-27 induced Type 1 regulatory T (Treg) cells. IL-27, a critical factor for Treg cell differentiation is instrumental in preventing autoimmune diseases and MS. We demonstrated that 25-OHC acts as negative regulators of Treg cells in particular on IL-10 secretion via LXR signalling. Furthermore, 25-OHC lead to intracellular cholesterol accumulation within Treg cells, another mechanism described in innate immune cells to enhance inflammatory processes.

**Conclusion:** Together, our findings show that Ch25h and 25-OHC act as negative regulators of Treg cells both in vitro and in vivo. The production of 25-OHC by Treg cells is in agreement with the existence of an autocrine and paracrine 25-OHC/LXR amplification loop, inhibiting both Treg cell polarization and cholesterol efflux as well as enhancing cholesterol production. Understanding the complex interaction between the metabolic and immune systems may lead to substantial therapeutic promises for harnessing autoimmune disorders.

**Disclosure**
Nothing to disclose

**P478**

**PARP-1 deregulation in MS**

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**Background:** Emerging evidence suggests poly (ADP-ribose) polymerase-1 (PARP-1) as a promising target for immunomodulation in MS. PARP-1 plays a pivotal role in immune/inflammatory responses. It regulates gene transcription in immune cells such as lymphocytes but also dendritic cells and macrophages. PARP-1 inhibition reduces the secretion of pro-inflammatory cytokines and ameliorates immune-mediated diseases in several experimental models. It has also been shown that a PARP-1 inhibitor suppresses in vitro replication of JC virus, the causative agent of progressive multifocal leukoencephalopathy (PML). The study was supported by the Swiss National Science Foundation (SNSF) and the Swiss Multiple Sclerosis Society (SMSG).

**Objectives:** We aim at exploring expression of PARP-1 and its downstream factors in MS and upon natalizumab treatment. We also seek to identify and validate specific cellular messenger RNA signatures that possibly contribute to PML development.

**Methods:** Peripheral blood mononuclear cells (PBMCs) were isolated from healthy volunteers (HVs), untreated and natalizumab treated MS patients (treatment duration: 1-24 months and >24 months) by a Ficoll density gradient centrifugation. Different cohorts of monocytes (n=12 from each group), CD4+ T (n=12 from each group), CD8+ T (n=11 from HVs and from patients treated >24 months, n=10 from MS untreated patients and from patients treated 1-24 months with natalizumab) and B cells (n=12 from each group), were separated with MACS technology. PBMCs from 15 patients, who developed PML, were included in the study. Total RNA was extracted and transcriptional expression of PARP-1 and its downstream molecules were analyzed by using real-time RT-PCR based assays.

**Results:** PARP-1 was significantly up regulated in CD4+ T, CD8+ T and B cells from untreated MS patients compared to HVs. Natalizumab treatment significantly restored deregulated PARP-1 expression in T cell subsets but not in B cells. Sustained upregulation of PARP-1 correlated with decreased expression of suggested targets of PARP-1 such as TGFBR1, TGFBR2 and Bcl-6 in B cells. Notably, significantly higher expression of PARP-1 was detected in patients developing PML.

**Conclusion:** Given the importance of PARP-1 in inflammatory processes, its up-regulation in lymphocyte subpopulations from MS patients suggests a potential role in the immune pathogenesis of MS. Strikingly higher expression of PARP-1 in PML cases suggests its involvement in disease pathomechanisms. The development of PARP-1 inhibitors might be a novel therapeutic strategy for MS.

**Disclosure**

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**Prof. Dr. med. Ludwig Kappos Institution** (University Hospital Basel) received and used exclusively for research support: consulting fees from Biogen, Novartis, Protagen AG, Roche, Teva; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, Genzyme; travel expenses from Merck Serono, Novartis, Roche; grants from ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030 160221), Bayer AG, Biogen, Genzyme, Merck, Novartis, Roche.
CD4+ T cells are the major pathogenic cells in many autoimmune and inflammatory disorders, including Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS. Th17 cells are important effector cells in the pathogenesis of MS, whereas regulatory T cells (Treg) are crucial in disease resolution. Studies on the mechanisms of enhancing anti-inflammatory responses, such as enhancing trans-differentiation of pathogenic Th17 cells into beneficial Treg cells, may lead to new therapies for MS. Protein kinase CK2 is a constitutively active serine/threonine kinase composed of two catalytic subunits (alpha and/or alpha’) and two regulatory beta subunits. CK2 is involved in the activation of multiple signaling pathways, including PI3K/AKT/mTOR, JAK/STAT and NF-kappaB, which are involved in the activation of multiple signaling pathways, including PI3K/AKT/mTOR, JAK/STAT and NF-kappaB, which are essential for the proliferation and differentiation of CD4+ T cells. However, little is known about the specific function of CK2 in T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells.

Th17 cells treated with CX-4945 are not able to transfer EAE disease, which is correlated with the pathology of Th17 cell responses and suppressing anti-inflammatory Treg cell development, thereby affecting the ratio of these two important CD4+ T-cell subsets. Furthermore, CK2 kinase activity could be targeted for the treatment of Th17 cell-driven autoimmune diseases.

Disclosure

Eitty Benveniste: nothing to disclose

P479

Protein kinase CK2 controls CD4+ T-cell differentiation and is critical for pathogenicity in autoimmune neuroinflammation

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CD4+ T cells are the major pathogenic cells in many autoimmune and inflammatory disorders, including Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS. Th17 cells are important effector cells in the pathogenesis of MS, whereas regulatory T cells (Treg) are crucial in disease resolution. Studies on the mechanisms of enhancing anti-inflammatory responses, such as enhancing trans-differentiation of pathogenic Th17 cells into beneficial Treg cells, may lead to new therapies for MS. Protein kinase CK2 is a constitutively active serine/threonine kinase composed of two catalytic subunits (alpha and/or alpha’) and two regulatory beta subunits. CK2 is involved in the activation of multiple signaling pathways, including PI3K/AKT/mTOR, JAK/STAT and NF-kappaB, which are essential for the proliferation and differentiation of CD4+ T cells. However, little is known about the specific function of CK2 in T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells. Our findings indicate that expression of the major catalytic subunit of CK2, CK2alpha, is induced in a time-dependent manner upon activation of CD4+ T cells.

We further identified an upregulation of KCNK6 upon cell stress using in vitro and upon induction of EAE in vivo. Utilizing a small molecule CK2 inhibitor CX-4945 (Silmitasertib), we find that inhibition of CK2 kinase activity significantly ameliorates the severity of EAE disease, which is correlated with the regulation of Th17 and Treg cell frequencies. Treatment with CX-4945 inhibits the differentiation of Th17 cells, while promoting the differentiation of Tregs. This is associated with an inhibition of pathogenic Th17 cells producing both IL-17 and GM-CSF or IL-17 and IFN-gamma. Moreover, Th17 cells treated with CX-4945 are not able to transfer EAE disease. Conditional deletion of CK2alpha in CD4+ T-cells also inhibits Th17 differentiation and promotes Treg polarization, comparable to what was observed with CX-4945 treatment. CK2alpha-deficient mice exhibit less severe EAE disease, which is associated with inhibition of AKT/mTOR activity and reduced Th17 cells. Thus, we propose that CK2 kinase activity in CD4+ T cells correlates with the pathogenesis of MS/EAE by promoting inflammatory Th17 cell responses and suppressing anti-inflammatory Treg cell development, thereby affecting the ratio of these two important CD4+ T-cell subsets. Furthermore, CK2 kinase activity could be targeted for the treatment of Th17 cell-driven autoimmune diseases.

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The two-pore domain potassium channel (K2P) KCNK6 was initially thought to be a “silent channel” due to low currents in the extracellular membrane of expressing cells. Recently it has been shown by electrophysiology and microscopy that KCNK6 forms functional ion channels in endo-lysosomes in different heterologous expression systems. Thus, KCNK6 was identified as the first lysosomal K2P channel. Recent reports have highlighted the pivotal role of potassium currents in organelle function. However, despite strong expression in the immune system, the functional role KCNK6 plays in immune cells is still unknown. Here, we show for the first time that KCNK6 is upregulated on CD4+ T cells in relapsing-remitting multiple sclerosis (RRMS) patients compared to healthy donors, both during stable disease course and even more strongly during clinical relapses. Immunocytochemistry demonstrated an intracellular expression pattern of KCNK6 in primary T cells confirming previous results in expression systems while co-localization with LAMP1 and RAB7 allocated the channel to the endolysosomal compartment. We further identified an upregulation of KCNK6 upon cell stress as well as during T cell receptor (TCR) stimulation in vitro using PCR and western blot techniques. PCR array analyses revealed key genes involved mainly in autophagy and apoptosis, such as TGM2, DAPK1 and DRAM1, to positively correlate with KCNK6 expression. Specific autophagy proteins have previously been described to be elevated in experimental autoimmune encephalomyelitis (EAE)-diseased mice and multiple sclerosis (MS) patients. Although the role of autophagy in T cells has to be further elucidated, increased autophagy has been discussed to be involved in autoimmunity by enabling autoreactive T cells to escape from endogenous controlling mechanisms via direct degradation of cell cycle proteins. Hence, our results point toward an important role of KCNK6 in T cell homeostasis and central nervous system autoimmunity.

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P481
Intrathecal oligoclonal bands synthesis: is it always a prognostic factor?
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Background: The presence of oligoclonal IgM bands (OCMB) was found associated with poor MS prognosis in adult MS patients. These data were validated in independent cohorts. Oligoclonal IgG bands (OCGB) also associate with an earlier disability progression in MS. The intrathecal immunoglobulin synthesis (ITMS) has recently shown to associate with the genetic background in MS. The aim of our study was to evaluate the prognostic value of ITMS in a big cohort of Sardinian patients.

Materials: We enrolled MS patients diagnosed in accordance with McDonald 2010 criteria. All of them were randomly recruited from the MS Centre of the University of Cagliari from 2007 until to 2013 and underwent lumbar puncture (LP) for diagnostic purpose.

Methods: For each patient were recorded demographic data, clinical course at LP, time to reach EDSS 3, 6, 8, 10, EDSS at last follow-up (2016), MS treatments until the last follow-up. The analysis of ITMS was performed by isoelectrofocusing and immunoblotting, using specific anti-human IgM antibodies, as described by Villar in 2011, but using different migration conditions. The influence of gender, clinical course, age at onset, disease modifying drugs and ITMS on reaching EDSS 3 was analysed with Cox regression, while Kaplan-Meier curves were used to study the time to reach EDSS 3 considering ITMS and therapies.

Results: The enrolled subjects were 503: 479 relapsing-remitting (RR) and 24 primary progressive (PP); 416 patients started a MS treatment. Cox regression showed that the variables influencing the achievement of EDSS 3 were male gender (p=0.005), clinical course PP (p=0.001), age at onset (p=0.001), and treatment with disease modifying drugs (p<0.001). The influence of OCGB and OCMB was not significant. The Kaplan-Meier analysis showed that the time to reach EDSS 3 is not different in patients with and without OCGB or OCMB both in treated and not treated groups.

Discussion and Conclusion: Our study did not confirm in a large sample size of patients the prognostic value of IgG and IgM in terms of clinical course and time to reach the EDSS 3. To explain our results, we could hypothesize a role of genetic factors, having MS Sardinian patients peculiar predisposing and protective genotype. We will study in the next future this aspect.

References:

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Microbiology and Virology
P482
Gut-brain axis: deciphering the role of mucosal and systemic IgA in gut dysbiosis associated with multiple sclerosis
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Background: Gut microbiota closely interact with immune cells at the mucosal barrier. While pathologic activation of autoreactive T lymphocytes by the microbiota has received much attention, the role of B lymphocytes and antibodies in immunoselection of and interaction with gut bacteria remains largely elusive. In this regard, immunoglobulin A (IgA), the most abundantly produced antibody in humans, has recently attracted interest. Some IgA-coated bacterial populations have previously been characterized as immunoreactive resident pathosymbionts that link mucosal and systemic Th17-dependent inflammation in autoimmune diseases including inflammatory bowel disease and peripheral spondyloarthritis.

Aim: To identify and quantify IgA-coated gut bacteria in relapsing-remitting multiple sclerosis (RR-MS) patients and healthy controls (HC), and to study the effects of IgA-coated bacteria on regulating T and B lymphocyte phenotypes in vitro.

Results: Quantification of IgA-coated gut bacteria from RR-MS patients and healthy controls indicated a trend towards higher IgA-coating in patients (RR-MS n=25, HC n=23). Coupling of IgA-coated microbiota with 16S ribosomal RNA-based analysis (IgA-seq) revealed a selective enrichment of several IgA-coated gut bacterial taxa in MS patients, which was followed by in vitro assays to characterize their immunoregulatory functions. Finally, to assess for indirect signs of bacterial translocation into the blood stream, we examined serum binding (IgA, IgG, IgM) of autologous gut bacteria, which revealed significantly higher binding in RR-MS patients compared to controls (RR-MS n=11, HC n=9: IgA p=0.007, IgG p=0.036, IgM p=0.036).

Conclusion: Our results reveal MS-associated changes in immunorecognition of gut bacteria by IgA both in the intestinal lumen and systemically, which suggests a potential mechanism for gut microbiota-dependent regulation of humoral autoimmunity. This study is the first to analyze the role of IgA in mucosal and systemic immunity in MS.

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P483
A bidirectional association between the gut microbiota and CNS disease in a progressive biphasic murine model of multiple sclerosis
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The gut microbiome plays an important role in the development of both auto-inflammation and immune regulation using experimental models that includes central nervous system (CNS) demyelination. Gut microbes influence the inflammatory response as well as immune regulatory cell populations in the gut-associated lymphoid tissue (GALT) that are intimately involved in acute and chronic EAE. The immune basis involved in the transition from inflammatory relapsing disease to progressive disease is poorly understood. Recent observations suggest that communication between the host and the gut microbiome is bidirectional. We hypothesized that the gut microbiota differs between the acute inflammatory and chronic progressive disease stages. We utilized the non obese diabetic NOD murine model of secondary-progressive multiple sclerosis (SP-MS). that develops a biphasic pattern of disease more closely resembling the human condition when transitioning from relapsing to progressive MS. We compared the gut microbiome of NOD mice with either mild or severe disease following disease induction only in mice that later developed severe EAE. Two weeks after EAE induction specific bacterial members of the order Lactobacillales were significantly increased in the severe disease when compared to controls. Alternatively, the genus Lactobacillus and an undefined genus of the family Christensenellaceae were reduced. The immunomodulatory properties of members of the family Lactobacillaceae have been shown to promote protection against murine EAE via the induction of IL-10-producing Tregs and is in active clinical trials as a probiotic in MS. Furthermore, we evaluated whether treatment with a cocktail of broad-spectrum antibiotics would modify the outcome of the progressive stage of EAE in the NOD model. Our results indicated reduced mortality and clinical disease severity in mice treated with antibiotics compared to untreated mice. Our findings support the hypothesis that there are reciprocal effects between experimental CNS inflammatory demyelination and modification of the microbiome providing a foundation for the establishment of early therapeutic interventions targeting the gut microbiome that could potentially limit chronic disease progression.

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P484
CD4+ T cells from multiple sclerosis patients acquire regulatory characteristics following exposure to a gut commensal-derived antigen
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The suggested importance of T and B regulatory cell dysfunction in human multiple sclerosis and other immune mediated auto-inflammatory conditions has been noted. An important mechanism by which current relapsing MS approved therapies abrogate disease is via the amplification and enhanced functional activity of these T and perhaps B regulatory populations. The role of the gut microbiome in a wide range of immune mediated human and animal models of disease is of increasing scientific interest. Studies from our lab and others demonstrate the pivotal activity of the gut microbiome in both the effector and regulatory phase of CNS demyelinating disease in EAE as well as implicated in human disease including MS and NMO. We have reported that polysaccharide A (PSA), a capsular antigen derived from the human gut commensal Bacteroides fragilis, can induce a population of protective CD39+ regulatory T cells in EAE and normal human PBMC following in vitro exposure. We herein demonstrate that naïve T cells isolated from patients with multiple sclerosis acquire regulatory characteristics when stimulated in vitro with polysaccharide A in the presence of dendritic cells. The regulatory population is phenotypically characterized as CD4+CD25+Foxp3+ with enhanced expression of the ectoenzyme CD39+. This important regulatory phenotype is known to be functionally insufficient in those with MS (Fletcher J. Immunol 2009). These in vitro converted regulatory cells produce significantly increased amounts of IL-10 when compared to naïve untreated MS patients. The significant increase in IL-10 production is further amplified in those individuals on current therapy with glatiramer acetate. Screening for IL-10 expression and secretion induced by this gut symbiont antigen at varying concentrations across 20 distinct human haplotypes demonstrated no definitive genetic restriction. These pre-clinical findings indicate that molecules derived from a human gut symbiot such as B. fragilis can induce and amplify the conversation of effector T cells into phenotypically distinct regulatory T cells. This conversion to a regulatory phenotype is associated with increased IL-10 expression that is known to be insufficient in those with relapsing MS. This study sets a paradigm for further studies into the therapeutic
Introduction: Vitamin D deficiency is a risk factor for multiple sclerosis (MS). Low vitamin D levels are associated with increased risk of brain lesions, relapses and early progression of disability. Vitamin D levels have been associated with disease activity mainly in relapsing remitting and to a lesser extent in progressive forms of the disease. 

Objectives: To examine the association between vitamin D levels and MRI features in progressive multiple sclerosis subjects (primary progressive [PPMS] and secondary progressive [SPMS]) from the ibudilast phase II clinical trial (NN201/SPRINT-MS).

Methods: 25 OH vitamin D levels (D3 and total D) were conducted on baseline serum samples from the subjects enrolled into the NN102/SPRINT-MS trial. Clinical and disease data included demographics, disease history, Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), T2 lesion volume, T1 lesion volume, brain parenchymal fraction (BPF), whole brain MTR (WBMTR), normal appearing brain tissue MTR (NABT MTR), and normal appearing grey matter MTR (NAGM MTR). Associations between vitamin D levels and MS features were determined using Pearson correlation and multivariate regression analyses.

Results: The sample included 267 patients (Age 55.6±7.4, 47.2% male, and 51.3% PPMS) who had both baseline key MRI data and vitamin D levels. No difference between PPMS and SPMS was found for mean D3 (40.7 vs. 39.9 ng/ml) and total D (43.8 vs. 42.9 ng/ml). Positive associations were found between D3 and MRI measures including WBMTR (r=0.17, p=0.007), NABT MTR (r=0.12, p=0.07) and NAGM MTR (r=0.15, p=0.02), but the associations with total D was not significant. There was no significant association between D3 or total D and other MRI measures including BPF, T2 lesion volume, T1 lesion volumes, or clinical measures. Associations between vitamin D3 level and WB MTR reminded significant (p=0.02) in multivariate analysis with consideration of age, gender, disease duration, time of serum obtained and latitude of study site. Every 10 ng/ml increase in vitamin D3 resulted in a 2.1 percent unit increase in WB MTR.

Conclusions: Vitamin D levels were significantly associated with whole brain MTR, but not with BPF, T2 lesion volume, T1 lesion volume, or clinical measures in progressive MS. Vitamin D may carry a protective role in myelin content in progressive MS patients.

Disclosure

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P487

Latent γHV-68 infection facilitates MS-like symptoms through memory B cells in EAE

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While the description of genetic and environmental factors responsible for the onset of Multiple Sclerosis has remained elusive, it is believed that previous infection with Epstein Barr Virus (EBV) plays an important role in the development of MS. Here, we demonstrate that latent EBV infection alters the immune system’s response in genetically predisposed individuals, exacerbating autoimmunity. To examine this hypothesis we developed a murine model where latent infection with gamma herpesvirus 68 (γHV-68), the murine homolog to EBV, enhanced the symptoms of experimental autoimmune encephalomyelitis (EAE), resulting in disease that more closely resembles MS development in humans. Latency of γHV-68 primarily occurs in memory B cells. We show that latent infected memory B cells are capable of enhancing EAE symptoms when transferred from mice latently infected with γHV-68 into uninfected mice. When B cells are depleted with an antibody similar to the drug Rituximab, a recovery of Th17 cells without a concomitant change in Th1 frequencies or an obvious antibody similar to the drug Rituximab, a recovery of Th17 cells during disease initiation and likely communicate with APCs prior to EAE induction for priming of Th1 cells. This suggests that these signals persist in the mouse even after B cell depletion. Using RNAseq analysis, we identified 22 genes that differ between B cells from latently infected and uninfected mice. Increased expression of Integrin alpha 4 (ITGA4) also called CD49d was confirmed by RT-PCR and flow cytometry analysis of memory B cells from latently infected mice. Interestingly, Natalizumab, a monoclonal antibody therapy for MS acts specifically on CD49d. Increased CD49d expression is critical to observed virus mediated disease enhancement and acts as a biomarker for disease and virus latency. Directing therapies focused on the latent virus could result in more effective and less aggressive treatments.

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P488

Synergistic effects of combined sodium chloride and saturated long chain fatty acid challenge on differentiation of Th17 cells in neuroinflammation

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Background: Growing evidence suggests that ingredients of a ‘Western diet’ like high intake of sodium chloride (NaCl) and long-chain saturated fatty acids (LCFA) may impact immune responses in multiple sclerosis (MS). Recently, we have shown that high dietary salt as well as LCFA, like lauric acid (LA), aggravate T helper (Th) 17 cell responses and the course of experimental autoimmune encephalomyelitis (EAE). However, there is still little understanding on the mechanisms linking environmental factors to disease pathogenesis, genetic predisposition, and the immune system in MS. Here, we investigate synergistic effects of combining increased NaCl concentrations and LA on CD4+ T cell populations in neuroinflammation.

Methods: Naïve CD4+ T cells were treated with an excess of 40 mM NaCl and/or 250 µM LA in vitro to investigate Th cell differentiation, cytokine secretion and gene expression. We employed ex vivo analyses of murine myelin oligodendrocyte glycoprotein induced EAE to investigate effects of a combined salt and LCFA challenge on disease severity and T cell subsets in vivo.

Results: The combined challenge of LA with NaCl enhanced the differentiation of Th1 (30.2% ctrl vs. 46.9% NaCl+LA) and Th17 cells (1% ctrl vs. 4.5% NaCl+LA) as well as pro-inflammatory cytokine and gene expression compared to controls in vitro (n=4-5; p<0.05). For Th17 cells, an additive effect of LA and NaCl was observed in differentiation assays (4.5% NaCl+LA vs. 2.5% NaCl resp. 2.7% LA, n=5, p<0.01) and on IL-17, GM-CSF and IL-2 gene expression (n=4; p<0.05). In EAE, the combination of a NaCl- and LA-rich diet aggravated the disease course (score 2.4±0.7 ctrl vs. 3.4±0.6 NaCl vs. 3.7±0.6 NaCl+LA, n=15-20 per group, p<0.01) and increased T cell infiltration into the central nervous system (CNS) by around one third (n=9-13, p<0.05).

Conclusions: Our findings demonstrate additive effects of NaCl and LA on Th cell polarization and pro-inflammatory cytokine expression in vitro. In the EAE model, a NaCl- and LA-rich diet exacerbated disease course and Th cell responses. These data further underline the relevance of a ‘Western diet’ as risk factor for MS.

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Fresh fish consumption is associated with a lower risk of multiple sclerosis independent of serum 25OHD levels

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Background: Oily fish is the best dietary source of both vitamin D and omega-3 polyunsaturated fatty acids (PUFAs), both of which may play a protective role in multiple sclerosis (MS).

Methods: We examined the association between fish consumption and risk of MS using data from the MS Sunshine Study, a multi-ethnic matched case-control study of incident MS or its precursor, clinically isolated syndrome (CIS), conducted in a Southern Californian population. Information on fish consumption over the 12 months prior to symptom onset/index date (567 cases, 618 controls) was collected via 2 questions during a structured in-person questionnaire. We used logistic regression models to test associations between fish consumption and MS/CIS, adjusting for age, sex, race/ethnicity, history of infectious mononucleosis, education, smoking and desesonalised serum 25-hydroxyvitamin D concentrations.

Results: Compared with consuming fresh fish less than once per month, consuming fresh fish 1-3 times per month (adjusted OR=0.71; 95%CI 0.54, 0.93; p=0.014) or once per week or more was associated with a 29% reduced risk of MS/CIS (adjusted OR=0.71; 95%CI 0.53, 0.95; p=0.022; p=0.017 for trend). There was no statistically significant association between consuming shrimp/canned/dried fish and risk of MS/CIS. No multiplicative interaction of fish consumption with race/ethnicity on risk of MS/CIS was detected.

Conclusions: These results support a protective effect of fresh fish consumption for risk of MS that is independent of vitamin D status and consistent across racial/ethnic groups. Future studies should elucidate whether specific components of fish (namely omega-3 PUFAs) are protective or whether the replacement of other potentially detrimental foods are factors in reducing the risk of MS.

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Short-term exposure to ambient air pollution and occurrence of multiple sclerosis relapses

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**P491**

**Different environmental stimuli may activate common biological processes potentially involved in multiple sclerosis**

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We used a “candidate interactome” (i.e. a group of genes whose products are known to physically interact with a given environmental or cellular factor) approach to identify and characterize cellular functions and molecular processes that may participate to the etiology of multiple sclerosis (MS), interacting with predisposing genetic variants. For this study, we considered interactomes representative of factors and biological processes known to be or not involved in MS. Twenty candidate interactomes were obtained from the literature: 9 viruses, 1 bacterium, 10 cellular factors (9 proteins and 1 noncoding RNAs target repository). The genome wide association data were obtained from the latest published GWAS in MS: a) the first data set published in 2011; b) Immunochip data, published in 2013, in which were studied SNPs selected from autoimmune associated loci. Association List Go AnnoTatOR (ALIGATOR) program was used to search for statistical enrichment of associations between interactome’s genes and genome-wide association data (considering all the SNPs with a p-value< 0.05 of association with diseases). We compared the interactome analysis performed on MS with that performed on other complex diseases: type 1 and type 2 diabetes, rheumatoid arthritis, inflammatory bowel disease, bipolar disorder, hypertension, coronary artery disease (GWAS obtained from the Wellcome Trust Case Control Consortium,2 (WTCCC2)). The viruses result as the interactomes more associated with MS, mainly herpes viruses and among them Epstein-Barr virus. The associations observed seems to be specific for MS and not shared with other complex diseases with autoimmune component (e.g. Rheumatoid arthritis). After ALIGATOR analysis we obtained a list of MS-associated genes (n= 741) and related SNPs that we further analysed highlighting biological functions (CD40 signalling and stress-induced antiviral cell response) and protein binding enrichment (POLR2A and CTCF) common to different MS-associated interactomes. The interactome approach allowed us to confirm and refine the association of viral infections with MS through the interaction with genetic factors. Our data suggest that different environmental stimuli may activate common biological processes potentially involved in pathological manifestations.

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**P492**

**Post-vaccination autoimmune CNS demyelination in a family with MOG antibodies - genes or environment?**

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**Background:** IgG (immunoglobulin G) antibodies against myelin oligodendrocyte glycoprotein (MOG) have been described in patients with acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorder, monophasic/recurrent optic neuritis (ON) or transverse myelitis (TM), and atypical MS. However, the processes leading to disease manifestation remain elusive. The high prevalence of MOG-IgG in ADEM, the manifestation of which is often preceded by vaccinations or infections, strongly suggests an environmental trigger.

**Objective:** To decipher the environmental, genetic and immunologic mechanisms underlying MOG antibody-associated autoimmune demyelination in a family after vaccination.

**Results:** A 44-year old female with a history of post-vaccination ON 13 and 10 years prior presented with cervical TM two weeks post-immunization against tetanus, diphtheria, polio, pertussis and rabies. High levels of MOG-IgG were detected at disease onset in serum and cerebrospinal fluid (CSF) and rapidly declined with clinical improvement over weeks following steroid treatment. Likewise, her daughter and son, but not the husband and another daughter, reported fever and temporary visual disturbances/paraesthesia following the same set of vaccinations and were MOG-IgG seropositive. HLA-typing was performed in all family members to assess for genetic predisposition.

To decipher whether molecular mimicry or bystander activation would account for the association between vaccination and MOG-IgG positive myelitis, we isolated B cells from the patient’s CSF and peripheral blood identifying MOG-specific B cells, which have been tested for reactivity against vaccine antigens. T cells from patient’s CSF were also cloned in order to identify their specificity towards MOG and vaccine peptide libraries.

**Conclusion:** To our knowledge, this is the first clinical and immunological study of post-vaccination CNS demyelination associated with MOG-IgG. Elucidating the immunological link between vaccination and autoimmune CNS inflammation in this family provides fundamental insights into the interplay between genetics and environment leading to disease manifestation. This study provides relevant insights for future investigations of environmental triggers of CNS autoimmunity with known and unknown antigenic targets.
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Dr. Jörg is Deputy Editor of Neurology, Neuroimmunology and Neuroinflammation and is a member of the advisory board for the International Society of Neuroimmunology. He has served on the Editorial Board of the Journal of Clinical Investigation, The Journal of Immunology and The Journal of Neurological Sciences, and has been a charter member of the grant review committee for the National Institutes of Health (NIH) Clinical Neuroimmunology and Brain Tumors (CNBT) study section and the National Multiple Sclerosis Society (NMSS). He has served as a consultant and received honoraria from Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc., and has served or serves on Data Safety Monitoring Boards for Lilly, BiomS, Teva and Opera Therapeutics. Currently, Dr. Jörg receives research grant support from the NIH, the NMSS, the Maisin Foundation, Biogen and Celgene.

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Salt-sensitive alterations in gut microbiota impact Th17 cells and neuroinflammation
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Background: Recently, we have shown that high salt concentrations promote pathogenic Th17 responses and aggressive autoimmunity. Furthermore, the importance of the gut microbiome for multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) has recently been recognized. The induction of Th17 cells was shown to depend on the gut microbiota, yet the effect of high salt on the gut microbiome is still unknown.

Methods: We analyzed fecal pellets from normal salt diet (NSD) or high-salt diet (HSD)-fed mice by 16S ribosomal RNA (rRNA) gene sequencing and AdaBoost classifier. We performed experiments in MOG induced EAE and analyzed spinal cord, splenic and intestinal cells by flow cytometry. In addition, we investigated indole-3-lactate (ILA) in Th17 differentiation assays and analyzed in vivo effects of ILA in MOG-EAE.

Results: HSD feeding resulted in a 1.9-fold higher sodium concentration in feces compared to feces of NSD-fed mice (0.252 vs. 0.133 M). The increased sodium concentrations altered the fecal microbiome, particularly by depleting Lactobacillus murinus. In EAE, exacerbated disease course due to HSD feeding could be prevented by concomitant treatment with L. murinus (NSD: 2.1 ± 0.3 vs. HSD: 3.1 ± 0.2 vs. HSD + L. murinus: 1.6 ± 0.4; n=6-11, p< 0.01). On day 3 p.i., HSD mice displayed a significantly higher frequency of Th17 cells in the small intestine compared to NSD mice, which was reduced in HSD mice concomitantly receiving L. murinus (NSD: 2.2 ± 0.3 vs. HSD: 6.0 ± 1.3 vs. HSD + L. murinus: 2.3 ± 0.6; n=4, p< 0.01). At the maximum of disease, spleen and spinal cord infiltrating Th17 cells were significantly reduced by L. murinus treatment compared to HSD feeding alone. HSD additionally reduced ileal ILA concentrations, a tryptophan metabolite that inhibited Th17 polarization in vitro (vehicle: 9.7 ± 0.4% vs. ILA 200µM: 3.9 ± 0.3%, n=3). Oral ILA treatment of HSD-fed mice beneficially influenced the EAE course and reduced the frequency of Th17 cells in the spinal cord (NSD: 12.9 ± 0.3 vs. HSD: 18.7 ± 1.7 vs. HSD + L. murinus: 13.2 ± 1.5; n=4-5, p< 0.05). ILA may thus link the HSD-induced suppression of L. murinus to the induction of Th17 cells.

Conclusion: Our results link the detrimental effects of high salt consumption to the gut-immune axis and highlight the gut microbiome as a new therapeutic target to counteract salt-sensitive pathologies.

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Comparison of humoral immunity against acid-fast bacilli lipophilic antigens in patients with Japanese MS and NMOSD

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Background: BCG is a live attenuated strain of Mycobacterium bovis, the causative agent of tuberculosis in cattle and occasionally in human, and it is mainly used as vaccine against tuberculosis. Even if the exact mechanisms behind the effects of BCG in neuro-inflammation are unclear, it is generally accepted a protective role of BCG vaccination on MS progression. Compared to Japan, BCG vaccination is not mandatory in European countries. Also, Japan not only shows a low prevalence of MS compared to Caucasian countries but also reports a low prevalence of MAP-infected individuals. Therefore it is likely the even the same acid-fast bacilli, BCG and MAP have different influence on MS individuals.

Objective: Since few studies have been carried out so far on the humoral response elicited by BCG, here, we evaluated the humoral immunity to MAP and BCG-specific antigens in Japanese patients with MS and NMOSD.

Patients and methods / material and Methods: A total of 51 MS, 46 NMOSD patients and 34 healthy controls were tested by indirect ELISA for the detection of IgG, IgM and IgA against MAP and BCG lipophilic antigens. Further, competitive assays to assess potential cross-reactivity between antibodies from different mycobacterial species were performed.

Results: Overall, the humoral response mounted against BCG lipophilic antigens was elevated but in the case of MS groups, the antibody-titer of majority of subjects were still below the cut-off point. Anti-BCG IgG antibodies were detected in 8% of MS, 32% of NMOSD and 18% of HC's, the difference between MS and NMOSD groups was statistically significant (AUC=0.66, p=0.005). The levels of anti-MAP IgG were higher in MS patients compared to NMOSD patients (AUC=0.59, p=0.02) and HC's (AUC=0.67, p=0.01), and the anti-MAP antibodies were more prevalent in MS patients treated with interferon-beta (OR = 11.9; p = 0.004). Competition experiments showed the specificity on the detection of anti-BCG antibodies, while nonspecific IgM were elicited by common mycobacterial antigens.

Conclusion: BCG subcutaneous vaccination seemed to be inversely related to the risk of developing MS. MAP exposure and sensitization through digestive organs seems to be the risk of MS. Further research is needed for the potential therapeutic use of the BCG vaccine in patients at risk of developing MS.

Disclosure

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Smoking is associated with increased relapse rate in natalizumab-treated MS


Background: Smoking has been associated with an increased MS risk, and interactions between smoking and HLA genes have been shown to exert an effect on MS risk. Furthermore, smoking seems to be important for disease worsening and progression in MS patients. Recently we found that smoking was associated to an increased relapse rate in interferon-beta treated relapsing-remitting (RR) MS patients. To our knowledge the effect of smoking on the natalizumab-treatment response has not been investigated. C-reactive protein (CRP), a marker of systemic inflammation, is increased among smokers, but the influence on treatment response has received little attention.

Objective: To investigate if smoking is associated with clinical disease activity in RRMS patients treated with natalizumab, and whether there is an interaction between smoking and HLA-DRB1*15:01 and HLA-A*02:01 on treatment response. Further, to investigate if CRP levels during treatment are associated with the relapse rate or smoking intensity in the patients.

Methods: In total 355 natalizumab-treated RRMS patients were assessed for this study. Pre-specified exclusion criteria excluded 46 patients. Clinical data from treatment start to either treatment stop or to the two-year follow-up visit were collected. Smoking status was obtained by a questionnaire survey, and smoking intensity was defined as cigarette packs per day. TaqMan allelic discrimination was used for genotyping of tagging SNPs for HLA-DRB1*15:01 and HLA-A*02:01. Negative binomial regression analysis and Spearman rank correlation analysis was used to analyse the association between relapse rate and smoking intensity, HLA and CRP. In the primary analysis sex and age was used as co-variates whereas BMI was included in the CRP analysis.

Results: 309 RRMS patients were eligible; 81 men and 228 women, of whom 305 answered the questionnaire. We found that smoking intensity was significantly associated with the number of relapses during treatment with natalizumab (incidence rate ratio=1.35, 95% CI: 1.04-1.74, p=0.023). The CRP concentration correlated with smoking intensity (SRCC=123, p=0.033), but there was no relationship between relapses and CRP levels or the two HLA types.

Conclusion: Smoking is associated with an increased relapse rate in natalizumab-treated patients with RRMS. We did not find an association between relapses and CRP or the two HLA types. These findings enhance our knowledge on the harmful effects of smoking in MS.

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Lars Børnøs has nothing to declare.

Cecilie Ammitzbøl has nothing to declare.

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Per Soelberg Sörensen has received personal compensation for serving on scientific advisory boards, steering committees or independent data monitoring boards for Biogen Idec, Merck Serono, Novartis, Genzyme, Teva Pharmaceutical Industries Ltd., GlaxoSmithKline, medDay Pharmaceuticals and Forward Pharma and has received speaker honoraria from Biogen Idec, Merck Serono, Teva Pharmaceutical Industries Ltd., Genzyme, and Novartis.

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P496
Vaccines increase the risk of relapses in neuromyelitis optica spectrum disorder among untreated patients

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Objectives: We investigated the temporal association of vaccinations with relapses in neuromyelitis optica spectrum disorder (NMOSD).

Methods: This is a multi-center retrospective analysis of 90 patients who received a total of 211 vaccinations and experienced 340 relapses over a median disease course of 6.6 years. The likelihood of a relapse occurring within 30, 60, and 90 days of a vaccine was compared to the likelihood of a relapse occurring within each time point of a randomly generated date. We also compared the relapse rate between patients who received any vaccination(s) given time frames (p < 0.011, 0.003, 0.009, respectively) only among patients with NMOSD who were not on preventive immunotherapy. Among patients with NMOSD who were on immunotherapy to prevent relapses, there was no significant risk of relapse associated with vaccines. Additionally, among patients on immunotherapy, the annualized relapse rate of those who received routine vaccinations was significantly lower than in unvaccinated patients.

Results: We identified seven patients with NMOSD who relapsed within 30 days of a vaccination, six between 31-60 days, and four who relapsed between 61-90 days. The rate of vaccine-associated relapses within 30, 60, and 90 days of a vaccine was significantly higher than the likelihood of a relapse spontaneously occurring within each of the given time frames (p < 0.011, 0.003, 0.009, respectively) only among patients with NMOSD who were not on preventive immunotherapy. Among patients with NMOSD who were on immunotherapy to prevent relapses, there was no significant risk of relapse associated with vaccines. Additionally, among patients on immunotherapy, the annualized relapse rate of those who received routine vaccinations was significantly lower than in unvaccinated patients.

Conclusions: The evidence suggests that there is a risk of vaccination-associated relapses among untreated NMOSD patients; however immunosuppressive therapy at time of vaccine aborts the risk.

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P498
Relevance of the microbiota during the autoimmune phase in a viral model of multiple sclerosis

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Background: Recent studies have begun to point out the contribution of microbiota to multiple sclerosis (MS) pathogenesis. Gut microbiota depletion reduced the onset and severity of EAE and lactobacilli mixture administration was able to mediate a therapeutic effect in the EAE model by IL-10 producing regulatory T cells.

Goal: To investigate the effect of gut microbiota changes during the autoimmune phase in a viral model of MS.

Methods: SJL/J mice were intracerebrally inoculated with Theiler’s virus and once the disease was established, mice were orally treated with the probiotic Vivomix (3x10^8cfu) during two weeks, three times a week (n=6). Other group of TMEV-mice was provided autoclaved drinking water supplemented with broad

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spectrum antibiotics (ampicillin, metronidazole, neomycin sulfate and vancomycin) during 14 days before and 14 after the disease was onset (n=6). The groups of control animals were taken into account. Motor function was assessed by the Activity cage as disease severity indicator. The inflammatory response by quantifying leukocyte infiltrates, microglia status and gene expression of cytokines in the spinal cord.

**Results:** Both antibiotic and probiotic treatment improves motor function in TMEV mice (p<0.05); decreased proinflammatory cytokines (IL-1 (TMEV+vehicle=1±0.3; TMEV+ABX=0.08±0.01; TMEV+Vivomixx=0.27±0.05); IL-6 (TMEV+vehicle=1±0.3; TMEV+ABX= 0.04±0.005; TMEV+Vivomixx=0.05±0.01)) and increased the anti-inflammatory cytokines (IL-4 (TMEV+vehicle=1±0.6; TMEV+ABX= 13.7±1.9); IL-10 (TMEV+vehicle=1±0.2; TMEV+ABX= 1.7±0.17; TMEV+Vivomixx=2.52±0.03) as well as the FoxP3 mRNA transcripts (TMEV+vehicle=1±0.3; TMEV+ABX= 7.14±0.8; TMEV+Vivomixx=2.96±0.6) . While probiotic administration did not modify CD4 and CD8 T cells infiltrated in the spinal cord, the antibiotic treatment shows a tendency to increase without reaching statistical significance. Antibiotics shape microglia inducing a morphologic activation state in the spinal cord of TMEV mice; although antibiotic treatment did not induce microglial changes.

**Conclusions:** These preliminary results show that both microbiota depletion and gut microbiota composition changes improve the clinical signs in the Theiler’s murine model of MS. Further experiments are being performed from a mechanistic approach.

**Disclosure**


XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanoﬁ-Aventis, Teva Pharmaceuticals and Almirall.

**P499**

**Smoking on disability accumulation in neuromyelitis optica and multiple sclerosis**

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**Introduction:** Smoking is a risk factor for developing Relapsing Remitting Multiple Sclerosis (RRMS) and has shown to accelerate conversion to Secondary Progressive MS (SPMS) through unclear mechanisms. The effect of smoking on Neuromyelitis Optica Spectrum Disorder (NMOSD) accumulation of clinical disability is unknown. We aim to compare the effect of smoking on relapse rates and accumulation of disability in these two diseases.

**Methods:** We collected the following data from the MS and NMOSD databases: smoking status (ever/never), age at onset, gender, disease duration, time to first relapse, the number of relapses within the first 2 years from disease onset, the time from disease onset to reaching EDSS 6 and time taken until conversion from RRMS to secondary progressive (SP) MS. Smokers and non-smoker were age and gender matched.

**Results:** We have included 101 NMOSD AQP4 positive cases (31 ever smokers, 70 never smokers) and 159 MS cases (53 ever smokers, 106 never smokers). Annualised relapse rate in the first two years did not differ when NMOSD smokers (0.41) were compared to NMOSD non-smokers (0.43) nor when MS smokers (0.53) were compared to MS non-smokers (0.51). Smoking increased the risk to reach EDSS 6 in NMOSD patients (univariate, HR=2.25, p=0.049, 95% CI 1.0-5.0). In MS, when controlling for age and sex, smoking did not influence the time to reach EDSS 6 (univariate, HR=1.4, p=0.317, 95% CI 0.7-2.6; multivariate, HR=1.6. p=0.171, 95% CI 0.8-3) but affected the risk of converting to SPMS (multivariate, HR=2.32, p=0.013, 95% CI 1.2-4.5).

**Conclusions:** Our study suggests that smoking impacts accumulation of disability in NMOSD and the risk of converting to secondary progressive MS but does not influence relapse rate in these two disorders.

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**Neurobiology**

**P500**

**Rapid and efficient generation of human oligodendrocytes from induced pluripotent stem cells to model demyelinating diseases**

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Multiple Sclerosis (MS) is the most frequent demyelinating disease of the central nervous system (CNS) in Central Europe. In chronic MS lesions oligodendroglial precursor cells (OPC) fail to differentiate into mature oligodendrocytes leading to chronically demyelinated axons which are prone to loss of function and axonal injury. An efficient protocol for the derivation of human oligodendrocytes (OL) from induced pluripotent stem cells (iPSC) is hence of great interest as it could offer novel opportunities to study demyelinating diseases. However, there is a lack of fast and efficient protocols for disease modelling and compound screens. To circumvent these obstacles, we developed a fast and reproducible protocol to generate O4+ OL from iPSC within 28 days using a combination of three transcription factors. Within an additional 7 days, these iPSC-derived OL (iOL) could further be differentiated into MBP+ cells.

We at first tested the iOL for drug screening applications. Therefore, we examined the differentiation ability of iOL with regard to several drug candidates known to promote oligodendroglial differentiation in rodents. We found increased percentages of MBP+ and O4+ cells in response to treatment with several of these candidates indicating the applicability of iOL for the identification and testing of drugs.

To determine whether iOL can be used for disease modelling we generated iOL from patients with frontotemporal dementia which harbor the N279K mutation in the gene encoding tau. Comparing these lines to gene-corrected controls, we found a significantly enhanced stress response in iOL from mutated lines demonstrating that iOL are suitable for disease modelling.

To address the question whether oligodendrocytes from MS patients may display an oligodendroglial phenotype, we generated patient specific iOL from MS patients and age-matched healthy control individuals. Comparison of the differentiation ability revealed no differences in their capability to differentiate into O4+ and MBP+ cells. Furthermore, we compared iOL from MS patients and controls with regard to migration and stress response.

In summary, we developed a protocol that allows for the generation of large numbers of iOL which are suitable for drug screening applications as well as disease modeling and thus holds great potential for improving our understanding and treatment of demyelinating diseases such as MS.

Disclosure

M.E. and T.K. have a pending patent application for the oligodendroglial differentiation protocol.

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PS03
Proteomic analysis of CNS-derived microvesicles in the cerebrospinal fluid of MS
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Background: Multiple Sclerosis (MS) is characterized by a diffuse inflammation, which involves both grey and white matter of the Central Nervous System (CNS). While higher concentrations of extracellular microvesicles (MVs) have been demonstrated in the cerebrospinal fluid (CSF) of MS patients, their role in the immune-pathogenesis of the disease is still unclear.

Aim of the study: To perform the proteomic analysis of MVs derived from the CSF of MS patients.

Methods: CNS-derived MVs were purified from the CSF of 3 patients with early-onset Relapsing Remitting Multiple Sclerosis, 3 patients with Clinically Isolated Syndrome (CIS) and one subject with unspecified white matter abnormalities. The diagnosis was achieved in agreement with the McDonald 2010 criteria. CSF specimens were analyzed by “proteomic phenotyping” approach. The proteomic analysis of CNS-derived MVs was performed using nanocapillary liquid chromatography-tandem mass spectrometry (nano-LC-MS/MS). Protein MVs were separated by SD-SAGE and the proteins were digested in-gel with trypsin to obtain peptides that were fragmented using nano-LC-MS/MS. All MS/MS data were searched against a human protein database downloaded from the NCBI database (www.ncbi.nlm.nih.gov).

The classification of MVs protein content was based on Gene Ontology for cellular localization and biological process, using DAVID and GORILLA softwares.

Results: Proteins identified by proteomic analysis showed a significant enrichment of GO-terms for extracellular vesicles-associated proteins (GORILLA software) exclusively in MS patients. Moreover, DAVID software disclosed that 93 out of 115 proteins (80.9%) were extracellular MVs' proteins, while 20 out of total 115 proteins (17.4%) were associated with myelin sheath.

Conclusions: We identified a higher concentration of extracellular MVs-related protein, as well as a relevant number of myelin-associated proteins in MS but not in CIS patients. A larger cohort of patients should be studied to identify MV-associated proteins as biomarkers of active inflammation/demyelination.

PS02
Astrocytic Junctional Adhesion Molecule-A promotes CNS inflammatory lesion pathogenesis
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Junctional Adhesion Molecule-A (JAM-A) is a versatile cell surface molecule involved in tight junction formation, leukocyte adhesion and signal transduction. During CNS inflammation, leukocytes must traverse the endothelial blood-brain barrier (BBB) and the astrocytic glial limitans (GL) in order to access the parenchyma and induce damage. Recently, we have found that reactive astrocytes at the GL upregulate JAM-A in vitro and in vivo. We hypothesized that astrocytic JAM-A mediates leukocyte adhesion and facilitates cell trafficking into the CNS parenchyma, and thus lesion pathogenesis and clinical disability. To selectively delete JAM-A from reactive astrocytes, we created a conditional JAM-A knock-out (CKO) mouse line by crossing mGFP:Cre mice with JAM-A-ΔC mice. To test the importance of astrocytic JAM-A in CNS inflammatory lesion pathogenesis, we induced two models of CNS inflammatory disease in CKO mice and controls: 1) cortical injections of adenovirally mediated IL-1 (AdIL-1) and 2) experimental autoimmune encephalomyelitis (EAE). Lesion size, leukocyte and soluble factor entry, neuronal death and demyelination were measured in both models, as well as clinical disability in EAE. To measure effects of JAM-A on astrocyte-lymphocyte binding and gene expression, we performed immunostaining and RNA sequencing on co-cultures of reactive astrocytes and CD3+ T-lymphocytes in the presence and absence of JAM-A. In CKO mice, cortical AdIL-1 lesions contained increased leukocyte numbers, but the location of most cells was restricted to the perivascular space, between the BBB and the GL, and overall lesion size and tissue pathology were reduced. In the EAE model, an increased proportion of CKO mice were resistant to disease, resulting in a decreased disability score compared with controls. In astrocyte-lymphocyte co-cultures, astrocytic JAM-A knock-down led to decreased astrocyte-lymphocyte binding. Collectively, these data suggest astrocytic expression of JAM-A promotes leukocyte migration and tissue damage during CNS inflammation, and clinical disability in an MS model.

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Candice Chapouly: nothing to disclose

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Neurodegeneration

P504
MS as a transmissible protein misfolding disorder
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The fundamental pathogenesis of MS is unknown. Two competing, but not mutually exclusive theories, propose that on the one hand, MS is driven by a dysregulation of the peripheral immune system promoting inflammatory attacks on the CNS, while on the other hand, an initial primary degenerative process may secondarily trigger autoimmunity. We hypothesized that like many human neurodegenerative diseases, MS is a protein misfolding disorder characterized by accumulation of pathological cytotoxic aggregates that can spread through the CNS. One defining property of such diseases is the transmission of pathology to susceptible hosts. We injected 36 human prion protein over-expressor mice intracerebrally with brain homogenate from 10 different primary or secondary-progressive MS patients. Mice were then followed by 9.4T MRI (anatomical and quantitative T2), and terminally, assessed by histology. After 6-12 months incubation, mice injected with MS brain developed variable but significant degrees of pathology, whereas control human brain inculoca (N = 23 mice from 6 different donor brains) did not cause pathology. Passaging (brain homogenate from affected mice injected into a 2nd generation of naïve transgensics) continued to transmit pathology (control: N=17, MS: N=15).

MS-injected mouse brains exhibited significant degeneration of myelin in the corpus callosum and leuкоkortical junction, assessed by QD9 immunohistochemistry. Formic acid-resistant, possibly myelin in the corpus callosum and leuкоkortical junction, assessed by QD9 immunohistochemistry. Formic acid-resistant, possibly disease-causing prion protein aggregates were detected in white matter, and also surrounding vacuoles and neurons in gray matter. Protease resistance, often seen in more conventional prionopathies, was not detected in either human MS brain nor MS-inoculated mice.

Conclusion: our results are consistent with the hypothesis that MS may be a primary degenerative disorder caused by accumulation and propagation of atypical pathogenic prion protein, that can transmit pathology to humanized murine hosts. We speculate that these pathological conformers are toxic to the myelinating unit, cause degeneration of myelin and release of antigenic debris that could secondarily trigger an autoimmune inflammatory response in genetically and environmentally predisposed hosts. Together, such a convolution of a primary degeneration, potentially driven by an abnormal prion conformer, with secondary inflammation could explain the broad spectrum of human MS phenotypes. Our observations may shed light on the fundamental cause of MS.

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P505
CD320-vitamin B12 links to MS thru S1P1 signaling in activated astrocytes
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Multiple sclerosis (MS) produces central nervous system (CNS) damage including demyelination and neurodegeneration. Sphingosine 1-phosphate (S1P) is a naturally occurring lysophospholipid with 5 receptors, 4 of which (S1P1,3,4,5) mediate effects of phosphorylated fingolimod (FTY720) that is an approved medicine for relapsing forms of MS. A proposed FTY720 mechanism of action (MOA) involves functional antagonism of S1P to reduce lymphocyte egress and pathogenic lymphocytes entering the CNS. However, another proposed MOA involves functional antagonism of CNS astrocyte S1P1, as was identified using experimental autoimmune encephalomyelitis (EAE), an animal model of MS, implicating direct CNS efficacy through astrocyte-intrinsic S1P signaling. How loss of astrocyte S1P1 promotes efficacy is
unknown. Here we identify transcobalamin-vitamin B12 receptor CD320/Tcbl receptor and augmented Type I interferon response genes as downstream effectors of reduced astrocyte S1P1 signaling, which ameliorate MS-like disease endpoints. An unbiased functional screen for cellular activation was developed combining TetTag c-Fos reporter mice with EAE induction to label activated cells with nuclear GFP, allowing construction of a temporal and 3-D CNS cell activation map. Remarkably, over 95% of GFP+ cells were astrocytes that increased linearly with disease. RNA sequencing of disease-activated astrocyte nuclei identified CD320 down-stream of astrocyte S1P1 signaling, which was validated by co-immunolabeling astrocytes and CD320 in mouse and human, and functionally evaluated using both CD320 knockout (KO) and B12-deficient (B12−/−) wild-type (WT) mice that both exhibited marked exacerbation of EAE severity. Notably, FTY720 efficacy in EAE was reduced in B12−/− mice, whereas FTY720 + B12 combination therapy showed synergistically enhanced efficacy. Our results identify astrocyte activation as a key step in EAE disease progression that can be limited in severity by astrocyte-specific S1P1 signaling to CD320/B12 and Type I interferon response genes. FTY720 and other S1P receptor modulators may therefore be optimized as combination therapy using B12 and/or interferons, with further implications for treating progressive forms of MS through direct CNS effects on astrocytes.

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P506
Demelination controls epigenetic changes in multiple sclerosis hippocampus

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Background: Multiple Sclerosis (MS) is an immune-mediated demyelinating disease of the human central nervous system (CNS). Memory impairments and hippocampal demyelination are common features in MS patients.

Objectives: Epigenetics is defined as modulation of gene expression in a manner that is not dependent upon changes in DNA sequence and is a term widely used to describe mechanisms of transcriptional and translational regulation within the cell. DNA methylation is a common epigenetic modifier of gene expression. The current study aims to identify DNA methylated positions and target genes following demyelination in MS hippocampus.

Methods: We compared levels of DNA methylation and de-methylation enzymes as well as global methylation profiles to identify altered methylation positions and target genes in MS hippocampus and to determine the cellular identity of the target genes in both mouse and human brain.

Results: DNA methyltransferase mRNA levels were increased while de-methylation enzymes were decreased in demyelinated MS hippocampus. Comparative methylation profiling identify hypo-methylation within upstream sequences of 6 genes and hyper-methylation of 10 genes in demyelinated MS hippocampus. Independent validation using RT-PCR revealed that DNA methylation inversely correlated with mRNA levels of the candidate genes. Queries across cell-specific databases revealed that a majority of the candidate genes are expressed by astrocytes and neurons in mouse and human CNS.

Conclusions: Taken together, our results identify additional candidate genes in MS hippocampus and establish DNA methylation as a mechanism to alter gene

Disclosure

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Conflict of interest: None

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Longitudinal follow up of optical coherence tomography determined MS phenotypes with retinal and brain imaging

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Background: Optical coherence tomography (OCT) is a reliable, reproducible non-invasive retinal imaging technique. There is growing evidence supporting OCT as a complementary tool to MRI for tracking neurodegeneration. In this regard, the ganglion cell layer+ inner plexiform layer (GCIP) thickness shows greatest utility due to its sensitivity and reproducibility. A number of OCT determined MS phenotypes have been described including macular thinning predominant (MTP; combination of average macular thickness < 5th percentile and retinal nerve fiber layer thickness between the 5-95th percentiles), and macular microcystoid pathology (MCP; cystoid changes mainly in the inner nuclear layer). Biological differences in these phenotypes over time remain unclear.

Objective: To determine longitudinal changes in MRI and OCT of MTP, MCP and non-MTP/MCP (nMTPC) MS patients.

Methods: 51 nMTPC, 26 MTP and 24 MCP MS patients were tracked for a mean duration of 5.4 years. Annual contrast enhanced 3T brain MRI and 6-monthly OCT scans were
performed. Validated image segmentation pipelines developed at Johns Hopkins University were used to analyze both the MRI and OCT data. Mixed-effects linear regression (Stata) was used for statistical analysis.

**Results:** Significant thinning was observed in all retinal layers across MS phenotypes. GCIP annual rates of change were -0.30%, -0.64% and -0.78% in nMTCP, MTP and MCP respectively (p<0.008 for all). The difference in rates of GCIP and outer nuclear layer atrophy were significantly different between the MCP and nMTCP cohorts (p=0.006 and p=0.012 respectively). The difference in rate of GCIP atrophy between the MTP and nMTCP cohorts trended towards significance (p=0.07). Across phenotypes, significant whole brain (p<0.001) and brain substructure (p<0.05, for all) atrophy was observed. In particular, thalamic atrophy was pronounced and faster in the MTP vs nMTCP cohorts (MTP: -0.83%/year vs nMTCP: -0.44%/year, P=0.04 adjusted for age, sex and disease duration).

**Conclusion:** OCT and MRI measures are valuable instruments for assessing tissue loss in MS. This study shows pronounced thalamic atrophy, underpinning the importance of gray matter pathology in MS. OCT defined MTP MS patient exhibit more prominent retinal and brain atrophy, indicating that this phenotype may follow a more aggressive course than nMTCP. Accordingly, phenotype identification and characterization of MTP patients with OCT may help inform clinical care.

**Disclosure**

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**P508**

**Serpina3n: potential biomarker in patients with progressive multiple sclerosis**

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**Background:** This study expands upon previous research from our group in which serpina3n was identified in a time-course transcriptomic and proteomic integrative study, as a candidate biomarker involved in the neurodegenerative process that takes place during the course of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis (MS). Here, we aimed to further investigate into the role of serpina3n in MS by determining the expression of serpina3n in the central nervous system (CNS) of EAE mice and measuring protein levels in the CSF of MS patients.

**Methods:** To investigate protein expression of serpina3n in the CNS during EAE, paraffin-embedded brain and spinal cord tissue sections (6um) obtained from mice at different timepoints during the course of the disease (8, 16, 22, 29, 36, 50 and 90 days post immunization - pi) were stained using immunofluorescent histochernistry (IFHC). Double immunostainings were performed with neuronal markers to determine serpina3n expression in neurons. Serpina3n levels were determined by ELISA in CSF samples from 30 non-inflammatory neurological controls and 65 MS patients [29 relapsing-remitting MS patients (RRMS), 20 secondary progressive MS patients (SPMS), and 16 primary progressive MS patients (PPMS)].

**Results:** Serpina3n expression was significantly increased in the spinal cord and brain of EAE mice compared to controls by day 16 pi and then expression decreased over time. Double IFHC staining revealed high serpina3n expression in neurons during EAE. Serpina3n levels in CSF were increased in RRMS, SPMS and PPMS patients compared with neurological controls (p=0.002, p=0.001, and 1.1 x 10^-4 respectively). Interestingly, PPMS patients had significantly higher levels of serpina3n compared with RRMS patients (p=0.04).

**Conclusions:** Results from this study suggest that serpina3n may be involved in the neurodegenerative process occurring in the CNS during EAE and MS. The finding of higher CSF serpina3n levels in PPMS patients may indicate an association of serpina3n with the progressive phase of the disease. Functional studies are currently underway to investigate the functional implication of serpina3n in the disease.

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**VEGF in cerebrospinal fluid from patients with RRMS, PPMS and ALS**

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**Introduction:** Vascular endothelial growth factor (VEGF) is a signal protein known primarily for promoting angiogenesis, but also has anti-apoptotic features and promotes inflammatory processes. VEGF can also alter blood-brain barrier (BBB) integrity. Its role in the pathogenesis of MS remains elusive. From animal studies in mice (EAE), increased angiogenesis and BBB breakdown is reported in inflamed CNS lesions. Whether VEGF shows different concentrations in CSF from patients with different clinical courses remains unknown.

**Methods:** VEGF was measured in CSF from consecutive patients with relapse remitting multiple sclerosis (RRMS, n=58), primary progressive multiple sclerosis (PPMS, n=55), amyotrophic lateral sclerosis (ALS, n=42) and pseudotumor cerebri (PTC, n=27) with a commercially available ELISA. VEGF concentrations were compared across all groups using the Kruskal-Wallis-test for non-parametric samples.

**Results:** Demographic data and CSF routine parameters are shown in table 1. VEGF-concentrations in CSF are shown in figure 1. VEGF concentration was statistically significantly lower in the RRMS patients compared to all other groups.

**Discussion:** VEGF concentrations are lower in CSF from RRMS patients (32.4 ng/ml) than in PPMS (36.9 ng/ml), ALS (30.5 ng/ml) and PTC patients (35.0 ng/ml). VEGF levels from patients with PPMS and ALS were similar (p=0.05). Our results are in line with Tham et al., who found decreased VEGF expression in CSF from MS patients. This decrease in VEGF levels could be due to a hypoxia-related neurodegenerative processes in PPMS and ALS as chronic progressive diseases, albeit similar levels of VEGF in CSF of patients with PTC may speak against this interpretation. The difference between RRMS and PPMS patients could be a sign of different underlying pathophysiological processes between these disorders.

**Disclosure**

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**P510**

**Leptomeningeal contrast enhancement in multiple sclerosis is associated with grey matter atrophy and higher disability**

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**Background:** Leptomeningeal contrast enhancement (LMCE) on fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI) is supposed to be a possible biomarker of disability and cortical atrophy in multiple sclerosis (MS). Recent studies consider LMCE to be associated with leptomeningeal B-cell infiltrates. In this study, we aimed to assess the prevalence of LMCE foci and their impact on neurodegeneration and disability.

**Materials:** LMCE were detected with a 3 Tesla scanner on post-contrast fluid attenuated inversion-recovery (FLAIR) sequence, using a specific MRI protocol based on original study by M. Absinta et al., 2015. Lesions were detected and characterized by two independent neuroscientists in a blinded fashion. Expanded Disability Status Scale (EDSS) score, number of relapses during 5 years from MS onset and number of contrast-enhancing lesions on T1 weighted MRI were counted. Statistical analysis of covariates (ANCOVA) including age, sex, disease duration and age at clinical onset was performed to determine the impact of LMCE on brain atrophy.

**Results:** 54 patients with MS were included into the study. LMCE was detected in 41% (22/54) patients. LMCE-positive patients had longer disease duration (p=0.0098) and higher EDSS score (p=0.039), but neither a higher relapse rate (p=0.091), nor older age (p=0.071). LMCE-positive patients had no difference in frequency of contrast-enhancing lesions on T1-weighted images compared to LMCE-negative patients (p=0.3842). The statistical analysis revealed a significant effect of LMCE on the grey matter volume (% intracortical volume (mean ± SD)): 44.8 ± 2.8 for LMCE-negative vs. 43.8 ± 2.9 for LMCE-positive, p=0.0391. LMCE showed no significant effect on normalized cortical volume: 33.4 ± 2.1 for LMCE-negative vs. 32.7 ± 2.3 for LMCE-positive, p=0.0912.

**Conclusions:** LMCE was shown to be an independent and significant biomarker of grey matter atrophy. LMCE is associated with longer disease duration and higher level of disability in MS. More studies are needed to define the pathogenesis of LMCE formation and its relevance to the clinical practice.

**Disclosure**

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**Repairing mechanisms**

**P511**

**Human stem cell-based screen for small molecules that promote oligodendrocyte differentiation, myelination, and neuronal survival**

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People with Progressive Multiple Sclerosis (PMS) are in need of effective therapies. While immune modulatory approaches have
provided benefit for many with Relapsing Remitting MS, they do not offer the same level of benefit to those with PMS. One leading hypothesis for this disparity in outcomes is that PMS may result from a more primary neural degenerative and/or myelination defect rather than an inappropriate immune response. Because of the inaccessible nature of human neurons and oligodendrocytes and their progenitors for study, development of new therapeutic approaches has been hindered. To address this need, we have been utilizing human stem cell and genome modification technologies to develop an in vitro assay to rapidly screen small molecule libraries to identify compounds that promote myelination and/or neuronal survival.

Specifically, we have exploited CRISPR/Cas9 technology to genetically modify human stem cells prior to differentiation so that we can then purify and identify the cells of choice. We have developed two distinct dual knock-in reporter systems to allow us to identify and purify oligodendrocytes (OLs) and retinal ganglion cells (RGCs) during various phases of differentiation. To monitor OL differentiation, dual reported human stem cell lines were generated that express the fluorescent protein tdTomato under control of the PDGFβRα promoter, and green fluorescent protein (GFP) under control of the myelin basic protein (MBP). To identify stem cell-derived RGCs, we used the same approach, but with a vector that expresses tdTomato driven by the regulatory sequences for the RGC-enriched gene POU4F2 (BRN3B). This strategy allows us to isolate highly enriched cultures of both OPCs and RGCs. With our OPC differentiation protocol, O4+ OPCs are detected as early as 60 days of differentiation culture, and MBP+ OLs are detected within 100 days; tdTomato+/POU4F2+ RGCs are detected within 25 days. After differentiation we can purify and culture PDGFβRα+ tdTomato+ OPCs and tdTomato+/POU4F2+ RGCs with 90% and 95% purity, respectively. Using these culture systems with a high content screening assay, we are working to identify small molecules that promote myelination and/or neuronal survival. This approach may help in the development of novel therapies that directly target neuronal survival and/or re-myelination.

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Reconstruction of the pan-glial network during induced pluripotent stem cell-derived remyelination process

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Astrocytes and oligodendrocytes make tight glial network providing trophic, structural and metabolic support to neurons. In the CNS oligodendrocytes, as part of glial synctium, are extensively coupled to astrocytes through making heterologous gap junctions on their somata or outer surface of myelin. Molecular disruption of astrocytes-oligodendrocytes communication (loss of Connexin43/Connexin47 connectivity) and thus its effect on neuronal function has been reported in demyelinating diseases. Loss of Cx34 in astrocytes has been shown to have a direct role in repair.

Our preliminary data showed that transplantation of mouse and human induced pluripotent stem cells (iPSCs)-derived neural precursors in adult demyelination condition results in functional remyelination of host axons. Although grafted cells differentiated mainly into oligodendrocytes, they also generated considerable amounts of astrocytes (~20%). Excellent integration of graft-derived oligodendrocytes in the adult CNS was concurrent with considerable astrogliosis (GFAP+/Nestin+) of both endogenous and exogenous sources. The possible impact of (reactivated) astrocytes (and their communication with the graft-derived oligodendrocytes through different connexins) on the observed successful remyelination has not been addressed. Whether graft-derived cells can help reconstruction of lost glial synctium in demyelinating lesion remains elusive.

Our preliminary data showed that both mouse and human iPSC-derived oligodendrocytes expressed Cx47 on their somata and in paranodes where they nicely connected to astrocytic Cx43. Future experiments will reveal the expression of Cx43 or Cx30 in the graft-derived astrocytes, Cx32 and Cx29 in the graft-derived oligodendrocytes, the connection between the endogenous or exogenous astrocytes and/or the endogenous/exogenous oligodendrocytes.

The results of this study will highlight the involvement of astroglial network in the biology of myelin regeneration. SM is recipient of an ECTRIMS postdoctoral fellowship.

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Nodes of Ranvier reclustering can precede remyelination: a role in repair?

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Nodes of Ranvier reclustering can precede remyelination: a role in repair?
Myelination of axons is an essential step to ensure the rapid propagation of action potentials by saltatory conduction, which relies on the nodes of Ranvier, short unmyelinated domains highly enriched in voltage-gated sodium channels (Na\(_\text{v}\)). Various cell adhesion molecules, namely neurofascin-186 and contactin, as well as scaffold proteins (ankyrinG and betaIVspectrin) are also enriched at the nodes and have a critical role in assembly and/or stabilization of Na\(_\text{v}\) clusters in the central nervous system. In demyelinating diseases such as Multiple Sclerosis (MS), nodes of Ranvier are disrupted, which participates in slowing down conduction velocity, leading to functional deficits. How these domains reassemble during remyelination is still poorly understood, though it is a crucial event for the restoration of nervous conduction. Furthermore, the potential influence of nodal re-clustering on remyelination and axonal repair (a crucial need in MS therapeutic strategy) is unknown.

Our aim is to decipher the mechanisms of nodal (re)clustering during development and repair in the central nervous system. Past studies of our laboratory (Coman et al, 2006; Freeman, Desmazières et al, PNAS 2015) showed that Na\(_\text{v}\) can be detected at discrete domains before (re)myelination, both during development and in MS early remyelinating lesions.

We are now studying these early events of nodal clustering \textit{ex vivo} in a model of mouse organotypic cerebellar slices and \textit{in vivo} in the mouse spinal cord, which allows us to follow remyelination. We show that nodal and paranodal structures are highly disrupted after demyelination and that nodal-like clustering can be detected prior to remyelination. Furthermore, we show a direct contact between nodal structures and microglial cells both in control and remyelinating tissue \textit{ex vivo} as well as \textit{in vivo}. We are now taking advantage of this model to decipher the mechanisms of nodal (re)assembly during (re)myelination and characterize its potential impact on repair.

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**Imaging**

**P514**  
Relationships between reorganization of functional brain network topology and cognition in clinically isolated syndrome: a 1 year Resting-state fMRI longitudinal study  
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**Background:** There is a lack of longitudinal study exploring topological organization of functional brain networks at early stages of multiple sclerosis (MS) that could help to understand cognitive compensation.

**Objectives:** To assess potential brain functional reorganization at rest in patients with CIS (PwCIS) in a 1-year longitudinal study and characterize the relationships between brain reorganization and cognitive functioning.

**Methods:** 53 patients recruited less than 6 months after a CIS and 35 matched healthy controls (HC) underwent a 3T MRI scan including 3D T1 weighted images, fluid-attenuated inversion recovery and Resting-State fMRI. 45 PwCIS and 20 HC were recruited 1 year after the first assessment. Destrieux parcellation was obtained using FreeSurfer. Graph-based network measures such as global and local efficiency (Eloc), betweenness centrality (BCN) and degree (Deg) were calculated. Hub disruption index (k) of each parameter was then determined using the slope of the following graph: (param\(_\text{object}\) - param\(_\text{environment}\)) = f(param\(_\text{environment}\)). Attention, working memory (WMem), episodic memory (EMem), executive functions (EF), visuoconstruction, and information processing speed (IPS) were assessed by a neuropsychological battery. Linear regression models were used to predict cognitive changes by baseline brain functional connectivity parameters. Correlations between functional connectivity and cognitive changes during one year of follow-up were performed.

**Results:** No global efficiency differences were observed neither at baseline nor at 1-year of follow-up between patients and HC. k\(_{\text{BCN}}\) was significantly negative at baseline in patients (p< 0.05). At 1 year, patients k\(_{\text{BCN}}\) switched to a significant positive value (p= 0.0001). k\(_{\text{Eloc}}\) and k\(_{\text{Deg}}\) did not differ between patients and controls at baseline and showed a negative value after 1 year in patients (p< 0.0001). Visuo-spatial memory changes were predicted by baseline global efficiency in patients. WMem change was predicted by initial k\(_{\text{Eloc}}\). Verbal EMem and Visuo-construction changes were both predicted by k\(_{\text{BCN}}\). Regarding changes during 1 year, global efficiency was positively correlated to IPS and k\(_{\text{Eloc}}\) to WMem in PwCIS.

**Conclusion:** For the first time, these results suggest dynamic changes of functional brain networks in patients at early stage of MS that are clinically relevant for cognition.

**Disclosure**

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Introduction: Information processing speed (IPS) deficits are amongst the first cognitive symptoms in multiple sclerosis (MS) and are highly debilitating. Although both structural and functional alterations have been associated with IPS impairment, studies overarching both modalities are lacking. In this study, we examined the relative importance of functional and structural brain damage in explaining different levels of IPS impairment.

Methods: IPS was measured using the symbol digit modalities test (SDMT) in 330 MS patients and 96 healthy controls (HC), who also underwent advanced MRI. The severity of structural MRI-damage was measured using whole-brain white matter integrity, atrophy and lesion load. The severity of functional damage was determined by the level of increased and decreased resting-state functional connectivity relative to HC. After comparing all measures between groups, significantly different measures were entered in a backward regression model to select the main predictors of IPS. Selected predictors were then used to create subgroups with mild or severe structural and functional damage, between which IPS performance was compared.

Results: Deep gray matter volume, whole-brain white matter integrity and severity of increased functional connectivity were significant predictors of IPS. Our findings show that MS patients with mild structural and functional damage had the best IPS, albeit still lower than HC (Grade I: z-score of -0.5). MS patients with severe functional damage but only mild structural damage had better IPS performance (Grade II: z-score of -1.0) than patients with severe structural damage but only mild functional damage (Grade III: z-score of -1.5). Patients with both severe functional and structural damage were worst off (Grade IV: z-score of -2).

Conclusion: IPS impairment was worst in patients with both severe functional and structural damage. Damage on either functional or structural measures results in distinct levels of IPS performance. Our findings suggest that the IPS performance of MS patients relies on a complex interplay between GM atrophy, WM damage and functional network changes.

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PS15
The severity of functional and structural brain pathology reflects information processing speed deficits in multiple sclerosis
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PS16
Cortical lesions and their correlates in multiple sclerosis: findings from a large cohort at 7T
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Background: Neuropathological and in vivo imaging studies demonstrated that ultra high field gradient-echo T2* imaging at 7 Tesla (7T) shows increased sensitivity to cortical lesion (CL) detection in multiple sclerosis (MS) relative to lower field strength MRI. Objective To cross-sectionally assess in a large cohort of subjects at different stages of MS the presence of CL pathology on ultra-high resolution 7T T2* scans and investigate their clinical relevance and association with cortical tissue loss.

Methods: Eighty-four MS subjects, 59 with RRMS and 25 with SPMS underwent acquisition of: a) 7T T2*-weighted images (0.33x0.33x1.0 mm) for intracortical (ICL), leukocortical (LCL) and white matter (WM) lesion segmentation, b) 3T 3D T1-weighted scans for cortical surface reconstruction and cortical thickness measurement. Patients were clinically evaluated by means of EDSS and Symbol Digit Modalities Test (SDMT).

General linear models were used to assess the relation between MRI metrics and possible predictors of clinical outcomes, as well as differences in patients with high vs low CL load, based on median CL values.

Results: CL were detected in all MS cases. Overall, subjects with high CL load disclosed a higher WM lesion load (p<0.0005) than cases with low CL load. This difference persisted in RRMS, however, it was lost in progressive disease stages where WM lesion volume was similar across patients with high and low CL load. Stepwise regression analysis demonstrated that the retained predictors of EDSS were ICL count and disease duration (p=0.0005, R²=0.481), while for SDMT LCL count and disease duration (p<0.0005, R²=0.294). Interestingly, cortical thinning was explained by WM lesion volume and disease duration (p<0.0005, R²=0.360).

Conclusion: Our results highlight the relevance of CL pathology in MS and its main contribution to clinical outcome measures. As suggested by previous studies in smaller cohorts, we demonstrate that CL subtypes may have different clinical relevance. Our findings on cortical thickness suggest that a comprehensive evaluation
of cortical pathology in MS needs to include both atrophy and CL assessments, as the pathogenic substrates of cortical tissue loss do not seem to be mainly driven by local cortical pathology.

Disclosure
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P517
Neuroinflammatory component of cerebellar pathology in multiple sclerosis by 11C-PBR28 MR-PET
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Introduction: Cerebellar involvement occurs early in multiple sclerosis (MS), frequently associated with neurological impairment. Pathology in the cerebellum includes demyelination, neurodegeneration and inflammation with microglia activation. The role of microglial cells in the pathogenesis of cerebellar pathology is unknown. Activated microglia upregulate expression of the 18kDa translocator protein (TSPO), which is imaged in vivo using the 11C-PBR28 radioligand.
Objective: To investigate, using integrated 3 Tesla (3T) magnetic resonance-positon emission tomography (MR-PET) imaging with 11C-PBR28, TSPO expression in the cerebellum of a MS cohort, and its association with lesions and atrophy.
Methods: Twenty MS subjects (11 SPMS and 9 RRMS; mean age=48±9; median EDSS= 3.75, range=1.5 to 7.5) and 18 healthy controls (HC; mean age=48±12) matched for PBR28 affinity underwent 90-min 11C-PBR28 MR-PET. Anatomical images for brain and cerebellum segmentation with Freesurfer were also obtained. In MS, cerebellar lesions were segmented on 7T T1 images obtained on a separate session. Quantification of 11C-PBR28 uptake in the whole cerebellum and lesions was assessed using 60-90min standardized uptake values normalized by a pseudo-reference region (SUVR) in the normal appearing basal ganglia. Linear regression models were used to compare cerebellar 11C-PBR28 uptake in MS vs controls, and to assess their relationship with EDSS. Age and/or binding affinity were included as covariates of no interest.
Results: Cerebellar lesions were found in all SPMS and in 6 out of 9 RRMS subjects. Cerebellar volume, normalized by intracranial volume, was reduced in MS vs HC (p=0.02), where it also inversely correlated with cerebellar lesion load (p=0.03). MS subjects showed significantly higher 11C-PBR28 uptake in cerebellar lesions relative to HC cerebellum (p=0.01). No differences in uptake, however, were found between the two groups when assessing the whole cerebellum, nor between SPMS and RRMS. There was a trend for correlation between EDSS and 11C-PBR28 uptake in the whole cerebellum (p=0.09), while no association was found with cerebellar volume.
Discussion: Our data provide in vivo evidence for the presence of microglia activation in the cerebellum in MS. Interestingly, in contrast to findings in the brain, activated microglia were mainly concentrated in lesions. Future studies will assess inflammation in the cerebellar gray matter and test for associations with cognition.

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P518
Preferential spinal cord volume loss in primary progressive multiple sclerosis
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Introduction: About 10-15% of MS patients are characterized by progressive worsening of neurologic symptoms from disease onset without remissions, pointing towards a separate underlying disease entity. In contrast to the relapse-onset subtypes, primary progressive (PPMS) patients frequently present with a progressive paraparesis suggesting involvement of the spinal cord. Furthermore, most clinical trials have failed to show a significant therapeutic effect in PPMS. Our aim was to evaluate cervical spinal cord volume (SCV) loss in PPMS and to determine the correlation to clinical outcomes in comparison to relapse-onset MS subtypes.

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Methods: In 3 groups of age-, sex- and disease duration-matched MS patients (12 PPMS, 24 RRMS and 24 SPMS) we measured upper cervical SCV over 6 years along with the total brain volume (TBV) and brain T2w lesion volume (T2LV) using 3D T1w MPRAGE images with an established semi-automatic software (CORDIAL, Amann et al. 2016), Expanded Disability Status Scale (EDSS) and Timed 25-foot walk test (T25fw) were recorded at each follow-up visit. Between-group differences and correlations between MRI metrics and clinical outcomes were assessed using linear mixed effects regressions.

Results: PPMS patients had a faster of SCV loss over time compared to RRMS (B=-258, p< 0.01) and by trend (p=0.066) also compared to SPMS. In contrast to RRMS and SPMS, in PPMS SCV loss was independent of TBV and T2LV changes. SCV changes were also the only MRI measure correlating with the EDSS change over time (B=8x10^-5, p< 0.01) in PPMS. In RRMS, both TBV and SCV were associated with the average EDSS over 6 years (B=-10^-6 and -5x10^-4 respectively, both p< 0.05), but not with the EDSS changes over time. No MRI measure correlated with the EDSS in SPMS patients.

Conclusions: PPMS patients as compared to RRMS had a higher speed of SCV loss over time, which was independent of global brain atrophy and brain T2w lesion load. PPMS patients also showed an atrophy pattern, which was more severe and restricted in the SC, in contrast to a more global CNS atrophy pattern in relapse-onset MS. Overall, SCV loss was the only strong predictor of disability progression in PPMS, thus making it a promising candidate outcome measure for clinical trials of new therapeutic agents in this patient group.

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P519 Dynamic functional network connectivity in CIS patients: a longitudinal study
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Background: Abnormal intra- and inter-network resting state (RS) functional connectivity (FC) has been described at the earliest stages of MS. However, time-varying properties of RS FC in such patients have never been studied.

Aims: To define the trajectory of dynamic functional network connectivity (d-FNC) changes over a two-year follow-up in patients with clinically isolated syndrome (CIS) suggestive of MS.

Methods: RS fMRI data were acquired from 50 CIS patients and 13 healthy controls (HC) at baseline (within 3 months from first attack), year 1 and year 2. An independent component analysis identified 41 relevant networks, subsequently classified according to their functional system. Between-group differences of dynamism measures and FC strength were analyzed.

Results: Forty-seven (94%) patients developed clinically definite (CD) MS at year 2. In HC and CIS patients, two d-FNC states were identified: state1, frequency=68%, characterized by weak inter-network connectivity; state2, frequency=32%, characterized by strong inter-network connectivity. At baseline, d-FNC properties were similar in CIS patients and HC. FC dynamism tended to increase over time in CIS patients vs HC, with a trend towards a higher distance travelled through connectivity states at year 1 (p=0.07), which further increased at year 2 (p=0.001). At year 2, trends towards higher number of states (p=0.06) and more frequent switches between states (p=0.09) in CIS patients vs HC were also detected. Abnormal FC strengths within the detected d-FNC states were also found. In particular, CIS patients showed a baseline increase of RS FC in state2, especially for the sensorimotor and default mode networks, which was maintained at follow-up visits. At year 1 and year 2, reduced RS FC of the executive and visual networks was also found.

Conclusions: Abnormal d-FNC patterns were detected in CIS patients, which changed significantly over time. After the first attack, CIS patients experienced increased dynamism of strength of RS FC in high-connectivity states, which might be related to acute inflammation. Subsequently, dynamism and strength of RS FC increased, possibly because of compensatory mechanisms. At medium-term follow-up, a "fragmentation" of connectivity was observed, characterized by a further increase of RS FC dynamism and a contemporary decrease of RS FC within defined states.

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Impact of removing facial features from MR images of MS patients on automatic lesion and atrophy metrics


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Background and purpose: Sharing magnetic resonance (MR) images and other information from multiple sclerosis (MS) patients offers many benefits to MS research. However, in this context protecting patients’ privacy is crucial. In addition to removing identifying metadata, MR images should be defaced (i.e. facial features removed from images). Yet, it is unknown whether using defaced images affects assessment of important features from MR in MS. For three recent face removal methods, we assessed their impact on automated MS lesion and whole brain volume measurement.

Material and method: 100 MS patients all with 3.0 T 3D FLAIR and 3D T1 images were included. Images were defaced using Quickshear (Schimke; 2011), Facemasking (Milchenko; 2012), and Defacing (Bischoff-Grethe; 2007). On native images and each type of defaced images, lesion volumes were quantified using LST (www.statistical-modelling.de/lst.html) and whole brain volumes were quantified using SIENAX (Smith; 2002). We first assessed whether defacing introduced systematic changes of whole brain or lesions volumes, by using repeated measures ANOVA with defacing method as categorical variable and testing its effect by an F-test. Next, to evaluate volumetric agreement, we quantified the intraclass correlation coefficient (ICC) for absolute agreement.

Results: At the group level, whole brain and lesion volumes were highly similar between native and defaced images. Median [interquartile range; IQR] lesion volumes were 15.37 [5.67-30.86] mL (native), 15.46 [5.75-31.96] mL (Quickshear), 15.53 [5.87-31.17] mL (Facemasking) and 15.53 [5.87-31.17] mL (Defacing). Median[IQR] normalized whole brain volumes were 1.45 [1.38-1.50] L (native), 1.45 [1.39-1.51] L (Quickshear), 1.46 [1.40-1.52] L (Facemasking) and 1.45 [1.39-1.51] L (Defacing). The defacing methods had no systematic effects on lesion volumes (p=0.46) or whole brain volumes (p=0.99) (F-tests). However, defaced volumes did differ from native volumes: For lesion volumes, ICC with native images was poor for Defacing (ICC=0.23), fair for Quickshear (0.54), and good for Facemasking (0.61). For whole brain volume, ICC was fair for Quickshear (0.59) and Defacing (0.58), and good for Facemasking (0.67).

Conclusion: Defacing has severe impact on the automated assessment of MS lesion volumes and brain volumes by currently popular software methods. Data sharing initiatives in MS research should devise methods to resolve these current shortcomings.
Aim: To investigate the relationship between DGM volume loss and disability progression in a large cohort of MS patients with long follow-up duration and annual assessment.

Methods: 230 MS patients were examined: 179 patients with relapsing-remitting MS (RRMS); 132 women; median expanded disability status scale (EDSS): 2.5) and 51 patients with secondary progressive MS (SPMS; 27 women; median EDSS: 4.5). Patients underwent annual EDSS assessment and magnetic resonance imaging at 1.5 Tesla. The DGM nuclei were identified on high-resolution T1-weighted MPRAGE images using the "multiple automatically generated templates" (MAGiT) algorithm.

Results: In the whole cohort, the thalamus (t=-2.8, p<0.01) and globus pallidus (t=-4.1, p<0.001) showed a faster aVL compared with other age-b, sex, DD-b, time points, total brain volume (TBV) and T2-weighted lesion load in the statistical model.

Discussion

DGM volumes and annual rate of volume loss (aVL) were investigated within groups using a paired t-test and between groups (RRMS vs SPMS) using an ANCOVA model with sex, age, (age-b) and disease duration at baseline (DD-b) as covariates. The relationship between DGM volume changes and EDSS changes was investigated using a linear mixed-effects model (LME) including age-b, sex, DD-b, time points, total brain volume (TBV) and T2-weighted lesion load in the statistical model.

Conclusions: The higher annual rate of volume loss observed in DGM nuclei compared with RRMS (p<0.01), however, no differences in aVL were observed between the groups. In RRMS, thalamic volume changes and changes in lesion load over time, age-b, DD-b, time points, together explained 24% of EDSS change over time. In SPMS, DD-b and the interaction between age-b and time points accounted for 21% of EDSS changes.

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PS22

Whole brain magnetic resonance fingerprinting in multiple sclerosis

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Background: Magnetic resonance imaging (MRI) signal relaxometry seems sensitive to tissue damage in multiple sclerosis (MS). Increased T1 relaxation times have been related to water content while decreased T2* times have been associated to myelin content in normal-appearing white matter (NAWM) and lesions. However, long acquisition times for multiple-parameter quantification so far prevented the integration of these measurements into clinical scan protocols.

Aim: We sought to evaluate the use of fast simultaneous whole brain T1 and T2* quantification based on magnetic resonance fingerprinting (MRF) and to explore the changes in relaxation parameters in patients with MS.

Methods: MRF-EPI was used to acquire 33 axial slices with a resolution of 1.1x1.1x3 mm³. T1 and T2* maps were calculated by matching the fingerprints with a precomputed dictionary. The measurement was performed in 5 MS patients (2 men, 37.6±12.3 years) and 4 healthy volunteers (HV) (2 men, 31.8±5.2 years). In patients, lesions were manually segmented in 3D-Magnetization Prepared Rapid Gradient-Echo and post contrast T1-spin echo images. Grey matter (GM) and NAWM segments were obtained by SIENAX and applied to the MRF images in order to calculate the average T1 and T2* of each compartment.
Results: Whole brain MRF was successfully obtained in all the participants within an acquisition time of 15 minutes. Average T1/T2* values in patients were 1353±236 / 45±12ms in GM and 1207±223 / 48±11ms in NAWM. No significant difference was found in those values compared with HVs, with a tendency to higher variability in NAWM relaxation times in the patients. White matter lesions were clearly visible in T1 and T2* maps. T1 values in lesions (1147±178ms) were lower than in NAWM (p=0.002) while T2* values were higher in lesions (56±9ms) than in NAWM (p=0.005). In one patient two contrast enhancing lesions were detected in T1-spin echo sequence in the brainsstem; those lesions had T1/T2*values of 1404±214 / 42±9 ms in MRF sequence.

Conclusions: Whole brain MRF acquisition is feasible and displays decreased T1 and increased T2* relaxation times in MS lesions, suggesting improved tissue damage characterization. Further, preliminary data indicates that new lesions which enhance with contrast in conventional sequences may have particular behaviour in MRF. Future studies combining MRF with advanced MRI or pathology data could help understanding the underlying pathophysiology mechanisms.

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P523
Longitudinal structural network reorganisation in early relapsing-remitting multiple sclerosis
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Background: Multiple sclerosis (MS) is characterized by relapses and remissions indicating damage and compensatory processes occurring early in the disease. Over time, cortical pathology is highly relevant for disability, while brain networks evolve towards a disconnected organization as the disease progresses. However, it is poorly understood how and when pathology impacts cortical networks and in particular, how the network responds to damage in the very beginning of the disease.

Aim: To address cortical pathology by quantifying structural connectivity patterns over 12 months in patients with early relapsing-remitting MS.

Methods: Here we investigated cortical grey matter networks longitudinally as derived from structural 3 Tesla MRI in 92 patients in the initial phase of the disease (65 female / 27 male; mean age: 32.9 ± 9.9 years; mean disease duration: 12.1 ± 14.5 months) and in 101 healthy controls (59 female / 42 male; mean age: 19.7 ± 0.9 years). Longitudinal brain volume atrophy was analyzed using SIENA and cortical thickness changes were quantified using FreeSurfer. Brain networks were computed based on cortical thickness inter-regional correlations between anatomical regions and fed into graph theoretical analysis. Finally, subgroup analyses were performed between patients with “no evidence of disease activity” (NEDA) during this period and those with disease activity (EDA).

Results: Over one year, increased local cortical connectivity and an emerging modular-constructed network were detected in patients - a pattern reported to be associated with adaptation, efficiency and compensation. These longitudinal dynamics were attested in both patients with NEDA and EDA, indicating continuous cortical reorganisation independent of disease activity. This local and modular cortical reorganisation was not detected in healthy controls over the same period of time and emerged beyond measureable signs of atrophy using established morphometric tools.

Conclusion: Our findings demonstrate that despite initiation of neuroinflammatory damage, substantial structural adaptation processes emerge cortically in the early disease stage. This subtle reorganisation of the cortex architecture is quantifiable by structural MRI in patients with and without disease activity, suggesting a principial response of the network evolving from the onset of this chronic disease.

Disclosure
The authors declare no conflict of interests.

P524
Multiple sclerosis patients who improve in their disability over time develop less brain atrophy compared to those who remain stable or progress
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Aim: To test whether patients with a history of improvement in disability show less atrophy than those who remain stable or progress.

Methods: We investigated a cohort of 69 patients who had improved in their disability (improvement (IMP) group, median age: 38 years; median disease duration: 5 years) over a median follow-up period of 6 years, compared to 41 patients who had remained stable or progressed (control group, median age: 38 years; median disease duration: 5 years) over a median follow-up period of 6 years.

Results: The IMP group had significantly less atrophy in all brain regions as compared to the control group, including the bilateral frontal lobes (p=0.03), right parietal lobe (p=0.03), right temporal lobe (p=0.04), left occipital lobe (p=0.03), and bilateral cerebellar hemispheres (p=0.03). The IMP group also showed less atrophy in the thalamus (p=0.04) and caudate nucleus (p=0.03). The IMP group had significantly lower atrophy rates in the right parietal lobe (p=0.03), right temporal lobe (p=0.04), left occipital lobe (p=0.03), and bilateral cerebellar hemispheres (p=0.03). The IMP group also showed less atrophy in the thalamus (p=0.04) and caudate nucleus (p=0.03).

Conclusion: Our findings suggest that patients who show improvement in disability over time have less brain atrophy compared to those who remain stable or progress.

Disclosure
The authors declare no conflict of interests.
**Background:** While the rate of brain atrophy is accelerated in multiple sclerosis (MS) patients who develop clinical disability over time, it is unclear whether patients who experience clinical improvement have different brain atrophy trajectories, compared to progressing and stable patients. Measurement of lateral ventricular volume (LVV) was recently proposed as a robust, clinically-feasible proxy for whole brain atrophy.

**Objectives:** To investigate whether MS patients who improve in their clinical disability over time develop less brain atrophy compared to those who progress or remain stable.

**Methods:** We enrolled 1,270 MS patients over a period of 10 years (mean time of follow-up 4.6 years). We used Neurological Software Tool for RELiable Atrophy Measurement (NeuroSTREAM) to measure LVV on 6,831 brain scans images (min 2, max 24, and median of 4.0 per subject). Percent LVV change (PLVVC) was determined between all-time points. Subjects were divided in 3 groups: disability progression (DP, n=355), disability improvement (DI, n=124) and stable (n=791). DP was defined as an increase from baseline Expanded Disability Status Scale (EDSS) of at least 1.0 point, or 0.5 if the baseline EDSS score was >5.5. DI was defined as a reduction from the baseline EDSS score of at least 1.0 point if the baseline score was 2.0-5.5, or 0.5 if the baseline score was >5.5. PLVVC differences between age groups were calculated using analysis of covariance, adjusted for age, disease duration and LVV at first MRI, gender, field strength and time of follow up in years.

**Results:** At first MRI, there were no significant LVV differences between stable, DP or DI MS patients. Over the follow-up period, the cumulative PLVVC was 9.0% in DI, 10.7% in stable and 14.8% in DP MS patients. All p values were significantly different (DP/DI/stable, p=0.014; DP/DI, p< 0.0001; DP/stable, p= 0.0001).

**Conclusions:** MS patients who improve in their clinical disability develop less brain atrophy over time when compared to those who progress or remain stable.

**Disclosure**

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**Conclusions:** Using early clinical and radiological predictors, 48% of the variance in physical disability and only 26%...
of variance in cognitive performance at year 6 was explained, indicating the need for more advanced measures to predict cognitive decline. Baseline EDSS and T1-lesion volumes appeared to be important predictors for both EDSS and SDMT scores. Relevant predictors for 12 year follow-up were mostly baseline variables, but not MRI derived volume changes.

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Improved visualization of cortical lesions in multiple sclerosis using MP2RAGE at 7T

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Objective: Cortical lesions (CL) are common and often extensive in multiple sclerosis (MS) but are difficult to visualize by MRI, leaving important questions about their clinical implications and response to therapy unanswered. We set out to determine if using a magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence on 7 tesla (7T) MRI would improve visualization of CLs compared to standard methods using T2* weighted (T2*w) sequences.

Methods: Brain MRI using T1 weighted (T1w) MP2RAGE at 500 mm isotropic resolution, T2*w gradient-echo (GRE), and T2*w echo-planar-imaging (EPI) sequences were collected for 13 patients with MS and 5 age-matched neurologically healthy controls on a 7T research system (Siemens). CLs were identified independently for each sequence and categorized as juxtacortical (JC), leukocortical (LC), or intracortical (IC). An MS case that came to autopsy underwent post-mortem MRI including T2*w GRE and T1w MP2RAGE sequences, after which cortical lesions seen on MRI were confirmed using immunohistochemistry.

Results: T1w MP2RAGE detected 205 CLs in 13 MS patients (median 16 lesions/subject, interquartile range (IQR) 16), compared to 91 CLs with T2*w GRE (median 7 lesions, IQR 9, p < 0.001) and 107 CLs with T2*w EPI (median 8 lesions, IQR 5, p < 0.01). 74 JC lesions were identified on MP2RAGE (median 4, IQR 6) vs 37 lesions on T2*w GRE (median 2, IQR 3, p < 0.05) and 38 lesions on T2*w EPI (median 2, IQR 4, p < 0.05). 99 LC lesions were identified on MP2RAGE (median 10, IQR 9) vs 41 on T2*w GRE (median 2, IQR 3, p < 0.001) and 50 on T2*w EPI (median 4, IQR 4, p < 0.01). For IC lesions, 32 lesions were identified on MP2RAGE (median 2, IQR 2) vs 13 on T2*w GRE (median 1, IQR 1, p < 0.05) and 19 on T2*w EPI (median 1, IQR 1, ns). 36% of all CLs were identified only on MP2RAGE. There was a significant correlation between JC (p < 0.001) but not IC or LC lesion volume with white matter lesion volume, suggesting pathophysiology or evolution may differ between lesion types. Of 4 suspected lesions seen on postmortem T1w MP2RAGE and T2*w GRE and subsequently examined by immunohistochemistry, 3 were found to be true CLs while 1 represented post-mortem tissue damage.

Conclusion: The T1w MP2RAGE sequence at 7T allows for detection of significantly more cortical lesions than T2* weighted sequences. Longitudinal in vivo study of cortical lesions seen on MP2RAGE is ongoing to further investigate the clinical significance of these lesions.

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Lesions with hyperintense rim on quantitative susceptibility mapping demonstrate more inflammation on PET-PK11195

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Background: A subset of chronic lesions, identified as chronic active or slowly expanding lesions have been described as having
an iron-laden rim of pro-inflammatory (M1) activated microglia/macrophages (MG/MΦ). Iron accumulation at the rim of these lesions may be identified as a hyperintense rim on quantitative susceptibility mapping (QSM). The tracer [11C]PK11195 selectively binds translocator protein (TSPO) on activated MG/MΦ and provides an in vivo proxy of inflammation.

**Objective:** To compare the uptake of [11C]PET-PK11195 (PK-PET) in QSM hyperintense rim+ lesions as compared to QSM rim- lesions.

**Methods:** Fifteen patients (10 with relapsing remitting, 5 with progressive MS) with PK-PET and corresponding QSM sequences were included. QSM hyperintense rim+ and rim- lesions were identified. Individual lesion masks were created, and co-registered to PK-PET images. Distribution of volume ratios (VTr) for PK-PET was calculated using Logan graphical method with image-derived input function as a blood input function and presented as a ratio to the individual patient’s NAWM. Differences in PK-PET uptake among rim+ and rim- were evaluated using a mixed-effects-model, controlling for patient variability, rim group, lesion volume and patient age.

**Results:** The 15 patients had a mean age of 40.9 years, a mean disease duration of 10.3 years and a mean EDSS of 1.6. The average time between PET and QSM was 8.7 days. 188 T2 lesions were identified, 37 lesions were QSM rim+ and 151 lesions were rim-. VTr value for rim+ lesions was 1.01, versus 0.91 for rim- lesions. The difference between rim+ and rim- VTr values was significant (p = 0.006) after controlling for multiple lesions per patient, patient age, and lesion volume. On average, VTr values were 0.067 units higher for rim+ lesions.

**Conclusion:** PK11195 uptake was significantly higher in QSM hyperintense rim+ lesions as compared to rim- lesions. This provides in-vivo evidence that QSM can be used to identify a subset of chronic MS lesions with activated MG/MΦ, represented by the presence of iron. Differentiating MS lesions, especially chronic lesions, may provide a biomarker for disease progression and a therapeutic target to reduce on-going inflammation and tissue damage.

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**P528**
Pattern recognition for neuroimaging toolbox PRoNTo: a pilot study in predicting clinically isolated syndrome conversion

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**Aim:** To test whether 3D-T1 weighted structural images in conjunction with the pattern recognition tool PRoNTo could differentiate between clinically isolated syndrome (CIS) patients that converted and CIS patients that did not convert to multiple sclerosis (MS). For that purpose, two different training approaches were used: CIS non-converters and CIS converters, for both training and testing; healthy subjects and MS-treated patients as training, and CIS non-converters and CIS converters as testing. The impact of using filled 3D-T1 weighted structural images has also been assessed.

**Material and Methods:** The study included healthy subjects (n=30), CIS converters (n=45), CIS non-converters (n=45) and MS-treated patients (n=30). Patients were recruited consecutively. CIS conversion was defined according to either MRI or clinical demonstration of dissemination in space and time according to the 2010 McDonald criteria for a 3 years follow-up period. PRoNTo classification training was run with a binary support vector machine and a cross-validation “Leave-one-subject-per-group-out”. Lesion filling was done with the Lesion Segmentation Toolbox.

**Results:** When CIS were used both for training and testing, 63% of CIS non-converters and 65% of CIS converters were correctly classified; the predictive values were 65% and 64% respectively. When healthy subjects and MS-treated patients were used as training, 90% of non-converters were classified as healthy subjects and 50% of CIS converters as MS, and a predictive value was 64% for CIS non-converters and 83% for CIS converters. When the filled 3D-T1 weighted images were used instead of the original 3D-T1 images, the accuracy and predictive values did not improve in any of the two approaches proposed.

**Conclusions:** Results showed that PRoNTo improves their performance when healthy subjects and MS-treated patients are used as training classes. In addition, the machine-learning approach implemented does not seem to be affected by the presence of brain lesions. Further studies are needed with larger group sizes to verify that accuracy and predictive values could not be further improved.

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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Actelion, Amrill, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme and Teva Pharmaceutical.
Normative rates of healthy age-related brain volume changes as assessed by SIENA on a large MRI dataset


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Background: Numerous studies in MS have used MRI-based methods to compute brain volumes, since this may represent a useful biomarker of clinical disability and progression. Brain volume (BV) changes occur at faster rates in MS patients than in healthy controls (HC). However, lack of normative reference data makes it difficult to discriminate the rates of BV changes due to aging from the pathological BV loss occurring in MS.

Objective: To provide age- and sex-corrected normative values of BV changes in a large HC dataset to be used as reference in clinical studies.

Methods: Percentage of brain volume change (PBVC) was assessed on MRI data from 392 HC by using the SIENA method (fsl.fmrib.ox.ac.uk). Data of 316 HC were collected from 10 research groups worldwide including a follow-up of at least 6 months; data of remaining 76 HC were from the Alzheimer’s Disease Neuroimaging Initiative and had follow-up of 1 year. The total number of PBVC computations was 1549 and the median length of the maximum follow-up per subject was 4.7 years. The overall age of the HC group ranged from 16 to 90 years (45.6 ±18.3) and the 54% were female. Data were stratified for MRI field strength (1.5 and 3T). Annualised PBVC (PBVC/yr) was calculated for each individual as the slope of the regression line fitted to all the PBVC measurements for that individual, with the first available scan as baseline. A multivariate regression using PBVC/yr as dependent variable and gender, age (with linear, quadratic and cubic terms) and field strength as predictors was performed.

Results: The best model (R²=0.2; p < 0.0001) had as predictors age with a linear term and the MRI field strength. Due to the dependence on age, PBVC/yr showed an acceleration over time of the 0.0047% (p < 0.0001) per year. Due to the dependence on the MRI field strength, PBVC/yr assessed on 3T MR scans showed significantly slower rates of PBVC/yr than those measured on 1.5 T (p < 0.0001). At the mean age of the population (45 years), the PBVC was -0.34% ±0.29% for 1.5T and -0.12%±0.29% for 3T, ranging from -0.23% at 1.5T and -0.02% at 3T at the age of 20 years and from -0.51% at 1.5T and -0.27% at 3T at the age of 80 years.

Conclusions: In a large MRI dataset of HC, values of PBVC/yr depend on age and MRI field strength. We provide here age-related physiological rates of BVL that can be used as reference in future clinical studies to interpret pathological BVL due to MS.

Disclosure

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Contrast enhanced susceptibility-weighted imaging of acute and chronic MS lesions

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Objectives: Susceptibility-weighted imaging (SWI) is an emerging neuroimaging technique in multiple sclerosis (MS) that has the potential to detect the presence of iron deposits and changes in myelination, connecting veins and to visualize different lesion characteristics. An evaluation of contrast-enhancing (CE) lesions on SWI has not been reported. We therefore investigated characteristics of active and chronic lesions detected by CE susceptibility-weighted imaging.

Results: We included 1323 lesions (77 acute CE lesions, 1246 chronic non-CE lesions). On CE SWI 33/77 acute lesions showed a ring-shaped enhancement, 10/77 a peripheral contrast-enhancement and 34/77 a homogenous contrast-enhancement. An association with veins was found in thirty-eight (81%) CE lesions. 374/1246 chronic lesions were homogenously hypointense, 162/1246 ring shaped, 199/1246 scattered, 75/1246 lesions showed a central dark region and 436/1246 lesions were not visible on SWI.

Discussion: An association of MS lesions with veins has been established in several studies and may be valuable for differential diagnostic considerations. We found a 81% of associated veins in contrast-enhancing lesions. This underlines one of the characteristics of MS lesions and taken together i) the location of a lesion ii) contrast enhancement and iii) a typical associated vein have the potential to become highly informative and specific elements in the diagnosis of MS lesions. In this regard CE SWI contains potentially valuable information for the characterization of focal MS pathology.

Background: Quantification of brain volume loss (BVL) at the individual patient level has raised controversial discussions among imaging experts. The aim of our study was to establish the range of fluctuation for single BVL measurements covering the measurement error of the methodology as well as biological variability of brain volumes from short-term repeated MRIs.

Methods: We used three publicly available datasets with repeated MRIs in an interval of days to weeks: dataset 1 contained 3 healthy subjects scanned 20 times within a month. Dataset 2 contained 20

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healthy subjects scanned twice with a median scan interval of 11 days. Dataset 3 contained two multiple sclerosis (MS) patients that received 5-6 MRIs, each on 3 different scanners with several days in-between.

BVL was determined with SIENA (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) using an optimized pre-processing pipeline including automatic reorientation of the images and a field of view reduction. Results deviating from zero were considered as measurement error plus short-term biological variation of brain volumes.

Additionally, the BVL/year was determined with the same SIENA pipeline for a validation cohort of 60 early MS patients to identify a subgroup of patients with a BVL beyond the level of fluctuation.

Results: Dataset 1 showed a median absolute BVL of 0.14% (inter-quartile range (IQR): 0.05-0.24%), dataset 2: 0.24% (0.14-0.30%) and dataset 3: 0.13% (0.07-0.34%). Combining the measurements from the three data sets an intra-patient fluctuation range of ±0.48%, (containing 95% of all measurements) was determined.

A cut-off of 0.4% BVL/year has been suggested to distinguish physiological from pathological BVL in MS. On an individual patient level, the fluctuation range - in addition - needs to be taken into account. In our validation cohort, the median BVL/year was 0.44% (IQR 0.12%-0.8%). In 23% of the patients BVL/year was greater than 0.88%, most likely reflecting pathological BVL, since it was greater than the 0.4% cut-off plus the 0.48% intra-patient fluctuation range.

Conclusion: Recently, others have reported a measurement error for SIENA even in a setting with short-term repeated MRIs can be greatly reduced by carefully optimizing the pre-processing parameters. The estimated fluctuation range of ±0.48% may be helpful when interpreting SIENA results on an individual patient level in MS.

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Quantitative MRI texture analysis of enhancing and non-enhancing T1-hypointense lesions without application of contrast agent in multiple sclerosis

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Introduction: Brain volume loss (BVL) has increasingly gained interest for monitoring degeneration in multiple sclerosis (MS). Healthy individuals (< 40 years) show a physiological BVL/year of about 0.1-0.3%, while MS patients of the same age feature a BVL/year of about 0.5-1.35%. To identify pathological BVL/year in MS, De Stefano and colleagues suggested values of 0.4% or...
Objective: To identify structural brain networks whose disruption relates most significantly with low Conscientiousness and to compare these results with BICAMS (Brief International Cognitive Assessment for MS) associations.

Methods: Neuropsychological assessment and brain MRI was carried out for 131 people with MS and CIS. Severity of lesion-based disruption between pairwise gray matter regions was assessed using the Network Modification tool. Each lesion was used as a seed region in a high-resolution reference cohort, and normative diffusion streamlines were followed to specific atlas-based gray matter regions. Next, network-level analysis, controlling for disease group, age, sex, and normalized whole brain volume, was carried out with the Network-Based-Statistics (NBS) tool. Results were controlled for multiple comparisons at a level of p< 0.05.

Results: Two networks of disruption were significantly associated with low Conscientiousness (p = 0.040 & p = 0.041). The larger network, consisting of 9 region pairs, was entirely composed of left frontal cortical connections. Within this network, Conscientiousness was most robustly correlated with left superior frontal to left lateral orbitofrontal (t = 3.21) and left superior frontal to left pars triangularis (t = 3.13). In comparison, the two networks significantly associated with processing speed were much larger, containing over 90 region pairs, but frontal cortex disruption was included in both. Other BICAMS measures were related to disconnection of networks including regions already known to be associated with those cognitive domains, e.g. decreased visual learning with hippocampus, thalamus, occipital cortex, and temporal cortex.

Conclusions: Our results suggest that low Conscientiousness in MS is explained by pathology in connections between frontal cortical regions, predominantly in the left hemisphere. This pattern of disruption overlaps with those related to processing speed, and may in part explain why decreased conscientiousness is associated with cognitive decline in MS.

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P534

Associations between low conscientiousness and cognitive impairment in MS may be due to shared pathophysiology: structural network disruption of frontal cortex regions

Background: Lower Conscientiousness is associated with cognitive impairment in MS. The physiologic basis of this association is poorly understood, but may be due to a shared relationship with disruption of frontal cortical networks. Newer network-based analysis methods are well suited for discriminating between pathology associated with Conscientiousness and other neuropsychological impairments.
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Altered subcortical sensorimotor integration in multiple sclerosis: a combined neurophysiological and MRI study

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Background and goals: Somatosensory temporal discrimination threshold (STDT) is a neurophysiological measure of sensory information processing, i.e. the shortest interval of recognition of paired stimuli as separate in time. Through mechanisms of sensory gating, sensorimotor integration ensures continuous monitoring of sensory inflow to adjust motor plan and performance. Voluntary movement modulates STDT through the interplay between basal ganglia and thalamus in healthy controls (HC). Although it has been demonstrated that STDT is altered in patients with multiple sclerosis (MS), subcortical mechanisms of sensorimotor integration have never been explored. Aim of our exploratory study was to combine neurophysiological and magnetic resonance imaging (MRI) measures to investigate STDT modulation during movement execution in MS.

Methods: Thirty-six patients with relapsing-remitting MS (mean age 40.4±7.9 years), a median Expanded Disability Status Scale of 1.5 (range 0-3.5) and without cognitive impairment (Montreal Cognitive Assessment scores > 24), and 20 age-matched HC were recruited. We tested STDT at baseline and during index-finger abductions and recorded kinematic features of the movement. All participants underwent a 3T MRI protocol including 3D-T1 and T2-FLAIR images (Siemens, Verio); we used the semi-automated software Jim (v5.0) for white matter (WM) lesions detection and FSL-FIRST for subcortical volume calculation.

Results: STDT at baseline was higher in patients compared to HC (p<0.05) and correlated with thalamic atrophy (r=-0.38, p=0.02). During voluntary movement, the percentage changes in STDT did not differ between patients and controls although mean movement velocity decreased in patients (p=0.003). In patients, changes in STDT and mean velocity positively correlated with putaminal volume (r=0.41, p=0.01 and r=0.42, p=0.02, respectively). Lastly, we did not find any correlation between neurophysiological measures and WM lesion load.

Conclusions: Altered STDT is related to thalamic atrophy and not to WM damage in patients with MS. Although sensory gating is preserved in MS, motor performance deteriorates during the task. The relationship between putaminal volume, STDT changes and movement kinematics suggests a key role of the putamen in this integrative function. Overall, our results shed light on the role of basal ganglia in sensorimotor integration in MS and could represent the background for new multitasking rehabilitation approaches.

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P536
Dynamic volumetric changes of hippocampal subfields in CIS patients: a 2-year MRI study

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Background: Subregional patterns of hippocampal involvement differ according to disease stage in multiple sclerosis (MS) patients. Dentate gyrus (DG) expansion has been observed early in the course of MS.

Objectives: Using MR-based radial mapping, we evaluated the patterns of regional hippocampal volume variations in clinically isolated syndrome (CIS) patients over a two-year period, the influence of focal white matter (WM) lesions on these volumetric changes and their possible prognostic implications.

Methods: Brain dual-echo and 3D T1-weighted scans were acquired from 14 healthy controls (HC) and 36 CIS patients within two months from clinical onset and after 3 (M3), 12 (M12) and 24 (M24) months. Radial volume distribution was assessed using 3D parametric surface mesh models.

Results: CIS patients experienced several clusters of reduced radial distance (RD) in the CA1 region at baseline (p<0.01 right, p<0.05 left), extending to the subiculum during the follow-up. RD negatively correlated with ipsilateral T2 and T1 lesion volume (LV). Increased RD of the DG was observed in the right hippocampus at M3 (p<0.01) and M12 (p<0.05), and in the left hippocampus at baseline (p<0.05) and M3 (p 0.05) and positively correlated with WM lesion measures. RD variations (both decreased and increased) were more pronounced in patients converting to MS at M24.

Conclusions: Regional hippocampal volume abnormalities occur in CIS patients and are characterized by atrophy of CA1 and subiculum and early expansion of the DG. Such regional hippocampal abnormalities are more pronounced in CIS patients converting to MS and are modulated by focal WM lesions.

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**P537**

**Leptomeningeal enhancement on Gadolinium-enhanced 3D-FLAIR MRI in MS vs. non-MS patients: demographic characteristics, and relationship to disease modifying therapy and white matter disease activity**

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**Background:** B-cell lymphoid aggregates have been implicated in meningeal inflammation, cortical grey matter demyelination, and disability progression in multiple sclerosis (MS) (1). Gadolinium-enhanced 3D-FLAIR (Gd-3D-FLAIR) MRI has recently been shown to identify foci of leptomeningeal enhancement (LME) in MS (2), thought to be an imaging biomarker for leptomeningeal inflammation. A recent study has analyzed the occurrence of LME in non-MS patients at a tertiary referral center (3). Awareness of demographics and relative frequency of LME will facilitate determining if LME is a potential biomarker for anti-B cell therapies.

**Goals:** To identify the relative occurrence of LME in MS and non-MS patients in community-based practice, and to assess relative frequency of LME by disease modifying therapy (DMT), and disease activity.

**Methods:** 133 consecutive MRI exams obtained with Gd-3D-FLAIR imaging were referred from outpatient MS specialists and from general neurology outpatient practices that request Gd and 3D-FLAIR imaging. Cases were reviewed for demographics, disease type and activity, and DMT.

**Results:** 13 of 88 (15%) MS patients revealed >1 LMEs, including 0/5 (0%) with isolated syndrome, 9 of 59 (15%) with relapsing remitting (RR), 4 of 22 (18%) with secondary progressive (SP), and 0 of 2 (0%) with primary progressive MS. Of 45 non-MS patients, 9 had other neuroinflammatory diseases, and 3 of the 45 (7%) showed 1 LME including patients with diabetes, non-specific numbness, and PML. There was no correlation with presence of LME and type of DMT. Among 11 MS patients who had imaging signs of active disease, 1 patient had 1 LME. 2 post Natalizumab-PML-IRIS patients and 1 post Natalizumab rebound patient showed no LME.

**Conclusions:**  
1. In the community outpatient setting, LME occurred in 15% of MS patients (15% in RRMS and 18% in SPMS).  
2. There was no association between LME and DMT or acute disease activity.  
3. LME is unusual in non-MS patients.

**References:**  
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P539
Column-specific demyelination in spinal cord normal appearing white matter occurring in multiple sclerosis: a preliminary study using inhomogeneous magnetization transfer and diffusion tensor imaging
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Numerous studies have reported evidences of spinal cord (SC) tissue demyelination in Multiple Sclerosis (MS) using MR imaging, especially using Magnetization Transfer (MT) imaging. This technique unfortunately lacks specificity toward myelin. Therefore, new methods, particularly the inhomogeneous MT (ihMT) technique, supposedly more myelin-specific than MT, may be more promising for MS characterization.
In this study, we used a multi-parametric MR protocol including anatomical, Diffusion Tensor Imaging and, for the first time in MS, MT/ihMT imaging, to assess the structural changes, especially demyelination, occurring within specific SC regions of interest (ROIs).
To do so, 9 remittent and secondary progressive MS patients (59±8yo) and 18 age-matched healthy controls (HC, 54±10yo) were scanned using a 3T Siemens Verio scanner. Functional deficits were assessed using Expanded Disability Status Scale (EDSS) and the Medical Research Council Scale (MRC), Post-processing relied on the SC Toolbox and dedicated SC templates allowing automatic gray/white matter (GM/WM) segmentation for cross-sectional areas (CSA) extraction from C1 to C6 and corticospinal/posterior sensory tracts (CST/PST) delimitation at C2 and C5. Regions with lesions were analysed separately.
Results showed significant decrease of WM CSA (28% in average, p<0.0001) and GM CSA (24%, p<0.05 at C4-C6) in MS relative to HC, suggesting GM/WM atrophies. Increase of radial diffusivity (38%, p<0.05, CST at C5), along with moderate MTratio decrease (10%, p<0.05, all ROIs), and important ihMTratio decrease (20%, p<0.005, all ROIs) were also observed in normal-appearing CST/PST, as well as in the lesion where changes were more important (ihMTratio decrease >35%, MTratio decrease ~15%). Significant positive correlations between radial diffusivity/EDSS (p=0.60/p<0.0001) and ihMTratio/MRC scale (p=0.80/p<0.0001) were found in normal-appearing CST/PST at C5 on this small sample size suggesting a significant clinical impact of SC tissue demyelination.
In conclusion, metrics variation in MS patients, especially ihMTratio, suggest important demyelination in normal-appearing WM, consistent with MS pathophysiology. They also highlight the myelin-sensitivity of the ihMT technique, which may therefore be of great interest to further objectively quantify the topography and progression of SC demyelination in MS.

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P540
MRI myelin water fraction provides evidence of long-term neuro-recovery in alemtuzumab treated multiple sclerosis patients
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Objective: To use MRI to monitor changes in myelin water fraction over 5 years in multiple sclerosis (MS) patients receiving 2 annual courses of treatment of 12 mg/day alemtuzumab.

Background: Alemtuzumab is an effective disease modifying therapy (DMT) for relapsing-remitting multiple sclerosis (RRMS). Myelin water imaging (MWI) quantifies the amount of signal from water trapped within myelin bilayers as the myelin water fraction (MWF) and is histopathologically related to myelin content. To test the potential neuroprotective and reparative properties of therapy, we used MWI to measure demyelination and remyelination in vivo in patients treated with either alemtuzumab, SC interferon beta-1a, or no DMT treatment.
Methods: Thirty-eight subjects had MWI at baseline and longitudinally up to 5 years on a 3T Philips MR scanner. Twenty-five subjects received alemtuzumab at baseline and 12 months. Thirteen subjects received a third cycle and one subject received a fourth cycle of alemtuzumab. Five subjects were treated with SC interferon beta-1a 3 times per week. Eight subjects were not treated. Four healthy volunteers were also scanned. The mean MWF was measured across all normal appearing white matter (NAWM) and in stable lesions at all time points up to year 5.

Results: MWF in NAWM showed an average 4% increase in subjects treated with alemtuzumab (baseline=0.094; year 4=0.098; p=0.004) whereas the MWF decreased by ~10% in subjects treated with SC interferon beta-1a (baseline=0.096; year 5=0.088; p=0.01) or without treatment (baseline=0.087; year 5=0.069; p=0.15) over the 5 years. Healthy volunteers MWF did not change over time (baseline=0.102; year 5=0.105). MWF in stable lesions showed no change in any MS cohort over 5 years.

Discussion: The MWF increase following treatment with alemtuzumab suggests modulation of the immune system can result in myelin recovery. This supports previous clinical trial findings of sustained improvement in EDSS scores in many alemtuzumab patients as well as markedly reduced rates of brain atrophy and provides further understanding of the biological mechanisms underlying observed clinical improvement. The sensitive, specific and quantitative nature of myelin water imaging allowed detection of a treatment effect in a small group, outside of areas of acute damage demonstrating that MWF is a powerful biomarker for neuroprotection in MS.

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R Carruthers is a site principal investigator for studies funded by MedImmune, Teva, and Guthy Jackson. He has received speaking fees for unbranded lectures from Biogen, Genzyme, and Teva. He has received consulting fees for Novartis, EMD Serono, and Genzyme.
A Traboulsee did consulting for Biogen, Roche, EMD Serono and Teva Pharmaceuticals, and received research support from Biogen, Chugai, CIHR, Roche, Michael Smith Foundation and the MS Society of Canada.

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**P542**

Occurrence of diffusely abnormal white matter in individuals with clinically isolated syndromes suggestive of multiple sclerosis

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1Radiology, 2Pathology & Laboratory Medicine, 3International Collaboration on Repair Discoveries, 4Medicine, 5MS MRI Research Group, 6Statistics, University of British Columbia, Vancouver, BC, 7Medicine, University of Calgary, Calgary, AB, Canada

**Background:** Diffusely abnormal white matter (DAWM) are poorly deﬁned regions with signal higher than normal appearing white matter but not as high as lesions on proton density (PD) and T2-weighted (T2W) MRI. Histologically, DAWM has blood-brain barrier breakdown, demyelination, and axonal loss. DAWM may be clinically important as patients with DAWM reach the same EDSS sooner than those without DAWM and then progress faster. DAWM occurs in 25% of relapsing remitting MS cases. The incidence of DAWM in clinically isolated syndrome (CIS) has not been evaluated.

**Objective:** To determine the prevalence of DAWM in CIS.

**Methods:**

**Participants:** 142 CIS subjects experiencing their ﬁrst focal clinical demyelinating event within the last 180 days with at least two 3mm lesions on a screening brain MRI (one had to be ovoid, periventricular or infratentorial) were evaluated (45M/97F; mean age: 36yrs, range: 18-57yrs).

**MRA:** Scans from 12 sites (1.5-3T) were performed using a standardized protocol: 180mm contiguous 3mm axial slices PD, T2W, post-Gad T1-weighted fast spin echo, and 1mm isotropic 3DT1, IR-prepped gradient echo.

**Analysis:** Co-registered scans were reviewed by 2 radiologists. DAWM was deﬁned as a region of white matter iso-intense to gray matter on PD, seen on 2 or more consecutive slices, and ≥10 mm in diameter. T2 lesion volume (T2LV, excluding DAWM), brain parenchymal fraction (BPF) and regional brain volumes were determined. Sex, ethnicity and presence of Gad lesions in CIS with and without DAWM were examined (X2 test). Age, T2LV, BPF and regional brain volumes were compared in CIS with and without DAWM (Mann Whitney U-Test).

**Results:** DAWM were seen in 39 subjects (27.5%). No differences in sex, ethnicity or Gad lesions in people with and without DAWM were seen. CIS with DAWM had 2.2% lower BPF [mean (SE), w/ DAWM: 0.801 (0.007), w/out DAWM: 0.819 (0.003), p=0.01] and 69% higher lesion load [w/ DAWM: 4542 (759) mm3, w/out DAWM: 2681 (381) mm3, p=0.001]. CIS with DAWM had lower putamen, thalamus, globus pallidus and frontal cortex volumes (p< 0.05).

**Conclusions:** The presence of DAWM in 27.5% of individuals with CIS is similar to its frequency in deﬁnite MS. CIS with DAWM had reduced brain volume, smaller gray matter volumes and higher lesion load, all features that correlate with clinical disability and progression. DAWM may have prognostic importance in CIS. Examining its impact on conversion to MS, disability and progression is warranted.

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**P543**

Identification of new cortical lesions on longitudinal 7-Tesla MP2RAGE subtraction MRI in multiple sclerosis

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**Background:** Cortical gray matter lesion burden contributes to the development of disability in multiple sclerosis (MS). High resolution images from 7-Tesla (7T) MRI are an effective tool for quantiﬁcation of cortical lesions (CL). However, manual methods for CL quantiﬁcation are time-consuming and burdensome,
hindered longitudinal analysis of large data sets. Here we describe a method for rapidly identifying new CLs on follow-up 7T imaging.

**Methods:** Participants with MS underwent MRI of the brain at baseline and 1 year on a Philips 7T Achieva scanner with a volume transmit/32-channel head coil. A 3D, magnetization prepared rapid acquisition gradient echo (MP2RAGE) sequence was acquired at 0.7 mm³ resolution. Raw MP2RAGE images were pre-processed for conversion to T1-weighted and T1 map images. The raw, 2nd inversion image was used for initial registration of 1 year follow-up scans to baseline and the resultant transformation matrix was applied to the post-processed images. Images were co-registered a 2nd time after skull stripping. Baseline T1-weighted images were then subtracted from follow-up scans and the resultant subtraction image was then inverted. Subtraction images were reviewed for hyperintensities in cortical gray matter, indicative of a cortical hypointensity that is present on T1-weighted images at follow-up, but was not present at baseline.  

**Results:** Scans from 23 participants with MS (relapsing-remitting = 16, secondary progressive = 5, primary progressive = 2) were reviewed. The cohort consisted of 14 females and 9 males, with a median age of 51 (range 26 - 60) years. Participants had a median baseline EDSS score of 3 (range 1 - 6.5), with 6/23 (30%) having EDSS progression at follow-up. Ten participants (43.5%) had at least 1 new CL at follow-up. Amongst those with new CLs, the median number of new CLs was 2.5 (range 1 - 12). A non-significant trend towards a higher mean number of new CLs was seen in those with EDSS progression (2.7 (SD = 4.7)) compared to those without (1.3 (SD = 2.3), p = 0.38).  

**Discussion:** Co-registration of baseline and follow-up 7T MP2RAGE with review of subtraction images is a simple, rapid method for identification and quantification of new CL development in MS. Use of this method may allow for confirmation of the longitudinal relationship between new CLs and disability progression, a trend towards which was seen in this study, and may have application as a future clinical trial outcome measure.

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**P544**  
Application of Neurite Orientation Dispersion and Density Imaging (NODDI) in clinically isolated syndrome (CIS)  
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**Background:** Neurite Orientation Dispersion and Density Imaging (NODDI) is a novel diffusion weighted (DW) MRI technique that enables neurite morphology mapping, and provides metrics of neurite density and dispersion. Preliminary applications to patients with relapsing-remitting multiple sclerosis (MS) have shown abnormal NODDI parameters in the brain normal appearing white matter (NAWM) and grey matter (GM).

**Objective:** To compare the NODDI parameters in NAWM and GM between CIS patients and healthy controls (HCs) at baseline and at 6 months follow-up.  

**Methods:** We recruited 30 CIS patients (16F, mean age 35.2 ±7.7yrs, median EDSS=1.0, range 0-2.5) within 3 months of onset and 14 HCs (9F, 34.3 ±7.1yrs); 21 patients and 8 HCs completed 6 months follow-up. We performed 3T brain MRI at each time point with structural images and multi-shell DW imaging. After lesion filling the 3D T1, brain segmentation was performed using GIF. We computed NODDI metrics in WM, GM and T2 lesions: orientation dispersion index (ODI), measuring the variability of neurite orientations; neurite density index (NDI), measuring the density of neurites; isotropic volume fraction (isoVF), measuring the amount of free water. We scored the EDSS and the Brief Cognitive Assessment for MS (BICAMS) in patients. Mixed-effect models were used to test differences in MRI measures between groups, at baseline and at follow-up, adjusting for age, gender, brain volume fractions and T2 lesion volume.  

**Results:** 7/21 (33%) patients converted to MS at 6 months (CIS-MS). At baseline, all CIS patients showed higher ODI values in NAWM than HCs (0.26 vs. 0.25, adjusted p = 0.001). At 6 months, this difference was not significant, but CIS patients showed lower NDI in GM than HCs (0.49 vs. 0.53, adjusted p = 0.008). At baseline, CIS-MS patients had smaller NAWM isoVF than non-converters (0.085 vs. 0.096, adjusted p = 0.012). There were no associations between changes in NODDI parameters over time and changes in clinical scores.  

**Conclusion:** CIS patients showed changes suggesting increased neuronal disorganization in NAWM as well as reduced GM neurite density. The reduced NAWM isoVF seen in converters at baseline may reflect increasing cellularity due to inflammatory activity, but it could also be a partial volume effect. The next step is to finish the 6-months follow up and to extend the analysis to 1-year.

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**P545**
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**Background:** GABA, the principal inhibitory neurotransmitter in the CNS, has been shown to be lower in multiple sclerosis (MS) patients. Chronic alteration of neurotransmitter homeostasis may lead to excitotoxic damage and neuronal death. Studies in EAE suggest that CNS pro-inflammatory cytokines contribute to synaptic dysfunction of both glutamatergic and GABAergic systems. **Objective:** The objective of this study is to utilize both [11C] Flumazenil (FMZ-PET) and [11C]-PK11195 PET (PK-PET) to explore the cross-sectional and longitudinal relationship between GABA receptor binding and activated microglia/macrophages (MG/MΦ) within MS patients. **Methods:** Sixteen MS patients (age= 37±11.0, disease duration 8.1±6.8 years) had a dynamic FMZ-PET and PK-PET imaging as well as a 3T MR imaging at baseline and five patients had 24 months longitudinal scans after treatment with Natalizumab. Ten age-matched healthy controls (HC) had FMZ-PET. Frontal, parietal, temporal, occipital, cingulate, and insula were considered as cortical regions of interest (ROI). BZD receptor binding was calculated by Logan reference model with the pons as a reference. Distribution of volume ratios (VTr) for PK-PET was calculated using Logan graphical method with image-derived input function as a blood input function and presented as a ratio to the individual patient’s NAWM. In MS, z-score was calculated for each ROI using mean and standard deviation of HC. **Results:** All cortical ROIs demonstrated a significant increase (18–28 %) FMZ-PET binding in MS compared to HC (z-score: 2.42, mean p-value: 0.0002). VTr of PK-PET demonstrated a significant correlation with FMZ-PET binding among all cortical regions (r=0.61, p<0.001). In 5 patients, at 24 months after Natalizumab treatment, FMZ-PET in all cortical ROI decreased on average by 23.2%, (p<0.0004) and reached a level similar to HC (z-score= -0.7, mean p-value: 0.39). To a lesser degree, a reduction was observed in PK-PET (0.5% to 3% decrease, mean p-value: 0.47). **Conclusions:** A higher GABA receptor density compared to HC was observed and correlated with activated MG/MΦ. GABA receptor was reduced after initiation of Natalizumab therapy, suggesting inflammation may contribute to the alteration of the GABAergic system. Our preliminary observations suggest that immune-driven synaptic abnormalities are present, can dynamically change and that utilization of multi-ligand PET studies may provide further insight into this relationship.

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**P546**
Cortical mantle thinning in the visual cortex in pediatric-onset multiple sclerosis
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**Background:** Cortical mantle thinning and its clinical impact is not well understood in pediatric-onset MS. While MS has a global impact on brain integrity, optic neuritis and lesions in the visual pathways are common in pediatric MS, and could directly lead to a negative down-stream impact on the visual cortex specifically. **Methods:** Pediatric-onset MS patients and healthy controls were imaged at the Children’s Hospital of Philadelphia using Siemens 3T Verio MRI scanner (32 channel coil). Cortical mantle thickness was measured on 1mm T1-FLASH sequence using freesurfer for the entire hemispheres, striate (V1), extra-striate (V2, V3) and subregions of fusiform gyrus. Cortical thickness measures were adjusted for age and sex using a general linear model and the adjusted measures were compared between MS patients with optic neuritis (MS-ON) and without ON (MS non-ON) and healthy controls. High-contrast acuity and Expanded Disability Status Scale (EDSS) scores were also computed. **Results:** 10 MS-ON (6 females, mean age 18 yrs [range 13-24], mean disease duration 3 yrs, median EDSS 1, 0-3.5), 10 MS non-ON (5 females, mean age 18 yrs [range 14-19 yrs], mean disease duration 1.6 yrs, median EDSS 0.5, 0-2), and 22 healthy controls (16 females, mean age 17 yrs [range 13-22]) were enrolled. Mean hemispheric cortical thickness was reduced in MS patients compared with controls [2.45mm (SD 0.1) versus 2.58mm (SD 0.2), p = 0.028]. EDSS scores correlated negatively with hemispheric cortical thickness (p=0.018). Cortical thinning was observed in the MS group across the entire visual cortex, showing bilateral reduction in V3 and fusiform gyrus (all p=0.001) and unilaterally in left V1 dorsal and V2 dorsal regions (p=0.013). Acuity scores did not differ between MS and controls and did not correlate with cortical thickness measures. ON did not influence results. **Conclusions:** Pediatric-onset MS is associated with overall hemispheric cortical mantle thinning that correlates with EDSS. More specifically, the thinning of the visual cortex is notable, and further research will evaluate the relationship with more sensitive measures of visual function.
Disclosure

Dr. Banwell serves as a consultant to Novartis, for work unrelated to her MS research.
Drs. Datta, Lavery, Waldman have nothing relevant to disclose.
Ms. Karoscik, Ficerai-Garland and Mr. Sollee have nothing to disclose.

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Coordinate based random effect size meta-analysis shows regions of GM atrophy do not develop independently in MS and CIS

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Background: Voxel-based morphometry (VBM) studies have reported regional grey matter (GM) atrophy in MS. In regions consistently reported as atrophied, it is not clear whether GM loss develops independently.

Objective: 1) use a novel coordinate based random effect size (CBRES) meta-analysis to locate GM regions consistently reported as atrophied in CIS or MS patients.
2) explore independence of regions by correlating the reported effect sizes (Z scores standardised by number of subjects to represent the extent of the atrophy).

Methods: Perform a search for VBM studies comparing MS or CIS to healthy controls. Use CBRES to perform a random effect meta-analysis in regions of statistically significant spatial clustering of reported coordinates and associated effect sizes. Use Pearson’s correlation to correlate effect sizes between clusters. High correlation suggest that GM loss does not develop independently.

Results: 43 valid studies met the inclusion criteria and reported 470 foci in total. Atrophy was reported consistently across studies in 6 locations, some of which merged multiple Talairach regions into single clusters: bilateral thalamus, left putamen/Brodmann area (BA) 13, bilateral BAS 3 & 4, and right BA 9. Pairwise correlations of effect sizes revealed multiple highly significant associations: bilateral thalamus (r=0.92; p<0.0001), bilateral BA 3 & 4 (r=0.97; p<0.0001), left putamen/BA 13 and right BA 3 & 4 (r=0.94; p<0.0001), and left putamen/BA 13 and left BA 3 & 4 (r=0.97; p<0.0001). Other correlations were also very high and positive, but with too few studies reporting in both clusters to estimate significance.

Summary and Conclusions: Multiple GM regions are reported as atrophied consistently by VBM studies comparing CIS and MS to healthy controls. The effect sizes are highly correlated between these regions suggesting GM loss does not develop independently.

Disclosure

Christopher Tench: nothing to disclose

P548
Longitudinal study to measure iron deposit in basal ganglia and related structures in patients with clinically isolated syndrome

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Background and Objective: Iron accumulation within basal ganglia and related structures has been described in multiple sclerosis (MS).

In early stages of the disease iron deposition may be associated with the progression of the disease. The aim of this longitudinal study is to assess the influence of iron deposit in basal ganglia and related structures in patients presenting with a clinically isolated syndrome (CIS).

Materials and Methods: 45 patients diagnosed of CIS (27 women; median age, 34 years; EDSS range, [0, 5]) with a clinical follow-up of at least 3 years, underwent two 3.0 T brain MRI scan, baseline and 1-year follow-up, that include a T1 magnetization prepared rapid acquisition gradient echo (MPRAGE), and a dual-echo susceptibility weighted (SW) sequences. Thalamus, caudate, putamen, pallidum and accumbens area masks were obtained on MPRAGE images using FIRST tool of FSL package (FMRIB software library, Oxford) and registered to SW images. Iron deposits within these regions were obtained by R2* maps measured on magnitude SW images for baseline, and 1-year scans. The increment of iron between 1-year and baseline scans was also measured for all these regions. Conversion to MS was assessed according to McDonald criteria and new relapse within three years was also studied. Statistical analysis involved U Mann-Whitney test to evaluate differences in iron measurements between groups.

Results: We only found significant differences for the increase of iron in thalamus region between 1-year and baseline scan when comparing the presence of a new relapse within 3 years (yes, 1.15; no, 0.56; p-value=0.014). With regard to the other regions, though we observed an increase of iron deposit for the group presenting a new relapse these did not show significant differences. Baseline and 1-year iron measurements did not present significant differences between those patients that converted to MS and those that did not in the first year.

Conclusions: The results of this longitudinal study suggest that just a reduced number of iron variables may be useful to discriminate CIS patients who fulfilled the criteria for establishing the diagnosis of MS.

Disclosure

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M Tintoré has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merck-Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, Novartis, Almirall, Genzyme, and Roche.
X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards

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of clinical trials in the past with Actelion, Amiral, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme and Teva Pharmaceutical. A Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, and OLEA Medical, has received speaker honoraria from Bayer, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis and Biogen Idec, and has research agreements with Siemens AG and Icometrix.

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Evolution of venous narrowing in acute MS lesions
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Background: Pathological studies have reported the perivenous distribution of multiple sclerosis (MS) lesions and that the venous diameter is significantly narrowed in MS lesions as a consequence of perivascular cuffing, fibrosis and collagen deposition. Susceptibility-weighted imaging (SWI) is a magnetic resonance imaging (MRI) technique that can visualize the cerebral venous architecture due its sensitivity to the presence of deoxyhemoglobin. While various MRI studies have demonstrated that veins can be detected in most MS lesions, only a few cross-sectional MRI studies have reported the pathologically described phenomenon of a decreased venous diameter in MS lesions.

Objective: To investigate the spatio-temporal evolution of venous narrowing in newly developing MS lesions in a longitudinal MRI study.

Methods: We analysed serial MR examinations of 18 MS patients for acute contrast-enhancing lesions with at least one MRI examination prior to contrast-enhancement. MRI data was acquired on a 3T MRI (Siemens SKYRA) system. Co-registered FLAIR-/SWI- and T1-Gd/SWI-images were investigated for lesion and venous identification. The mean diameter of veins was measured at the time point of contrast-enhancement (CE) on high resolution SWI source images and compared to the mean diameters of veins prior to and after contrast-enhancement.

Results: A total of 40 serial studies of acute contrast-enhancing lesions containing an intralesional central vein were included in the study. The mean diameter of intralesional veins at the time of CE (0.80 ± 0.12 mm) was smaller than prior to the phase of CE (1.16 ± 0.19 mm) and after cessation of CE (1.07 ± 0.15 mm; p < 0.001 for all comparisons).

Conclusions: Our findings confirm previous cross-sectional analyses on venous appearance during plaque development and evolution. The smaller diameter of intralesional veins on SWI at the time of blood-brain-barrier breakdown may reflect morphological changes due to perivascular inflammation and/or decreased levels of deoxygenated haemoglobin.

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Dr. Brück served on the advisory board for Genzyme, Novartis, Biogen, and Teva Pharmaceuticals; received speaker honoraria from Teva, Sanofi, Genzyme, Novartis, Merck-Serono, Biogen, and Bayer

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P550
Normative data of MRI-derived thalamic volumes from a large dataset of healthy subjects
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Background: Recent Magnetic Resonance Imaging (MRI) studies have shown that thalamic atrophy is one of the most relevant MRI correlate of physical and cognitive disability in MS patients and probably one of the earliest neuropathological processes occurring in the disease. Studies on MRI-derived thalamic volumetric measures obtained from large datasets are scanty, which can represent an important limitation for the use of this measure in clinical studies.

Objective: To assess normative data of the thalamic volume (ThV) obtained from MRI of healthy subjects (HS) to be used as a reference in clinical studies.

Materials: The ThV of HS (n=727) was assessed from freely available MRI datasets. The age at scan-time ranged from 20 to 80 years. Data were stratified for gender and magnetic field strength (1.5 and 3 T). Volumes were obtained using a semi-automated approach, based on the manual editing of the masks obtained with FIRST (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST). In 100 MRI scans, the accuracy of the method was compared with a fully manual segmentation output and with the fully automated outputs of FIRST and FreeSurfer. Finally, a multivariate regression using ThV corrected for head size as dependent variable and gender, age and their interactions as predictors was performed.

Results: Volume masks from our semi-automated approach were very similar to those obtained with the fully manual approach (14.3±1.3 cm³ Vs 14.3±1.3 cm³; DICE=0.93; p=0.99) and significantly lower than those obtained fully automatically with FreeSurfer (15.4±2.1 cm³; DICE=0.82; p< 0.001) and FIRST (16.4±1.6 cm³; DICE=0.89; p< 0.001). A model including age, gender and their interaction provided the best fitting (R²=0.22, p< 0.001). Due to the dependence upon age-gender interaction, ThV decreased with age significantly more (p< 0.001) in males (-0.27% per year) than in females (-0.15% per year). Values of ThV were similar in both genders at the age of 20 years (males=20.47 cm³; females=20.39 cm³), but reached a difference larger than 1 cm³ at the age of 80 years (males=17.1 cm³; females=18.5 cm³).

Discussion: This study provides accurate, normative data of ThV volume, separately for males and females. This could be useful as
reference in future MS studies at both group and individual levels.

Disclosure

G. Gentile, L. Luchetti, M. Battaglini, A. Giorgio have nothing to disclose.
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P551

Spinal cord ring enhancement patterns in neuromyelitis optica spectrum disorder: comparison with multiple sclerosis

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Although open ring enhancement (RE) lesions on magnetic resonance imaging (MRI) are considered specific for demyelination, there have been very few studies on spinal cord RE patterns in neuromyelitis optica spectrum disorder (NMOSD). The purpose of this study is to compare frequency and characteristics of spinal cord RE between NMOSD and multiple sclerosis (MS). We analyzed 90 spinal cord MRIs from 44 NMO-IgG-positive NMOSD patients and 88 spinal cord MRIs from 63 MS patients from 2010 to 2016. All patients underwent MRI scans within 3 months of their spinal attacks. The frequency of contrast enhancing spinal cord lesions did not differ between NMOSD (n=73) and MS (n=74), but ring enhancing lesions were more common in NMOSD (n=33, 36.7%) than MS (n=14, 15.9%) (p=0.002). Open ring type enhancement was predominant in both NMOSD (n=32) and MS (n=14). On axial images, whole cord involved RE was more frequent in NMOSD (n=19, 57.6%) than MS (n=2, 14.3%) (p=0.006). Irregular rings were more common in NMOSD patients (n=31, 93.9%) compared with MS patients (n=5, 35.7%) (p<0.001). There were no significant differences in age, gender, the mean expanded disability status scale score, mean lesion length between NMOSD patients with RE and without RE. However, the mean duration from a first manifestation of NMOSD to myelitis attacks was shorter in patients with RE (3.3±3.4 years) than patients without RE (5.7±3.9 years) (p=0.014). Based on our results, spinal cord RE is not uncommon in NMOSD. Different patterns of RE may provide additional information to differentiate NMOSD from MS during acute myelitis attacks.

Disclosure

All authors have nothing to disclose.

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Myelin deterioration occurs in relapsing remitting multiple sclerosis patients meeting criteria for “no evidence of disease activity”

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Background: “No evidence of disease activity”(NEDA), defined by absence of clinical events (relapses or EDSS worsening) and radiological activity (new/enlarging T2 or enhancing lesions), is the goal of therapy for MS. However, conventional MRI measures correlate modestly with disability and do not detect diffuse damage in normal-appearing tissue. Diffusion tensor imaging (DTI) quantitatively measures white matter (WM) integrity, yielding better correlation with disability. We recently presented data showing that NEDA patients exhibit significantly slower rates of change in fractional anistropy (FA) compared to those not meeting NEDA criteria, but surprisingly, the rate of change of mean diffusivity (MD) was similar in both groups. In order to study this discrepancy, we examined the rate of change in two other DTI parameters, axial diffusivity (AD, which corresponds to axonal loss) and radial diffusivity (RD, which corresponds to myelin loss).

Methods: We included RRMS patients who visited our MS center over a three month period, met NEDA criteria for ≥2 years, and whose MRIs included DTI data. Patients who did not meet NEDA criteria served as controls (EDA group). MRI sequences included T2-, T1-, FLAIR, and a single-shot echo-planar sequence for DTI. Tract based spatial statistics were used to create a WM skeleton and mean values of AD and RD were obtained over the skeleton. Annual rates of change were calculated.

Results: 85 RRMS patients were included, 39 of which met NEDA criteria. AD was stable over time in both NEDA and EDA groups, suggesting preserved axons. However, RD significantly increased over time at a yearly rate of 1.1% (p=0.0006) in the NEDA group and at a yearly rate of 1.5% (p=0.0001) in the EDA group, suggesting ongoing myelin loss. While the EDA rate of deterioration was faster than that of the NEDA group, this did not reach statistical significance.

Conclusions: We previously showed that FA increases and MD decreases over time, even in the setting of NEDA. We now show RD increases significantly over time in the NEDA group, suggesting ongoing myelin loss even in the absence of overt disease activity, whereas AD is stable, suggesting preserved axonal fibers. While patients meeting NEDA criteria showed a somewhat slower rate of RD increase, this did not reach statistical significance. Taken together, this data demonstrates that DTI is more sensitive at detecting ongoing myelin loss than routine measures.

Disclosure

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Resting state fMRI and graph theory for the automatic classification of relapsing remitting multiple sclerosis with different disease duration


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Conclusions: Graph theory has emerged as a powerful tool to model complex systems by characterising relationships between distinct brain regions. Resting state fMRI (rs-fMRI) has also provided important insights into functional reorganization in subjects with Multiple Sclerosis (MS) at different stages of the disease. In this study we coupled graph theoretical analysis, based on rs-fMRI images, with a machine learning approach to assess the ability of graph metrics to discriminate relapsing remitting MS (RRMS) subjects with short disease duration (MSshort) from those with similar (mild) disability but longer disease duration (MSlong).

Methods: 36 RRMS patients with recent disease onset (≤5yrs, mean EDSS=1.4±0.9; MSshort) and 26 RRMS patients with later disease (>5yrs duration; mean EDSS=2.2±1.4; MSlong) underwent 3T MRI examination including rs-fMRI and 3D T1-weighted imaging. 29 healthy controls (HC) were also scanned.

For each subject, rs-fMRI images were preprocessed using FSL and then parcellated into 116 distinct regions using the automatic anatomical labelling (AAL) atlas. For each region, the mean rs-fMRI signal was extracted and used to calculate the graph edges defined as the Pearson’s correlations between all pairs of AAL regions (graph nodes). The resulting cross-correlation matrix was thresholded and then processed to calculate graph metrics. Extracted graph metrics were used as input features to run a Support Vector Machine (SVM) classifier.

Results: SVM applied to graph metrics identified small sets of features (brain graph measures) to discriminate MSshort, MSlong, and HC. SVM achieved the best classification performance when considering the discrimination between MSshort and MSlong, reaching a classification accuracy (ACC) equal to 93.3% using 10 features from 8 distinct nodes (Cbl-7b, Cbl-9, Vermis-45, Vermis-8, Cuneus, Inf. Par. Gyr, Mid. Cing. Gyr, Sup.Temp.Gyr) all located in the right hemisphere of the brain. SVM reached ACC=88.9% to classify MSshort from HC (using 8 features) and ACC=90.9% to classify MSlong from HC (using 11 features).

Conclusions: Results demonstrate the potential of machine learning (SVM) combined with graph methods to automatically classify RRMS patients’ clinical profiles. The proposed method was particularly efficient in discriminating MSshort from MSlong. This warrants future longitudinal studies of early RRMS patients to assess the ability of the classifier to provide insights into their possible evolution.

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References:
Disclosure

Authors have nothing to disclose.

P555

Mapping neuroeconomic decisions in multiple sclerosis: a connectivity approach

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Background: Decision-making refers to the process by which a person chooses its actions, and neuroeconomics analyse the neural basis of choices. Choice behaviour in patients with multiple sclerosis (MS) is slower and characterized by higher risk aversion and a tendency for higher preference of immediate options. However, the neural substrates of decision-making in MS are poorly known.

Goal: To map the structural connectivity that supports the decision-making process in patients with MS.

Methods: We analyzed a crosssectional cohort of 74 MS patients (age: 43.3±9.4 years; disease duration: 10.9±6.8 years; Expanded Disability Status Scale: 1.5 (0-7.5)), and 9 healthy controls (HC). All participants underwent a magnetic resonance session with high angular resolution diffusion imaging (HARDI) and 3D-structural sequences. Grey matter (GM) regions from prefrontal, parietal, cingulate, insula and deep GM associated with decision-making process were selected a priori as nodes of the network and connections were reconstructed through probabilistic tractography in HC. Then, a mask of the network was applied to the network links. Decision-making was assessed using the risk task and the temporal discounting task (delay of gratification) and we recorded the reaction time (RT) for each task.

Results: Reduced FA in the decision-making network was correlated with higher risk aversion, especially in connections involving left striatum (r=0.30 to 0.51, p<0.01) and with increased higher preference of immediate rewards in connections from right insula and amygdala (r=-0.32, p<0.01). Also, decreased FA correlated with lower RT in several network links, including connections from left anterior cingulate and right ventromedial prefrontal cortex (r=-0.30 to -0.41 for correlations with risk task RT, r=-0.30 to -0.62 for correlations with temporal discounting task RT, p<0.01).

Conclusions: Damage of the structural connectome supporting the decision-making process, preferentially in connections from deep grey matter, influence the choice behaviour in MS patients. Differential connections in the network are involved in higher risk aversion and preference of immediate rewards.

Disclosure

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P556

Probing myelin and axonal integrity in multiple sclerosis brains

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Lack of an in vivo surrogate marker of axonal integrity represents a critical barrier to the development of neuroprotective drugs for patients with multiple sclerosis (MS). We successfully implemented 2 imaging methods namely selective inversion recovery quantitative magnetization transfer imaging (SIR-qMT) and multi-compartment spherical microscopic diffusion imaging using spherical mean techniques (SMT). We previously proved that the SIR-qMT derived macromolecular to free pool size ratio (PSR) and the SMT derived axonal volume fraction (Vas) are indirect but histologically specific metrics of myelin and axonal integrity. We here hypothesize that PSR and Vas are sensitive to...
were derived. PSR and Vax differed (p≤0.0001, paired t-test) between NAWM and NWM. Vax ranged from 22% to 60% in between each lesion type and NAWM but not (unpaired t-test) between lesions with different appearance on conventional scans, pathological changes in vivo as they allow quantifiable indices reflective of myelin and axonal content, hence showing hallmarks of neurodegenerative tissue injury in MS brains. Ten patients with MS and 4 healthy controls were imaged on a 3.0 Tesla whole body scanner equipped with a 32-channel receiver head coil. Clinical 2-mm thick sequences, SIR-qMT and SMT were obtained. Anatomically matched regions of interest in normal appearing white matter (NAWM), T2-hypointense and T1-hypointense lesions in patients and normal white matter (NWM) in healthy controls were contoured; PSR and Vax values of these regions were derived. PSR and Vax differed (p<0.0001, paired t-test) between lesions with different appearance on conventional scans, between each lesion type and NAWM but not (unpaired t-test) between NAWM and NWM. Vax ranged from 22% to 60% in between T1-hypointense lesions and was reduced by 36% and 100%, in T2-hypointense and T1-hypointense lesions, respectively, compared to NAWM. In lesions, axonal content was associated to that of myelin (r=0.714, p<0.0001, Pearson correlation analyses). We provide for the first time an indirect quantitative estimate of the amount of residual axons in vivo demonstrating that nearly 75% of axons are lost in T1-hypointense lesions. Combining SIR-qMT and SMT improves our ability to discern axonal and myelin pathology and delivers biomarkers of neurodegeneration and repair in MS.

Conclusion:
Linear measures are highly reproducible, but only two of them had a strong correlation with their equivalent volumetric measure. Correlations between linear and whole brain volume measures were stronger in patients with more advanced disease.

Disclosure
Nothing to disclose

P557
Comparative study of brain atrophy measures in CIS and MS patients: preliminary results of a cross-sectional analysis
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Purpose:
Linear measures such as corpus callosum index (CCI), normalised corpus callosum area (nCCA) and width of the third ventricle (W3V) could be a good alternative to global brain volumetric measures in clinical practice for assessing the neurodegenerative component of multiple sclerosis (MS). Our objective is to test this hypothesis by comparing linear and volumetric measures.

Materials and Methods:
Fifty-eight patients with a clinically isolated syndrome (CIS) (group 1), 48 MS patients treated with interferon β (group 2) and 26 treated with natalizumab (group 3) underwent a brain MRI (58 on 3T and 74 on 1.5T) at two time points (baseline and one year). Baseline and follow-up CCI, nCCA and W3V measurements were obtained by two raters using Jim v.6.0. Volumetric tools (SIENA/x and Freesurfer) were used to calculate normalised brain volume (NBV), brain parenchymal fraction (BPF), annualised percentage of brain volume change (aPBVC), corpus callosum volume (CCvol), volume of the lateral ventricles (LVV) and volume of the third ventricle (3VV). Correlation analyses were performed with SPSS v.13.

Results:
Statistical analyses were performed with SPSS v.13.

Discussion:
S. Cappelle has nothing to disclose.
M. Alberich has nothing to disclose.
R. Alyafeai has received MSIF fellowship grant.
A. Vidal-Jordana has received honoraria as speaker and/or for participation in Advisory Boards from Novartis, Roche, Sanofi-Genzyme, and Biogen.
D. Pareto has received speaking honoraria from Novartis and Genzyme.
A. Vrosira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Stendhal, Novartis and Biogen Idec, and has research agreements with Siemens AG.
C. Auger has received speaking honoraria from Novartis and Stendhal.
M. Tintoré received speaking honoraria and travel expenses for scientific meetings in the past with Amiral, Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Roche and Teva.
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P558
Altered cerebellar functional connectivity is associated to clinical disability in multiple sclerosis
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Connections between brain regions are modified leading to brain functional reorganization, as a consequence of the structural damage in multiple sclerosis (MS). Whether functional plasticity may limit disability burden is still matter of debate.
Aim of this work is to evaluate global functional connectivity (FC) in a large series of MS patients by using graph theory analysis. We acquired resting-state functional magnetic resonance images (fMRI) with a Siemens Verio 3T scanner in a sample of 96 clinically defined MS patients (age: 36.8 +/- 8.5 years, 22 males) with a median Expanded Disability Status Scale (EDSS) of 2 (range 0-6). Thirty-six healthy subjects (HS, 32.3 +/- 6.5 years, 12 males) were included as a control group.

To explore the relation of FC with disability, we analytically divided subjects into two groups on the basis of the scores: group 1: < 1.5 (47 subjects); group 2: > 2.0 (49 subjects).

Results: The reliability of all identified patterns were high (ICASSO values ≥ 0.95). No significant differences were detected when comparing MS patients and HCs in terms of ICA-derived loading factors. After correction for multiple comparisons, no significant relationships were detected when correlating loading factors obtained from the entire cohort analysis with EDSS. P-values were corrected for multiple comparisons using the false discovery rate method.

Conclusions: MS-specific spatial patterns associated with clinical disability.
P560
Microstructural alterations precede subcortical deep grey matter volume loss in patients with clinically isolated syndrome

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Background: Identifying microstructural biomarker is relevant at early stages of multiple sclerosis (MS) before the apparition of irreversible grey matter (GM) damage that has been associated to cognitive impairment. Whether abnormalities at microstructural level could predict early GM volume loss has not been investigated longitudinally yet.

Objective: To compare volumes and diffusion metrics in subcortical deep grey matter (SDGM) and cortical thickness (CTh) between patients with clinically isolated syndrome (PwCIS) and healthy controls (HC), and whether they can predict cognitive changes after 1 year of follow-up.

Methods: 56 patients recruited less than 6 months after a CIS and 37 matched HC underwent a 3T MRI scan including 3D TI weighted images, fluid-attenuated inversion recovery and diffusion tensor imaging. After filling lesions, V olBrain was used to segment SDGM and FreeSurfer was used for CTh. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were calculated within each SDGM structure using FSL. 45 PwCIS and 20 HC were rescanned 1 year after the first assessment.

Attention, working memory (WMem), episodic memory (EMem), executive functions (EF) and information processing speed (IPS) were assessed by a neuropsychological battery. Linear regression models were used to assess cognitive changes by previously described baseline MRI parameters.

Results: At baseline: PwCIS had no SDGM atrophy. Right frontal lobe CTh was reduced in PwCIS (p < 0.01). Amygdala FA was lower (p < 0.05), hippocampus MD and RD were higher in PwCIS compared to HC (p < 0.01). During 1 year of follow-up: lateral ventricles volume increased and caudate, putamen, globus pallidus, hippocampus and accumbens volumes decreased in patients (p < 0.05). CTh decreased in left temporal and insular lobes and also in right frontal and temporal lobes in PwCIS (p < 0.01). Longitudinal microstructural changes were detected in thalamus, globus pallidus and accumbens in PwCIS (p < 0.05). Hippocampus RD and globus pallidus MD predicted best, respectively, hippocampus and globus palildus volume loss in PwCIS. CTh, SDGM volumes and diffusion parameters were also able to predict changes in WMem, EMem, EF, attention and IPS.

Conclusion: SDGM microstructural alterations precede atrophy in PwCIS. Hippocampus and Globus Pallidus volume loss can be predicted by their RD and MD at baseline. Grey matter alterations predict cognitive changes in PwCIS.
can be affected in multiple sclerosis (MS). The improved delineation of GM and WM tissue at 7 Tesla (7T) MRI can be used to better characterize in-vivo pathology in the brain and SC in MS.

Objective: To assess, using 7T MRI, 1) cervical SC pathology in GM and WM throughout stages of MS; 2) the relative contribution of SC and brain pathology to EDSS, 9-Hole Peg Test (9-HPT) and Timed 25-Foot Walk (T25-FW).

Methods: Twenty-seven MS subjects (17 with RRMS and disease duration ≤ 5 years; 10 with SPMS) and 11 age-matched healthy controls (HC) underwent 7T imaging to acquire gradient-echo T2* images of the cervical SC (0.41x0.41x3.6 mm³) and of the brain (0.33x0.33x1 mm³) for cortical and brain WM lesion segmentation in MS. Cortical thickness estimates were also obtained from anatomical 3T scans. The cervical SC WM and GM were segmented using semiautomatic segmentation in Spinal Cord Toolbox 3.0.1, and the cross-sectional areas (CSA) were calculated from C2-C3. SC lesions were characterized as the proportion of lesioned tissue in GM and WM respectively. Correlation between MRI metrics and clinical data and comparisons across groups were assessed using non-parametric tests.

Results: SC lesions were found in all SPMS and in 12 out of 17 RRMS cases and in none of the HC. Of patients with SC lesions, SC GM lesions were identified in all except two. Relative to HC, MS subjects had lower SC CSA in both GM and WM (p=0.02), with SPMS showing greater atrophy than RRMS (p=0.04). No differences in WM or GM SC lesion volumes were found between the MS subgroups. Cortical lesions were found in 90% of MS cases. Relative to HC, however, cortical thinning was found in only in SPMS (p=0.004). A stepwise linear regression, which was performed by including the MRI variables significantly associated with EDSS at Spearman test (SC GM and WM CSA, cortical lesion volume, cortical thickness), showed that the best predictor of EDSS was cortical thickness (r²=0.23, p=0.027). 9-HPT was only positively correlated with GM (p=0.003) and WM (p=0.004) CSA; T25-FW inversely correlated with mean cortical thickness (p=0.02).

Conclusions: We demonstrate an early and progressive involvement of cortex and SC GM in MS, in addition to the well-characterized WM pathology. Although both contribute to clinical outcome, cortical pathology shows the greatest association with disability.

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P562

Distinct associations of cross-sectional spinal cord areas with clinical disability in Japanese patients with multiple sclerosis and neuromyelitis optica spectrum disorder with aquaporin-4-IgG

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Background: Spinal cord atrophy in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) correlates with clinical progression in Caucasian patients while such a correlation remains to be established in Asian patients. We aimed to clarify whether spinal cord atrophy is associated with disability in Japanese patients with MS and NMOSD, and to identify the spinal cord levels that best correlate with disability.

Methods: Cross-sectional spinal cord areas at the disc levels of C2/C3, C3/C4, T8/9, and T9/10 were manually measured in 117 relapsing-remitting MS (RRMS), 27 progressive MS (PMS), and 47 NMOSD with aquaporin-4 (AQP4)-IgG patients. Expanding disability status scale (EDSS) scores were used to assess disability.

Results: PMS patients had smaller cervical cord areas than RRMS patients (mean 57.2 vs. 61.2 mm², p = 0.03 at C2/C3; 58.8 vs. 63.7 mm², p = 0.006 at C3/C4). NMOSD patients had significantly smaller thoracic cord areas compared with MS patients (mean 28.7 vs. 31.3 mm², p = 0.02 at T8/T9; 29.7 vs. 32.1 mm², p = 0.047 at T9/T10), but there were no significant differences in cervical cord areas between the two diseases. Both cervical and thoracic cord areas significantly correlated with EDSS scores in MS (r = −0.34, p < 0.0001 at C2/C3; r = −0.38, p < 0.0001 at C3/C4; r = −0.32, p = 0.0001 at T8/T9; r = −0.31, p = 0.0002 at T9/T10), while only thoracic cord areas correlated with EDSS scores in NMOSD (r = −0.45, p = 0.002 at T8/T9; r = −0.33, p = 0.02 at T9/ T10). Multivariate analyses revealed that age (p < 0.0001), PMS (p < 0.0001), number of relapses (p < 0.0001), and smaller cervical cord area at C2/C3 (p = 0.006) were independently associated with disability in MS. By contrast, age (p = 0.02), and smaller thoracic cord area at T9/T10 (p = 0.007) were independently associated with disability in NMOSD.

Conclusions: Cross-sectional spinal cord area significantly correlates with disability in Japanese patients with MS and NMOSD. Our study suggests that cervical cord area is the most valuable predictor for disability in MS while the thoracic cord area is the best predictor for disability in NMOSD with AQP4-IgG. It is important to measure the relevant spinal cord level, according to the disease to be treated.

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P563
Regional patterns of brain atrophy development in pediatric and adult multiple sclerosis patients: a 3.5 year study
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Background: It has been widely demonstrated that pediatric multiple sclerosis (MS) patients have, at short-medium term, a more favorable clinical course than adult ones. A few studies have investigated the pathobiological basis of such a different clinical course identifying brain plasticity and heightened myelin reparative capacity as possible causes.

Objectives: This study is aimed at comparing brain atrophy development between pediatric and adult MS patients.

Methods: Using a 3 T scanner, dual-echo and 3DT1-weighted images were acquired from 31 pediatric and 30 adult disease duration-matched MS patients at baseline and after a mean follow-up of 3.5 years. As control groups, 26 pediatric and 30 adult age- and sex matched healthy controls (HC) were enrolled. Voxel-wise techniques were used to assess volumetric differences at baseline and atrophy progression.

Results: Compared to age-matched HC, pediatric MS patients showed atrophy of the bilateral thalamus, right hippocampus, middle frontal gyrus, left inferior temporal gyrus and calcarine cortex. Compared to age-matched HC, adult MS patients showed a broader pattern of atrophy, involving bilateral thalamus, hippocampus, cingulate cortex and corpus callosum and several cortical areas in the frontal, temporal and parietal lobes. At baseline, compared to pediatric, adult MS patients had atrophy of the cingulate cortex and right precentral gyrus. During the follow-up, compared to adult, pediatric MS patients developed less atrophy in bilateral temporal pole, precentral and postcentral gyrus, left insula, hippocampus, middle frontal gyrus and cerebellum.

Conclusion: Pediatric MS patients compared to disease duration-matched adult patients showed less atrophy, indicating increased resilience against structural damage and neurodegeneration.

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P564
Regional brain atrophy differences and relationship to disability in NMOSD and MS
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Background: Selective patterns of central nervous system atrophy have been investigated to distinguish neuromyelitis optica spectrum disorder (NMOSD) from multiple sclerosis (MS), and have been correlated with disability as determined by the expanded disability status scale (EDSS). However, many studies have been limited by a small sample size, especially for NMOSD. Additionally, there have been conflicting results in the previous studies that investigated the different pathological processes in regional brain structures between NMOSD and MS. Thus, here, we compare regional brain structures, such as cerebellum, brainstem and ventricles, between a large NMOSD cohort, relapsing-remitting MS (RRMS) and healthy controls.
Objective: To compare the volumes of various brain structures in a large NMOSD cohort compared to RRMS and healthy controls, and examine the correlation between volumes and EDSS.

Methods: T1-weighted MRIs (3T) were analyzed in 52 RRMS patients (mean age: 36 (range: 19-50); median EDSS: 2 (range: 0-5.5)), 91 NMOSD patients (34 (20-48); 20-7)), and 42 healthy controls (HC) (38 (20-49)). Brain structures were segmented using the FreeSurfer pipeline and normalized for intracranial volume. Group differences were calculated using one-way analysis of variance and Tukey’s test.

Results: Brainstem (MS: 0.01±0.002; NMOSD: 0.01±0.002; HC: 0.014±0.001) and cerebellar (MS: 0.09±0.01; NMOSD: 0.09±0.01; HC: 0.09±0.01) volumes did not significantly differ between any of the groups. Lateral ventricle volume in MS (0.017±0.007) was significantly greater than in NMOSD (0.012±0.006) or in HC (0.009±0.004) (p<0.0001). There was no significant difference between NMOSD and HC. Third ventricle volume was significantly different between all groups (MS: 0.001±0.0004, NMOSD: 0.0008±0.0003, HC: 0.0006±0.0002) (p<0.0001). Fourth ventricle volume showed a similar trend (MS: 0.001±0.0005; NMOSD: 0.0013±0.0004; HC: 0.0011±0.0003), but only significantly between MS and HC (p=0.008). EDSS only correlated with lateral ventricle volume and only in NMOSD (Pearson correlation coefficient=0.23, p=0.03).

Conclusion: Third ventricle volume may be most sensitive in detecting differences between MS, NMOSD and HC. In this large cohort of NMOSD patients, regional atrophy in NMOSD appears less affected than in MS, suggesting that NMOSD damage may be more localized.

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Longitudinal characterization of MRI phenotypes based on cerebral lesions and atrophy in multiple sclerosis: a five year study

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Introduction: Multiple sclerosis (MS) is a CNS autoimmune disease, characterized by MRI as multifocal demyelinating T2-hyperintensities and diffuse progressive tissue atrophy; processes that are at least partially independent. Our previous work showed dissociation between MRI-defined cerebral T2 lesion volume (T2LV) and global atrophy affecting nearly 25% of subjects. We investigated stability and clinical relevance of these MRI phenotypes over a 5-year period.

Methods: In 153 patients with clinically-isolated syndromes, relapsing-remitting, or secondary progressive (SP) forms of MS, clinical data and MRI were available at baseline and 5 years later. Cerebral T2LV and brain parenchymal fraction (BPF) were determined by a semi-automated pipeline. MRI phenotypes were defined (per our prior work) using median splits: Type I: low T2LV, low atrophy (i.e. high BPF); Type IV: opposite of Type I; Type II: high T2LV, low atrophy; Type III: low T2LV, high atrophy. Thus, Types I and IV had concordance between lesions and atrophy, Types II and III discordance. ANOVA, t-tests, and linear mixed effect model were performed.

Results: Baseline phenotypes were: Type I (n=57), Type II (n=24), Type III (n=26), and Type IV (n=46). Thus, 33% of subjects showed a lesion-atrophy dissociation. BPF differed (p<0.05) among phenotypes except in Type I vs. II. T2LV also differed (p<0.001) except in Type I vs. III. Type IV had the highest Expanded Disability Status Scale (EDSS) scores, longest disease duration, the most men, and the highest proportion of SP subjects (p<0.05). At 5-year follow-up, all types experienced on-study brain atrophy (p<0.001); with type II showing the most (BPF -2.28%). Only Type IV showed an on-study increase in EDSS (p=0.011) and this was a higher change than in Type I (p=0.048). Regarding phenotype stability, Types I and II showed a 5-year conversion rate of 33% and 46%, whereas III/IV had ~90% stability. Among converters, Type II switched primarily to Type IV (91%), whereas Type I switched mostly to Type II (47%) or III (37%). Baseline age (p=0.006), BPF (p<0.001), and T2LV (p=0.04) predicted phenotype conversion.

Conclusion: MRI-defined phenotypes on the basis of cerebral lesions and atrophy show large numbers of patients with dissociation, supporting the partial independence of these two disease aspects. Higher age, higher T2LV, and lower BPF are risk factors for phenotype progression of Types I and II. The brain atrophy rate is highest in Type II.

Disclosure

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A semi-automatic method to segment multiple sclerosis lesions on FLAIR magnetic resonance images

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**Background:** The analysis of disease burden using MR images from patients with multiple sclerosis (MS) requires the quantification of the volume of hyperintense lesions on a T2-weighted MRI sequence. Several automatic methods for MS lesion segmentation have been proposed. The majority of these techniques have been optimized and validated on FLAIR MR sequences, which benefit from CSF signal suppression and better contrast between focal lesions and the surrounding tissue, compared to dual-echo (DE) PD/T2-weighted MRI scans. One of the open issues for these methods remains the high rate of false positive and false negative lesions identified. Therefore, manual segmentation is still the gold standard.

**Aims:** To adapt and validate on FLAIR MR images a semi-automatic method we recently developed for MS lesion segmentation on DE MRI.

**Methods:** The method was validated in a cohort of 17 patients with clinically isolated syndrome (CIS) suggestive of MS (mean lesion load=2.5 ±2.3 ml) on FLAIR MRI scans acquired on a 1.5T Philips scanner. Adapting the method to the FLAIR sequences, the intensity standardization and the training were avoided. Starting from the lesion seed point (manually identified by an expert physician), the expansion of the segmented region continued to the adjacent pixels until the stop condition was reached combining intensity and edge detection constraints. The algorithm was implemented in Matlab®. Manual segmentations by an expert operator were used as the gold standard. The metrics evaluated were Dice Similarity Coefficient (DSC), Root Mean Squared Error (RMSE) of lesion load, True Positive Fraction (TPF), False Positive Fraction (FPF), and False Negative Fraction (FNF) for each patient.

**Results:** The validation measures averaged over all patients were obtained: DSC = 64%; TPF = 0.8; FPF = 0.32; FNF = 0.19; RMSE = 0.65 ml.

**Conclusions:** High similarity with the gold standard was found, as well as low misclassification of lesion voxels and low measurement error. Moreover, the operator time required to extract lesion volumes was importantly reduced. The method did not require training on manual segmentation, making it applicable for research and clinical trials.

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G. Comi has received compensation for consulting services for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, and Forward Pharma, and compensation for speaking activities for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, and Roche.
M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).
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**P567 Trans-synaptic neurodegeneration 12 months following optic neuritis - a longitudinal OCT and DTI study**

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Neurodegeneration is a key pathological process leading to disability in MS. However, the downstream contribution of discrete relapses to remote neurodegeneration via trans-synaptic processes remains unclear.

We assessed whether neuro-axonal injury in the anterior visual pathway correlated with white matter integrity via fractional anisotropy (FA) in the in the optic radiations (OR), in a prospective, longitudinal cohort of patients with acute optic neuritis (ON) and 6 and 12 month follow up. Participants aged 18-55 years were recruited within 28 days onset with a first episode of unilateral ON. Macular ganglion cell volume (GCV) was acquired using Heidelberg Spectralis OCT and Heyex 6.0 segmentation software. All MRI scans were performed with a 3T Siemens Verio using the same sequences. OR were identified using the registration to standard space template inherent in the FSL tool Tract based spatial statistics (TBSS) and OR mean FA was calculated.

40 patients were included in the analysis. Change of GCV over 12 months correlated with FA change bilaterally (p=0.004 r=0.493), and separately in the right (p=0.004 r=0.448) and left (p=0.042 r=0.324) OR, all of which survived in a bootstrapped analysis. Significant correlations were also demonstrated in axial and radial diffusivity at 12 months. Early changes in the same direction were visible even at the 6 months correlation analysis, although not all reached statistical significance.

In summary, we demonstrate the ability to detect, with imaging, retrograde neurodegeneration contributing to anterograde reduction of white matter integrity, through trans-synaptic processes, following a discrete CNS inflammatory event. This appears to be...
a dynamic event progressing over the 12 month follow up period. These data suggest the importance of exploring the mechanisms that underlie both antero- and retro-grade neurodegeneration in the development of future neuroprotective strategies.

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Results: We report four major findings:
1- Early responses were detected in HS in superior parietal, visual, and associative areas. Similar behaviour in the same areas was observed in MS, but with much less spatial extent and additionally in regions such as the thalamus and the posterior cerebellum.
2- Late response was not observed in HS. In MS, however, late responses were observed in the cuneus and calcarine visual areas and the right Rolandic operculum.
3- Narrower responses were seen mainly in HS especially around the post central gyrus and sub-cortical areas.
4- Wider responses were seen mainly in MS especially around the frontal lobe, left putamen, and visual areas.

Discussion: We characterised functional responses during a visuomotor task in MS. The observation of early responses localized in areas responsible for translating signals from the visual to the motor system is likely due to the applied visually guided motor task. Additional areas were seen in MS especially in the posterior cerebellum, which may indicate the greater attention needed due to compensatory mechanisms. It is also interesting that some visual areas showed a delayed response in MS. Whether this is related to lesions in the visual pathway needs to be investigated. Future studies should focus on understanding these characteristics in detail, in combination with structural and clinical measurements.

Disclosure
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Characterization of the haemodynamic response function in multiple sclerosis

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Background: An important methodological consideration regarding measuring functional responses using blood oxygenation level dependent (BOLD) fMRI is to use a subject-specific haemodynamic response function (HRF), characterising the timing and amplitude of the vascular response to a stimulus. However, in general practice a canonical HRF is used. It is therefore possible to use derivatives of the canonical HRF which show early, later, narrower or wider responses. We aimed to investigate these responses in MS using a gripping motor task.

Methods: 14 right-handed (RH) healthy subjects (HS) (9 F; 31 (± 4.64) years) and 14 RH relapsing remitting MS (RRMS) patients (10 F; 35 (± 5.36) years; median (range) EDSS score 3.5 (1.5-6.5)) were assessed with fMRI whilst performing a dynamic gripping visuomotor task using a squeezeball with their RH. The paradigm consisted of 75 event-related trials. The canonical HRF and its temporal and dispersion derivatives were calculated. A full factorial design at the second level was applied and significant voxels defined using FWE (P< 0.05) corrected at the cluster level.

Conclusions: The observation of early responses localized in areas responsible for translating signals from the visual to the motor system is likely due to the applied visually guided motor task. Additional areas were seen in MS especially in the posterior cerebellum, which may indicate the greater attention needed due to compensatory mechanisms. It is also interesting that some visual areas showed a delayed response in MS. Whether this is related to lesions in the visual pathway needs to be investigated. Future studies should focus on understanding these characteristics in detail, in combination with structural and clinical measurements.

Disclosure
A.A, K.F, E.D have nothing to disclose; R.S.S. is funded by the UK MS Society and INSPIRED (a spinal cord imaging grant jointly funded by the Spinal Research, Wings for Life and the Craig Nielsen Foundation); A.T.T has received speaker honoraria from Biomedia, Sereno Symposia International Foundation, Bayer and meeting expenses from Biogen Idec and is the UK-PI for two clinical trials sponsored by MEDDAY pharmaceutical company (MD1003 in optic neuropathy [MS-ON] and progressive MS [MS-SP12]); C.G.W.K. receives research grants (PI and co-applicant) from Spinal Research, Craig H. Neilson Foundation, EPSRC, Wings for Life, UK MS Society, Horizon2020, NIHR/MRC.

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Methods: 129 MS patients and 33 healthy controls (HC) underwent an MRI session with diffusion-weighted and 3D-structural sequences. In 102 patients and 25 HC from this cohort, chemical shift imaging spectroscopy with a box of 78 cm³ over the corpus callosum, including the cingulate, was also acquired. Frontoparietal network was reconstructed through probabilistic tractography and network integrity was analysed using graph theory metrics. Metabolic information in white matter included levels of N-acetylaspartate (NAA/Cr), as marker of neuroaxonal integrity, myo-inositol (ml/Cr), as marker of astroglialis and ml/ NAA ratios. Cognition was assessed with the Paced Auditory Serial Addition test (PASAT) and the Symbol digit modalities test (SDMT). A mean z-score of both tests was obtained (zAttention).

Results: Thirty three patients were considered cognitively impaired (CI; zAttention below -1.5). A significant reduction of global efficiency, assortativity and clustering coefficient was observed in patients, especially in CI (p< 0.05). MS persons displayed decreased NAA/Cr, and increased ml/Cr and ml/NAA levels (p< 0.01). Metabolic changes were correlated with worse strength, transitivity, global efficiency and clustering coefficient of the network (r=-0.37 to 0.51 for correlations with NAA/Cr, and r=-0.26 to -0.49 for correlations with ml/Cr and ml/NAA, p< 0.01). Worse zAttention was correlated with decreased global efficiency, clustering coefficient and NAA/Cr (r=0.21 to 0.38, p< 0.05), and with increased ml/NAA levels (r=-0.29, p< 0.01). When these variables were included in a multiple regression model, cognitive worsening was mainly driven by the reduction of NAA/Cr (β=0.331, p< 0.01).

Conclusion: Astrogliosis and neuroaxonal damage impair frontoparietal network efficiency in MS. Worse attention performance is influenced by the reduction of neuroaxonal integrity of this network.

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P570 Reduced dynamism of functional connectivity is associated with cognitive impairment in MS patients: a dynamic functional connectivity study in a multi-center setting

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Background: A large proportion of MS patients has cognitive deficits. One of the core features of cognitive impairment in MS is decreased information processing speed.

Aims: To investigate the relationship between MS-related cognitive deficits and time-varying functional connectivity (FC) using a dynamic resting state (RS) FC approach.

Methods: RS fMRI scans were obtained at 3.0 T from 62 MS patients and 65 healthy controls (HC) at seven European sites participating to the MAGNIMS network. MS patients underwent a standardized clinical and cognitive evaluation. Independent component analysis was used to identify 43 relevant intrinsic FC networks. Between-group differences of functional network connectivity were evaluated using a dynamic approach, i.e., assessing network FC on small temporal segments using sliding windows, and then grouping FC correlation matrices into recurrent states of transient FC using a k-means algorithm. Summary dynamism measures were computed for each study group.

Results: Twenty-three MS patients (37%) were cognitively impaired (CI) (> two abnormal neuropsychological tests). Dynamic FC analysis revealed the presence, in HC and MS, of 3 recurrent FC states: two states (State1 and State2) were characterized by strong inter-network connectivity, while one state (State3)
was characterized by a lower inter-network connectivity. CI MS patients had a significantly lower dwell time in the high-connectivity State2 compared to HC (p=0.05) and CP MS patients (p=0.08). On average, CI exhibited significantly lower dynamic fluidity, defined as less frequent switch between states, than CP MS patients (p=0.01) and operated over a restricted dynamic range (less distance travelled through connectivity states, p=0.01).

Between-group comparison of connectivity strengths revealed lower FC in MS vs HC between subcortical networks and both somatomotor and cognitive networks in all connectivity states. MS patients showed also higher FC between subcortical and visual networks. In connectivity State3, CI MS patients showed reduced FC between subcortical and default mode networks compared to CP MS patients.

Conclusions: In both HC and MS patients, dynamic RS FC analysis was able to detect recurrent patterns of strong and weak inter-network RS FC. Time-varying RS FC patterns were markedly less dynamic in CI than in CP MS patients and HC, suggesting that slow inter-network connectivity is associated with a worse cognitive profile in MS.

Disclosure


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F. Barkhof serves as a consultant for Bayer Schering Pharma, Sanofi-Aventis, Genzyme, Biogen-Idec, Teva, Novartis, Roche, Synthon BV and Jansen Research.

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M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merk-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla (FISM), Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARISLA (Fondazione Italiana di Ricerca per la SLA).

P571
Do multiple sclerosis lesions affect automatic brain structure segmentation?

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Background: In multiple sclerosis (MS) and in other neurodegenerative diseases, it has been demonstrated that grey matter atrophy is relevant to disease progression. For this reason, automatic brain structure segmentation algorithms have been proposed. However, the effect of MS lesions on their performance has not been deeply evaluated.

Aim: To analyse the effect of focal lesions on three well-known automatic brain structure segmentation methods (FreeSurfer, FIRST and majority voting) when segmenting the deep grey matter structures (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens) and the brainstem.

Methods: We analyse how lesions affect the performance of each method based on structure and lesion location. To perform a quantitative analysis, 2174 MS lesions were simulated on four healthy subjects (controls) from two public databases with brain structure ground truth (IBSR18 and MICCAI12), obtaining a total of 100 synthetic MS patient images. The Dice similarity coefficient (DSC) differences and the volume differences between the healthy controls and the simulated MS patients were calculated for the deep grey matter structures and the brainstem. Statistical tests were applied to prove significant differences in the robustness of the three methods for each analysed structure.

Results: We observed that the three strategies were affected when MS lesions were present. The obtained results show that FreeSurfer (with mean DSC differences ranging from -0.11±0.54 to 9.65±9.87) is the most affected method by the presence of lesions whereas FIRST (differences from -2.40±5.54 to 0.44±0.94) is the most robust against lesions. The lesion location is not important for the global strategies such as FreeSurfer or majority voting, where structure segmentation is affected wherever the lesions exist. On the other hand, FIRST is more affected when the lesions are overlaid or close to the structure of analysis. The most affected structure by the presence of lesions was the thalamus (from -0.12±2.53 to 9.65±9.87), whereas the structures that showed less variation include the thalamus (from -0.48±1.08 to 0.74±0.89) and the brainstem (from -0.20±0.38 to 1.03±1.31).

Conclusion: The three segmentation methods were affected by the presence of MS lesions, which demonstrates that there exists a problem in the automatic segmentation of the deep grey matter structures that has to be taken into account when using them as a tool to measure the disease progression.

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M. Cabezas: nothing to disclose.
D. Pareto: nothing to disclose.
Objective:
The main goals of the study were:
i) to investigate whether changes in cervical cord tissue quantified using MTR were already present in patients with early relapsing-remitting MS: a magnetization transfer study

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Background: Magnetization transfer ratio (MTR) imaging is sensitive to tissue integrity in MS lesions and normal-appearing tissue. Previous studies including patients with well-established MS have shown a significant and disability-related reduction in MTR values in the spinal cord (SC). However, early damage and its predictive utility have yet to be investigated.

Objectives: The main goals of the study were:
i) to investigate whether changes in cervical cord tissue quantified using MTR were already present in patients with early relapsing-remitting MS (RRMS), and
ii) to examine their relationship to EDSS scores at baseline (M0) and one year later (M12).

Methods:
Thirty patients with RRMS (disease duration < 18 months) and 11 aged-matched healthy controls were included. Using 3T scanners in 2 centers, 0.7 × 0.7 × 3 mm^3 axial T2*-weighted images and images with/without MT saturation pulse (mt1/mt0) were acquired, spanning from C1 to C7. The SC was automatically segmented on mt0. MTR maps were computed. Cervical SC lesions were manually labeled on T2*-w images and total lesion volume was calculated. T2* images and lesion masks were non-rigidly aligned to the MTR maps. Finally, mean MTR values were computed for each of the vertebral level in the whole SC, normal-appearing SC and lesions.

Results:
The median EDSS score at M0 for the 30 patients was 0 (range: 02). A total of 54 cervical cord lesions were found in 21 patients. Mean whole SC MTR was significantly lower in patients compared with controls (33.7 pu vs. 34.9 pu, p < 0.001). When lesions were excluded, mean normal-appearing SC MTR remained significantly lower in patients compared with controls (33.8 pu vs. 34.9 pu, p = 0.013). Lesions exhibited varying reductions in MTR values compared with the surrounding normal-appearing SC (median = -4.1 pu; IQ = [-6.1,-1.8]). Only subtle and nonsignificant correlations were found between the mean whole SC MTR value and T2 lesion load (R = -0.25, p = 0.18), and between the mean whole SC MTR value and EDSS scores at M0 (R = -0.18, p = 0.32) and M12 (R = -0.28, p = 0.19).

Conclusion: MTR values for normal-appearing SC and lesions in patients with early RRMS already have a distinctive and variable pattern. No relationship with clinical status can be highlighted at this stage of the disease, owing to the low level of disability. Longitudinal analyses on an extended sample size are ongoing to evaluate the long-term prognostic utility of these values.

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P573
Accelerated thalamic atrophy occurs following acute optic neuritis
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Background: Multiple sclerosis (MS) is a demyelinating disease that predominantly affects the white matter (WM). However, WM lesion load exhibits only modest correlation with clinical disability, an observation known as the clinico-radiologic paradox. Accelerated brain atrophy occurs in MS and grey matter (GM) atrophy is present early in the disease course and exhibits stronger correlations with clinical measures than WM measures. The exact cause of GM atrophy is unclear but proposed mechanisms include primary GM damage, retrograde degeneration following axonal transection and trans-synaptic degeneration (TSD), a process which involves neuronal loss following damage to a pre- or postsynaptic neuron, termed anterograde and retrograde TSD respectively. The visual pathway provides an excellent model to study TSD. Cross-sectional and limited longitudinal studies have suggested that TSD may occur in the visual pathway in MS.

Objective: To evaluate for presence of anterograde TSD following acute optic neuritis (AON).
Methods: 38 patients within 45 days of onset of AON (AON cohort) and 32 relapsing-remitting MS patients without a history of prior AON (non-AON cohort) were followed with annual 3T brain MRI and regular optical coherence tomography (OCT) scans (Median follow-up: 4.2 years). Validated segmentation algorithms developed at our institution were utilized to obtain volumes of cortical/subcortical regions from MRI scans and retinal layer measurements from OCT scans. Analyses were performed with mixed-effects linear regression.

Results: In the AON and non-AON cohorts calcarine cortex atrophy was observed during follow-up but the rate of decline did not differ between the two cohorts (AON:-0.81%/year; non-AON:-0.67%/year; p=0.76). Thalamic atrophy occurred across cohorts but was significantly accelerated in the AON vs. non-AON cohort (AON:-0.95%/year; non-AON:-0.40%/year; p=0.001). Global atrophy occurred in both groups as evidenced by significant decreases in cerebral volume fraction, but this did not differ between the two cohorts (AON:-0.39%/year; non-AON:-0.37%/year; p=0.78).

Conclusions: Accelerated thalamic atrophy occurs following AON, despite similar rates of global atrophy in AON and non-AON patients, raising potential support for anterograde TSD. However, calcarine atrophy was observed at similar rates in AON and non-AON MS patients. Future study should assess the clinical significance of accelerated thalamic atrophy following AON.

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P574
The relationship between network measures and magnetic resonance imaging metrics in multiple sclerosis
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Background: Brain network analysis offers a complementary approach to conventional magnetic resonance imaging (MRI), providing new insights into the pathophysiology of multiple sclerosis (MS). Although several studies have demonstrated network changes in MS patients, the relationship between network metrics (NM) and brain damage defined as either visible lesion load (LL) or as brain atrophy due to decreased volumes of white matter (WM), cortical grey matter (CGM) and deep grey matter (DGM) (hereafter structural volumes [SV]), has not been examined.

Objective: To examine the relationship between NM and SV in MS patients and subtypes.

Methods: 58 relapsing-remitting (RR) MS (18M, mean age [±SD] 42±11 years), 28 primary progressive (PP) MS (10M, mean age 52±9 years) and 36 secondary progressive (SP) MS (8M, mean age 57±7 years) with disease duration 11±8, 14±7 and 22±10 in years respectively, were scanned using 3T (3DT1-weighted [1x1x1mm³] and diffusion-weighted images [DWI, 2x2x2mm³]). Lesion filled 3DT1 scans were segmented and parcellated using GIF. DWI were corrected for eddy currents (FSL) and geometric distortions (BrainSuite). We performed whole brain probabilistic tractography using MRtrix3. The generated streamlines were assigned to brain areas to obtain a structural network for each subject. NM (edge density [ED], global efficiency [GE] and mean local efficiency [mLE]) were derived using TractoR. We used multiple linear regression analysis to investigate the associations between the NM (dependant variables, in turn) and SV (independent variables, in turn) adjusting for age and gender.

Results: In the entire MS group, lower values of all NM are associated with higher LL (all p<0.05) and lower ED is associated with lower volumes of WM, CGM and DGM (all p<0.05). When the MS subtypes were examined separately, lower ED was associated with lower volumes of WM, CGM and DGM in all groups (all p<0.05). In the PPMS we found an association between lower GE and greater LL (p< 0.01). In SPMS, lower network efficiency (GE and mLE) was associated with higher CGM and/or DGM volumes (p< 0.05).

Conclusion: Lower network connectivity and efficiency are associated with greater brain tissue damage, especially in earlier stages of the disease. Interestingly, in later stages of the disease (i.e. in the SPMS group), lower network efficiency is associated with higher GM volumes, perhaps reflecting a compensatory phenomenon that deserves further research.

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P575
Automated detection of central vein sign in white matter lesions for the diagnosis of MS
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Background: Central vein sign (CVS) is a promising diagnostic biomarker for multiple sclerosis (MS), but its use is limited by the potential for inter-rater differences in the judgment of CVS, and the time and effort required to adjudicate CVS for patients with heavy lesion loads. The goal of this study was to develop an automated technique for the detection of CVS in subcortical and deep white matter lesions.

Methods: Magnetic resonance imaging (MRI) was performed on 39 patients: ten had MS and no comorbidities for MRI white matter abnormalities, ten had MS and comorbidities for MRI white matter abnormalities, ten had migraine with an MRI showing white matter abnormalities, and nine had migraine with an MRI showing no additional comorbidities, and ten had migraine with an MRI showing white matter lesions. 

3D T1-weighted, T2-weighted fluid attenuated inversion recovery (FLAIR), and high resolution segmented echo-planar imaging (EPI) sequences were acquired. A multi-stage algorithm was used to detect veins, segment white matter lesions, partition confluent lesions, remove periventricular lesions, and determine the centrality of veins inside candidate lesions.

Validation: Lesion segmentation and vein quantification techniques were calibrated using data from one participant with MS and nine were previously incorrectly diagnosed with MS. 3D white matter abnormalities and no additional comorbidities, and ten had migraine with an MRI showing white matter lesions. Ten had MS and no comorbidities for MRI white matter lesions.

Results: Among the lesions segmented (n = 381), CVS was identified in a greater proportion of the lesions from all participants with MS compared to lesions from all participants without MS (propMS+MSc = 65%, propMig+Mis = 53%, p < .03). Additionally, within-person proportions of CVS were higher in participants with MS compared to participants who were misdiagnosed with MS (meanMS+MSc = 70%, meanMig+Mis = 52%, p < .04).

Conclusion: This study introduces an automated method for detecting central vein sign in white matter lesions and provides preliminary evidence for its validity and potential diagnostic utility. After further study and refinement, the ability to detect the presence of this biomarker using automated methodology could prove instrumental for future clinical application.

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Results: Accounting for lesion load and age, $C_n$ was negatively associated with EDSS ($r_{SS} = -2.86, p = .006$), suggesting that for a given lesion load, a higher lesion count (thus a lower average size) is associated with lower disease severity. The inclusion of $C_n$ in the model explains an additional 10% of the variance in EDSS, providing support to the idea that lesion count contains disease information independent of lesion load.

Conclusion: This study introduces a technique for separating spatially connected lesion tissue into pathologically distinct lesion components, and shows it to be both valid and clinically relevant. These findings demonstrate that it is possible to recover the natural history of MS lesion formation in an automated fashion using MRI scans from a single cross-sectional visit.

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P777

Shrinking of T2-hyperintense white matter lesions in early multiple sclerosis

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Background: New or enlarging T2-hyperintense white matter lesions (WML) are associated with clinical disease progression in multiple sclerosis (MS). The impact of WML shrinking, which might be a sign of repair, has not been investigated to the best of our knowledge.

Aim: We aimed at assessing causes and clinical relevance of WML shrinking in early MS patients.

Methods: We performed 3 consecutive brain MRI scans (3D, 3T, FLAIR and T1w +/- gadolinium) at baseline (MRI1) and after 1 (MRI2) and 3 years (MRI3) in a cohort of 152 early (mean disease duration 1 year) MS patients. All patients were therapy naïve at baseline and most of them treated with different disease modifying drugs (DMD) at MRI 2 and 3. We determined total WML volumes at all time points by an automatic lesion segmentation tool (LST version 2.0.15, lesion growth algorithm) and extracted the number of gadolinium-enhancing and new WML from the radiology report. The volume of WML decrease and increase (MRI1-2; 2-3) was determined by LST’s longitudinal pipeline based on changes of each individual WML. Clinical disability was measured simultaneously to each MRI scan by Expanded Disability Status Scale (EDSS). We determined the association of WML decrease (MR1-2; MRI2-3) with EDSS at MRI3, EDSS change between MRI1 and 3, number of relapses within the study period and with the number of new (MRI2) and gadolinium-enhancing WML (MRI1; 2) by partial correlation analyses correcting for age, gender, DMD and total WML volume (MRI1; 2).

Results: WML decrease between MRI1 and 2 was associated with none of the clinical parameters but with the number of gadolinium-enhancing WML at MRI1 ($r = 0.215, p = 0.009$). WML decrease between MRI2 and 3 was also associated with the number of gadolinium-enhancing WML at MRI1 ($r = 0.268, p = 0.002$); it was further associated with the number of new ($r = 0.299, p = 0.001$) and gadolinium-enhancing ($r = 0.225, p = 0.01$) WML at MRI2 but with none of the clinical parameters. EDSS was low at all 3 time points (mean EDSS MRI1, 2, 3; 1.2, 1.1, 1.2) and correlated with total WML volume only at time point 2 ($r = 0.243, p = 0.003$) but not 1 or 3.

Conclusion: In treated MS patients, WML decrease as observable during the first years after diagnosis with conventional MRI, seems to reflect disease activity at baseline rather than repair processes.

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P578  
Evidence for progressive neurodegeneration in the cervical cord of patients with early primary progressive MS during 3-year follow-up

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Background: The mechanisms underlying disability progression in primary progressive MS (PPMS) are poorly understood. Q-space imaging (QSI) is a diffusion-weighted MR imaging technique that detects microstructural abnormalities. We previously reported abnormal QSI-derived indices of perpendicular diffusivity (water movement perpendicular to the cord axis) in the cervical cord of patients with early PPMS at baseline, suggesting a breakdown in myelin and axonal membranes.

Objectives:
(i) to investigate whether cord changes in QSI measures occur over 3 years and
(ii) to explore their association with disability progression.

Methods: 23 patients with PPMS (12F, mean age: 50yrs±12), median EDSS 5.5 [range2.5-6.5]) and 23 healthy controls (HC) (18F, mean age: 43yrs±9) were studied at baseline, 1 year and 3 years. They underwent brain and spinal cord MRI at 3T. Cord cross-sectional area (CSA) and QSI metrics of the cervical cord were obtained. Patients were clinically assessed with the Expanded Disability Status Scale (EDSS), grip strength, 9-hole peg test (9-HPT), timed 25-foot walk test (T25-FW) and vibration-perception.

Linear regression testing was used to compare MRI measures between patients and HC at follow-up; mixed-effect linear regression models assessed longitudinal changes in MRI measures between groups and their association with changes in clinical scores, corrected for age and gender.

Results: 17 patients with PPMS patients (8F, mean age: 53 years±8), median EDSS 6.5 [range 3.5-7]) and 14 HC (9F, mean age: 46 years±12.3) attended for 3 year follow-up. Patients deteriorated clinically on the EDSS, T25-FW, HPT, grip strength (all p< 0.001) and vibration perception (p=0.04). Similar to baseline results, at 3 years patients showed higher perpendicular diffusivity (p=0.02) and lower CSA than HC (p=0.008). Over time, patients showed a decrease in parallel diffusivity indices (ADCy, FWHMy, P0z [p=0.04, 0.02, 0.04]), which were not observed in HC, and were associated with a deterioration in vibration-perception (p=0.01) in patients. Patients also showed a higher rate of decline in CSA than HC (p< 0.001), which correlated with an increase in EDSS (p=0.02).

Conclusion: The decrease in parallel diffusivity and the development of cord atrophy over time found in our study suggest neurodegeneration, with a reduction in microstructural coherence that may contribute to progressive clinical deterioration in early PPMS.

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P579
Cervical spinal cord volume and diffuse spinal cord abnormalities distinguish multiple sclerosis patients with different levels of disability already 5 years after disease onset

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Objective: To explore significance of spinal cord (SC) pathology in terms of volume, focal lesions and diffuse abnormalities in multiple sclerosis (MS) patients with different levels of disability and disease duration.

Background: SC involvement is common in MS and contributes importantly to disability in progressive disease. The relationship of SC pathology and disability in early and benign MS remains less clear.

Methods: Relapse-remitting and secondary progressive MS patients were selected retrospectively from a large group of over 1000 MS patients examined with SC MRI between January and May 2016. We compared spinal cord volume (SCV) in three groups of patients according to disease duration [0-5; 5-15 and >15 years(y)]. In each group, patients with EDSS >3.0 and ≤3.0 were compared. To eliminate confounding effects of sex, age and disease duration (DD), we matched patients by these parameters. The matching resulted in following group pairs: 1.DD 0-5y (n=76, 26 men); 2.DD 5-15y (n=388, 80 men); 3.DD >15y (n=160, 22 men). SCV was measured as a sum of SC areas from 21 slices centered at intervertebral disk C3/4 on axial 3D-T2w-FatSat sequence acquired at 3T scanner by using an in-house developed semiautomatic method. Types of SC involvement were assessed by neuroradiologist and neurologist, resulting in 4 categories: 1.normally appearing SC, 2.focal lesions, 3.diffuse abnormalities with- or 4.without lesions.

Results: We found lower SCV in patients with higher disability level. In early MS (DD 0-5y), SCV (in cm³) was 1.72 in patients with EDSS>3.0 and 1.85 in patients with EDSS≤3.0 (t-test p =0.003). In patients with DD 5-15y, SCV was 1.67 in patients with EDSS>3.0 and 1.77 in patients with EDSS ≤3.0. (p<0.001). In longstanding MS (DD>15y), SCV was 1.63 in patients with EDSS>3.0 and 1.75 in EDSS≤3.0 (p=0.001). Number of lesions was higher in patients with greater disability levels in all respective group pairs (Mann-Whitney: p =0.01, < 0.001 and 0.005). Presence of diffuse changes was more frequent in patients with higher disability levels. The strongest association between diffuse changes and higher disability level was observed in early MS (DD 0-5y) (45% in EDSS>3 vs. 2.7% in EDSS≤3; χ²-test p< 0.001), followed by patients with DD 5-15y (51 vs. 36.6%; p=0.004), and with DD>15y (57 vs. 43%; p=0.046).

Conclusion: Lower SCV and presence of diffuse SC abnormalities, especially early in the MS course are associated with higher levels of disability.

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PS80 Structure and function of the corticospinal tract and motor cortex in multiple sclerosis
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Introduction: Disability in multiple sclerosis (MS) is mediated by dysfunction of a number of brain structures. Cortical dysfunction, as measured by transcranial magnetic stimulation (TMS); and corticospinal tract (CST) diffusivity correlates with disability in MS patients.

Objective: To assess the structure and function of the corticospinal tract and motor cortex in a cohort of patients with relapsing remitting MS (RRMS), and examine correlations of each to disability.

Methods: 16 patients with RRMS and 17 healthy controls (HCs) were assessed. EDSS, Pyramidal FSS (pFSS), 9-hole peg test (9HPT) and 25-foot walk test (25FWT) were performed in the MS group. The CST was delineated using probabilistic tractography from diffusion weighted tensor imaging (DTI) acquired on 3T-MRI; and the primary motor cortex parcellated with Freesurfer. Threshold tracking TMS (TT-TMS) values included resting motor threshold (RMT), short interval intracortical inhibition (SICI), average intracortical facilitation (Avg ICF), cortical silent period (CSP) and central motor conduction time (CMCT). Patients were grouped according to their worse side by clinical examination. Independent T-test analysed differences between the groups and associations were explored by Pearson’s correlation.

Results: Mean DTI metrics along the CST did not differ between patients and controls (p range 0.30-0.75). The cortical silent
period (CSP) was reduced (mean difference -24.738ms) in MS patients vs HCs (p=0.016). Within the MS group, CST T2LV correlated with 25FTW (0.907, p=0.001), EDSS (0.685, p=0.019) and 9HPT (0.687, p=0.02). CST T2LV also correlated with mean FA (-0.660, p=0.027) and RD (0.689, p=0.019) along the CST. Average SICI (0.803, p=0.003) and peak SICI (0.821, p=0.002) correlated with precentral gyrus thickness, however no TT-TMS metrics correlated with either clinical outcomes or CST DTI parameters.

**Conclusion:** Pathology within the CST contributed more to motor disability than cortical injury, as measured by structural MRI and TMS, in patients with RRMS. Shortening of the CSP suggests a degree of cortical dysfunction in this cohort of patients with RRMS, but did not contribute to disability. Mean CST diffusivity is insensitive to variation in clinical motor outcomes, and regional/lesional CST DTI should be further explored as a biomarker of disability.

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**Introduction:** The objective of this study was to identify individual profiles of microglial activation in patients with MS using positron emission tomography (PET) with the 18-kDa translocator protein tracer 18F-DPA714, and to investigate their impact on clinical progression.

**Methods:** Patients with MS (n=35) were classified according to their clinical evolution over the 2 years preceding study entry (stable disability, moderate progression or severe progression), and along with a group of healthy controls (HC; n=19), underwent 18F-DPA714 PET. Individual maps of microglial activation derived from voxel-wise maps of differences in the tracer binding between patients and HC were employed to calculate: (i) the percent volume of activated microglia over T2-w lesional, normal-appearing white matter (NAWM) and grey matter (GM) volumes in patients, and over WM and GM volumes in HC; (ii) in patients, the number of WM lesions classified as active, inactive and smoldering based on the extent and localization of activated microglia. General linear model was used to compare the percent volume of activated microglia between patients and HC and to correlate the number of lesion subtypes with the patient clinical evolution before study entry.

**Results:** In patients, the percent volume of activated microglia was significantly higher in T2-w lesions (mean±sd=32.7±2.6%, p=0.0001), NAWM (14.4±1.2%, p=0.0001) and GM (16.1±1.5%, p=0.0001), compared with HC (WM=5.8±1.1%; GM=8.4±1.0%). Progressing patients showed a higher number of active lesions compared with clinically stable patients (10.2±1.6 vs 4.5±1.0, p=0.009). Severely progressing patients showed a higher number of smoldering plaques (2.3±0.69) compared with patients with stable disability (0.53±0.21, p=0.005) or with moderate clinical progression (0.82±0.23, p=0.032). There was a strong correlation between the number of smoldering plaques and the changes in clinical disability scores over the 2 years preceding study entry (p=0.0001, beta-coeff=0.73).

**Conclusions:** Individual mapping of microglial activation allows to classify MS lesions according to their neuropathological features and to detect patient-specific profiles of innate immunity activation which may drive clinical progression. These PET-derived metrics may provide novel prognostic indices and may be employed to stratify patients in clinical trials of neuroprotective treatments.

**Disclosure**


**Disclosure**

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Daniel S. Reich: nothing to disclosure.

**PS82**

**Phase 1 safety study of ferumoxytol, an ultrasmall superparamagnetic iron oxide nanoparticle, in multiple sclerosis and healthy volunteers at 7-tesla**


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**Objective:** To determine if iron accumulates in brain structures of healthy volunteers and/or multiple sclerosis (MS) patients following ferumoxytol infusion using 7-tesla (T) MRI and quantitative iron-sensitive pulse sequences.

**Background:** Ferumoxytol is a solution of ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles approved by the United States Food and Drug Administration for iron-deficiency anemia in patients with chronic kidney disease. Prior studies of USPIO suggest no long-term consequences of infusion, but those studies are limited by descriptive outcomes, short follow-up times, and lower field-strength MRI. Ultrahigh-field MRI (7T) provides increased sensitivity to paramagnetic substances, thus improving the ability to detect small changes in USPIO-related MRI signal.

**Method:** 5 healthy volunteers and 4 MS patients underwent a single 510 mg intravenous dose of ferumoxytol, diluted in 50 ml of normal saline, and infused over 17 minutes. Subjects had longitudinal 7T MRI at baseline, ~1 hour after ferumoxytol infusion, ~40 hours, 1 month, and 6 months. An 8-echo gradient echo (meGRE) sequence was acquired at 1 mm³ resolution. A monoexponential fit of the echoes was used to calculate T₁* and generate R₂* (=1/T₁*²) quantitative maps. For each subject, at the baseline and 6-month time point MRIs, deep gray nuclei (globus pallidus, putamen, and caudate) and normal appearing white matter, were manually segmented. Four subjects (1 healthy volunteer and 3 MS) had repeat meGRE scans during a baseline or 6-month session to determine the reproducibility of R₂* maps.

**Results:** No subject had an adverse event or change in vital signs during ferumoxytol infusion. Scan-rescan reproducibility of R₂* maps for the putamen, globus pallidus, caudate, and subcortical white matter were 1.4%, 2.1%, 2.1%, and 2.1%, respectively. The mean percent changes in R₂* between baseline and 6-month MRI scans in corresponding anatomical structures were -0.38%, 0.95%, -0.03%, -0.39% (Mann-Whitney t-test, all p >0.05) for healthy volunteers, and 2.5%, 1.8%, 1.04%, and 3.25% (Mann-Whitney t-test, all p >0.05) for MS patients.

**Conclusion:** Ferumoxytol was well tolerated by healthy volunteers and MS patients and did not show evidence of iron accumulation at 6 months in deep gray nuclei or within white matter. This study suggests ferumoxytol to be a safe MRI contrast agent in MS and healthy subjects.

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**PS83**

**Sources of variability in brain atrophy measurements in individual MS patients**


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**Objective:** To determine and compare various sources of variability in brain volume (BV) measurements in MS.

**Background:** BV measurements fluctuate, even when using standardized MRIs and precise measurement techniques, complicating interpretation of changes in individuals. The degree to which various sources of variability contribute to fluctuations in BV has not been extensively studied.

**Methods:** MS patients were enrolled in a scan-rescan study at 3 MS PATHS participating healthcare institutions. Each patient had 2 visits within 7 days, with 2 MRIs at each visit for a total of 4 MRIs. MRIs were acquired on 2 different Siemens 3T scanners for each patient using identical protocols that included 1 mm isotropic 3D sequences (FLAIR, MPRAGE). Half of the patients had MRIs done on the same scanner on the same day. BV was measured using fully-automated software to calculate brain parenchymal fraction (BPF) (autosegmS, Cleveland Clinic). Measurements performed on different scanners were analyzed before and after calibration. Measurement errors (intra- and inter-scanner variability) and physiologic (between-day) variability were expressed as relative standard deviations (RSD) estimated from a variance components model; 95% confidence intervals for the RSD were estimated via a bootstrap percentile method.

**Results:** Thirty patients participated: Expanded Disability Status Scale (EDSS) 0-6, age 23-55, disease duration 2-27 years. Scanner models: 1 Verio, 5 Skyras, 1 Prisma, and 1 MR/PET. In total, 120 images were analyzed. The components of variability in BPF were estimated as: 0.17% [0.13-0.21%] due to intra-scanner measurement error, 0.21% [0.10-0.29%] and 0.05% [0.00-0.14%] due to inter-scanner measurement error before and after scanner calibration, respectively, and 0.20% [0.09-0.28%] due to physiologic variability. The worst-case variability estimated from scans acquired on a different day and different scanner was 0.34% [0.30-0.42%] before calibration and 0.25% [0.23-0.32%] after calibration.

**Conclusion:** The worst-case variability in BV can be reduced by approximately 25% using a simple linear calibration between scanners. Day-to-day physiologic variability was similar in magnitude to the inter-scanner measurement error. A better
understanding of the sources of variability may lead to improved techniques for estimating the extent of true tissue loss and enable the use of BV measurements in routine clinical care of MS patients.

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P584
Automated, modular MRI processing for multiple sclerosis using the BRAINMAP framework
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Background: Magnetic resonance imaging (MRI) is a critical tool for the diagnosis and ongoing investigation of multiple sclerosis (MS). Manual analysis of MRI data, however, is expensive and time consuming. Automated processing significantly reduces the amount of time and manual interaction that is required in the processing of MRI data. New methods for automated processing are introduced in the literature constantly, but these are often difficult to interchange in a large-scale processing pipeline. We developed a modular, automated framework, BRAINMAP (Bridging Radiology And Investigative Neurology using Modular, Automated Pipelines), which we implemented for the analysis of a longitudinal MS study.

Objective: To implement and apply BRAINMAP to a large-scale, longitudinal MS study, and determine rates of failure.

Methods: 166 MS patients (740 MRI scans) underwent MRI as a part of a longitudinal study (mean of 5.4 annual visits). BRAINMAP was implemented in Python using Nipype and executed in parallel on a high-performance supercomputing cluster. All images within a time point were coregistered to the time point T1-weighted image and then registered longitudinally to the baseline for analysis. Multi-Contrast Brain Stripping Method was used for skull removal, Subject-Specific Sparse Dictionary Learning for lesion segmentation, Multi-Atlas Cortical Reconstruction Using Implicit Surface Evolution for brain segmentation and Random Forest Thalamus Segmentation for refined thalamic segmentation. Lesions were inpainted for later analysis. Results underwent manual quality assurance (QA). Global atrophy was calculated on subjects that had at least 2 time points, after removal of failed sessions.

Results: After QA, 13 scans were removed due to excessive artifacts, as noted by raters. Of the remaining 727 scans, BRAINMAP passed QA on 699 scans (96.1%). Of the 28 failed scans, 17 (2.3%) failed in skull removal, 2 (0.2%) failed in brain segmentation, and 4 (0.4%) had gross lesion segmentation errors, after visual inspection. Global atrophy was measured at an annual rate of -0.45% for the whole brain, -0.50% for the cortical grey matter (CGM), -0.41% for the WM and -0.69% for the thalamus. All rates were statistically significant with p<0.0001.

Conclusion: BRAINMAP completed with a 96.1% success rate. Statistically significant atrophy in CGM and thalamus was observed, as expected, showcasing the ability of automated processing to produce quality research results.

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P585
Grey matter connectivity in clinically isolated syndromes
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Background: Grey matter (GM) atrophy occurs early in multiple sclerosis evolution and is linked with disability. However, GM morphology and structural connectivity has been poorly studied at this stage of the disease.

Aim: The aim of this project was to characterize GM morphology in clinically isolated syndrome (CIS) patients using a graph theoretical approach, and to assess whether an association between network properties and disease burden, measured as the brain lesion volume, can be observed.

Material and Methods: A group of subjects with CIS (n=30) and a convenience sample of CIS patients (n=35) were included in this study. Images were acquired in a 3.0T scanner (Tri, Siemens) and the protocol included 3D-T1 MPRAGE and 2D-FLAIR sequences. Lesion volume was determined with the Lesion Segmentation Toolbox. Single subjects GM networks were extracted from the original GM segmentations. The degree, path length, betweenness centrality, lambda, gamma and small world parameters were quantified for each subject. Differences in each network properties were determined between controls and CIS with an analysis of variance, including age and gender as covariates. The relationship of network properties with lesion volume was assessed with partial correlation corrected for age and gender.

Results: CIS patients showed a significant decrease in the values of path length, betweenness centrality, gamma, lambda and small world parameters compared to controls. Larger lesion volumes were associated with a loss of clustering (r=-0.40; p=0.025). When CIS male and female patients were analyzed separately (correcting by age), males additionally showed significant negative correlations between lesion volume and clustering, gamma, lambda and small world.

Conclusions: GM networks are disrupted in MS patients very early in their disease evolution. Some GM network parameters worsen with disease burden, particularly in male patients.

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PS86

Improving the accuracy of brain tissue loss assessment in patients with multiple sclerosis: a role for diffusion imaging?

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Introduction: Multiple sclerosis (MS) T2 lesions contribute to brain volume loss (BVL) through focal tissue loss and associated Wallerian and retrograde degeneration. However, the correlation between baseline T2 lesion volume (T2LV) and BVL is weak, potentially due to underestimation of tissue loss within chronic lesions, in which astrogliosis reduces the susceptibility to structural collapse associated with axonal loss. Diffusion magnetic resonance imaging (dMRI) is sensitive to changes in tissue microstructure, and provides an opportunity to refine BVL measurements with an indicative measure of tissue loss.

Objective: To develop a composite biomarker for assessing brain tissue loss (BTL) in MS by combining macro- and micro-structural imaging techniques.

Methods: dMRI, 3D T1, and 3D FLAIR were acquired at baseline and 12 months on a 3T GE MRI scanner from 64 RRMS patients. T2LV and percentage brain volume change (PBVC) over 12 months were assessed by SIENA/FSL. dMRI was motion, eddy-current and EPI susceptibility distortion corrected, prior to tensor-reconstruction and co-registration with structural images. Whole brain mean diffusivity (MD) was weighted and averaged with the co-registered brain parenchyma partial volume estimation map (Sienax/FSL) using lesion-impaired 3D T1 images. A voxel-wise 2-compartment (tissue-free water) model was developed and used to ‘correct’ PBVC results based on MD change within the brain.

Results: Sixty-four patients with RRMS; 83.1% female; mean age 36.7 (8.83) years; mean disease duration 7.55 (6.92) years and mean baseline EDSS 1.9 (1.4) were evaluated. The association (Pearson’s r) between baseline T2LV and PBVC was -0.523 (p< 0.001) and -0.610 (p< 0.001) prior to and after application of the BTL model respectively.

Conclusion: The improved correlation between baseline T2 lesion burden and short term PBVC following adjustment for change in whole brain MD supports the hypothesis that MS lesions contribute directly, and indirectly, to BVL in MS. Conventional volumetric analysis underestimates tissue loss and a composite biomarker based on a 2-compartment (tissue-free water) model has the potential to more faithfully delineate BTL in MS.

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P587
Investigating resting-state BOLD variability in early multiple sclerosis
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Background: Patients with Multiple Sclerosis (MS) show altered functional connectivity, even at the early stages of the disease, thus indicating that a network reorganization occurs and constantly evolves along with the disease. Variability of the BOLD signal amplitude is receiving increasing attention as a direct index of neural activity[1]. Several studies have shown that variability reflects the capability of adaptation of the brain and that it decreases with age and it varies in neuropsychiatric disorders [2,3]; moreover variability of the signal has been found to differ among distinct areas of the brain and to relate to the performance accuracy.

Aims:  
1) to investigate changes, if any, in rs-fMRI variability in patients with Clinically Isolated Syndrome (CIS) and early Relapsing Remitting (RR) MS, as a function of disease severity;  
2) to assess the relationship between variability changes and clinical measures.

Materials and Methods: Fractional Standard Deviation (f-SD, as a measure of the variability of BOLD signal, in the standard frequency bands 0.01-0.10 Hz), was measured in 36 MS patients (17 with CIS and 19 with RR-MS) and 27 healthy subjects (HS); pre-processing analysis was performed using AFNI and FSL on the resting-state fMRI sequences.

Results: Whole brain f-SD was significantly increased in the pre-cuneus in the whole MS group compared to HS (p=0.02) and in the subgroup of RR patients compared to HS (p=0.03); CIS patients had an increased variability in the inferior parietal lobe (IPL) when compared to RR patients. On the other hand, a reduced variability in the posterior cingulate cortex (PCC) (p=0.002) was found in the whole MS group compared to HS and in RR patients compared to both CIS patients and HS (p<0.001). An inverse correlation was found between variability in the IPL and PCC and EDSS (p=0.16, rho=-.397 and p=0.007, rho=-.440, respectively) in the whole group of MS patients.

Conclusions: the functional reorganization occurring in patients with MS results in changes of variability in the precuneus, PCC and IPL; a higher variability in the cingulate and parietal cortex could represent a mechanism to compensate clinical deficits.

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P588
Validation of fully automated machine-learning algorithm for T2 lesion segmentation from clinical MRI in multiple sclerosis
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Introduction: Multiple sclerosis (MS) is an immune-mediated disease hallmarked by sclerotic plaques/lesions in characteristic locations in the central nervous system. Lesional measures are clinically importantly because they are surrogates of disease activity, predict disease course/relapses, and correlate with clinical disease measures. Manual segmentation of T2 lesions can be time-consuming and is subject to inter/intra-rater variability. Existing semi-automated and automated methods can be prone to misclassification errors and require standardized MRI sequences. This study proposed a novel fully-automated machine-learning method using random forest (RF) in clinically acquired images across different scanners and platforms. Comparative analysis with manual segmentation was conducted for validation.

Methods: MRI scans were abstracted from an existing retrospective cohort study of MS patients. A training set consisted of 10 scans from 10 unique subjects with all 5 MRI modalities (FLAIR, PD, T2, T1, and T1 post-contrast) were constructed to train a RF with manual segmentation. Next, a validation set comprised of 12 MRI scans from subjects different from the training set were segmented manually by 3 independent raters. Consensus delineation was constructed from the 3 manual segmentations. Symmetric metrics (Dice coefficient, Pearson’s r, volume difference) were
used to compare the manual segmentations, consensus delineation, and RF method.

**Results:** In T2 lesion volumes (T2LV) segmented, metrics for RF method compared to consensus delineation: \( r = 0.979, \) mean Dice (SD): 0.624 (0.206), average volume difference in ml (SD): 8 (7). For inter-rater comparisons, mean Dice ranged from 0.621 to 0.685, and \( r \) ranged from 0.962 to 0.984. There was a greater range in Dice between raters for scans with low T2LV; for scans with moderate to high T2LV, there was a more unified consensus with Dice between 0.702 and 0.859.

**Conclusion:** Our fully-automated RF method is similar to manual segmentation in spatial overlap and correlation measures. Dice scores were also comparable to currently published machine-learning methods. Advantages for our RF method include full automation and ability to analyze across various acquisition parameters, scanners, and platforms. We will apply our RF method for lesion segmentation to the dataset of a comparative effectiveness study of two oral MS medications (dimethyl fumarate and fingolimod).

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**P589**

Comparison between the 2010 McDonald and 2016 MAGNIMS MRI criteria for dissemination in space in patients with a clinically isolated syndrome. Does the recent recommendation regarding the current criteria improve diagnostic accuracy?


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The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group recently proposed new dissemination in space (DIS) criteria that include lesions in the optic nerve, cortex and symptomatic region, in addition to an increase in the required number of periventricular (PV) lesion from 1 to 3. We aim to compare the diagnostic performance of the 2010 McDonald and 2016 MAGNIMS magnetic resonance imaging (MRI) criteria for DIS in predicting the conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS).

Inclusion criteria:

1) CIS suggestive of central nervous system demyelination (since 2008);
2) clinical assessment and baseline brain MRI within 6 months of CIS onset;
3) spinal cord MRI available if patients presented with spinal cord syndrome; and
4) clinical follow-up of at least 24 months.

We included 161 CIS patients, 113 (70.2%) women, with a mean age at onset of 34 years. After a mean follow-up of 58 months, 102 (63.4%) patients were diagnosed as having MS according to the McDonald 2010 criteria. The overall conversion rate to CDMS was 48.4%. Forty-six (45%) patients initiated a disease-modifying treatment (DMT) before the second clinical event. The 2010 McDonald DIS criteria were met in 100 (62.1%) and the 2016 MAGNIMS DIS criteria in 95 (59%) patients with CIS. Six patients with 1PV lesion fulfilled the 2010 McDonald criteria but did not the 2016 MAGNIMS criteria. In contrast, when symptomatic infratentorial/spinal cord lesions were included, two more patients met the 2016 DIS criteria than the 2010 McDonald criteria. The sensitivity, specificity, and positive and negative predictive values of 2010 McDonald criteria were 80.7%, 55.4%, 63% and 75.4%, and those for 2016 MAGNIMS criteria were 75.6%, 56.6%, 62.1, and 71.2%, respectively. Both DIS criteria identified a subset of patients with CIS who were at high early risk of developing CDMS (hazard ratio: 2.17, \( p < 0.001 \); and 2.07, \( p < 0.002 \), respectively). In our CIS patient cohort, 2016 MAGNIMS MRI criteria for DIS showed lower sensitivity with similar specificity than 2010 McDonald criteria in predicting conversion to CDMS, probably related to the increase in the required number of PV lesions. Because DMT can delay or prevent the conversion to CDMS, the high number of patients that initiated these therapies before the second relapse, would explain the intermediate specificity values obtained with both MRI criteria.

**Disclosure**


**P590**

Increased between-network functional connectivity as a compensatory mechanism to maintain walking ability in MS patients

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**Background:** Functional disconnection has been variously reported in patients with multiple sclerosis (MS), but how changes in between-network connectivity are associated with clinical impairment remains poorly understood.

**Aim:** To investigate between-network functional connectivity (FC) and their association with cognitive and motor impairment in patients with MS.

**Method:** A cohort of 90 MS patients (age: 36.9+-8.6, 22 males, median Expanded Disability Status Scale [EDSS] 1.5, [range 0-5.5]) and 35 healthy subjects (HS, 32.3+-6.5 years, 12 males) underwent clinical examination and 3T MRI (Siemens Verio 3T scanner). Inclusion criteria were a) 18-65 years of age; b) clinically definite MS, according to the revised McDonald c) stable clinically (relapse- and steroid-free) for at least 3 months prior to study. MRI protocol included T2w-TSE, 3D-T1w, RS-fMRI. Scores obtained at 25-Foot Walking Test (T25-FW)
Larger maximal lifetime brain growth is associated with faster motor speed in early relapsing multiple sclerosis

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Background: The brain reserve hypothesis states that persons with larger maximal lifetime brain growth (MLBG, estimated with intracranial volume, ICV) can better withstand disease without cognitive impairment. Specifically, larger MLBG has been linked to faster cognitive processing speed, but not preserved memory. The concept of brain reserve has recently been applied to physical function in persons with multiple sclerosis (MS), but it is unknown whether this relates to motor speed, strength, and/or coordination.

Objective: To determine whether a novel double inversion recovery MRI technique has the potential to distinguish MS from non-MS white matter lesions.

Methods: Patients with early MS (18 clinically isolated syndrome, 87 relapsing remitting MS) completed tasks of fine motor speed (Finger Tapping Test), strength (hand dynamometer), and coordination (Nine Hole Peg Test). MLBG was estimated with ICV measured from 3D T1-weighted MRIs acquired in a 3.0T scanner. Normalized cortical and subcortical grey matter volumes were measured with FreeSurfer. We performed partial correlations between MLBG and the three motor tasks, controlling for age, sex, and grey matter volumes. Given a possible link between body size and motor function, we repeated analyses also controlling for height and weight.

Results: Larger MLBG was linked to faster motor speed ($r_p=0.256$, $p=0.010$) and greater strength ($r_p=0.230$, $p=0.020$), but not better coordination ($r_p=0.40$, $p=0.688$). When controlling for height and weight, larger MLBG was still related to faster motor speed ($r_p=0.207$, $p=0.040$), but not strength ($r_p=0.154$, $p=0.127$). This relationship persisted when controlling for cognitive processing speed.

Conclusion: These findings help isolate the protective effect of larger MLBG on physical function in MS to motor speed, rather than strength or coordination. This is consistent with work in cognition showing that larger MLBG is linked to faster processing speed, but not preserved memory. Further elucidating the impact of MLBG is potentially beneficial in trial design, with the goal of selecting a population at higher risk for worsening physical disability. Additional analyses are planned in this population of patients with early relapsing disease and well characterized physical and cognitive profiles.
Methods: This is a cross-sectional observational study. MRI data was acquired between 2011 and 2016, using a novel double-inversion-recovery sequence that suppresses CSF and grey matter signal (GM-DIR). The study was performed in a single Multiple Sclerosis clinic, at Mayo Clinic, Rochester, MN. MRIIs were obtained in a group of patients with relapsing remitting MS and in a group of positive controls (PC) without MS. We compared and combined our MRI rim marker on GM-DIR with the 2001 and 2010 McDonald dissemination in space criteria. Multiple MRI markers including lesion location, size and presence of hypo-intense rim were compared between groups as well as quantitative measures of lesion T1-hypointensity.

Results: MRI scans from 107 patients with RRMS (median age 32) and 36 positive control (PC, median age 39) subjects were analyzed. No significant differences were present in age and sex distribution. In MS subjects, 1120/3211 (35%) had a rim on GM-DIR; the PC group had only 9/893 rim lesions (1%). Rims were associated with a decrease in lesion T1-ratio. Using the 2010 MRI criteria plus the presence of rims on GM-DIR, we achieved 78% and 97% specificity in subjects with respectively ≥1 and ≥2 rim-lesions.

Conclusions: The addition of a novel GM-DIR technique enhanced specificity for diagnosing MS compared to established MRI criteria.

Disclosure

This study was supported by Grant number KL2 TR000136 (National Center for Advancing Translational Sciences (NCATS)) and W81XWH-13-1-0098 (Department of Defense). Mayo Clinic has filed a patent on behalf of Drs. Port, Shu, Lucchinetti and Tillema that is broadly relevant to this work. Specifically, the GM-DIR sequence described in the patent was used for this study.

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P593

Structural MRI correlates of hand motor performance in patients with multiple sclerosis

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Background: Multiple Sclerosis (MS) is characterized by alterations in brain structural integrity and worsening of motor performance.

Objectives: We applied structural MRI techniques in a large cohort of MS patients to evaluate the correlation between abnormalities of regional brain gray matter (GM) volumes and white matter (WM) architecture and measures of manual dexterity and Expanded Disability Status Scale (EDSS).

Methods: From 134 HC and 366 right-handed MS patients, brain 3D T1-weighted and diffusion tensor (DT) MRI scans were acquired and used to performed a Voxel-based Morphometry and a Tract-based Statical Statistic. Correlations between altered MRI measures and EDSS as well as manual dexterity tests [9 Hole Peg Test (9HPT) and Finger Tapping (FT) test] were investigated.

Results: Compared with HC, MS patients show a widespread pattern of GM atrophy involving the frontal, parietal and occipital lobes. The analysis of WM architecture showed a distributed reduction of fractional anisotropy (FA) and an increased axial (AD), radial (RD) and mean diffusivity (MD) in MS patients compared to HC. In MS patients, better performance at 9HPT correlated with higher volume of the putamen, insula and cerebellum, whereas lower 9HPT performance correlated with R cerebellum atrophy. Better FT performance correlated with higher left superior temporal gyrus volume, whereas higher EDSS correlated with atrophy of the cerebellum, temporal lobe and putamen. Finally, a negative correlation between reduced FA and increased AD, RD and MD with worse manual dexterity performances was found.

Conclusions: Tissue loss and microscopic tissue abnormalities of the cerebellum and deep GM structures contributes to explain motor dysfunction in patients with MS.

Disclosure

C. Cordani, C. Piazza, M. Roselli, F. Esposito, M. Radaelli, B. Colombo have nothing to disclose.
G. Comi, has received compensation for consulting services for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, and Forward Pharma, and compensation for speaking activities for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, and Roche.
M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), the Jacobs and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).
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OCT

P594

Retinal inner nuclear layer volume: a potential new outcome measure for optic neuritis treatment trials in MS


Background:

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Background: The association of peripapillary retinal nerve fibre layer (pRNFL) and ganglion cell-inner plexiform layer (GCIPL) thickness, with neurodegeneration in multiple sclerosis (MS) is well established. The potential relationship of the adjoining inner nuclear layer (INL) with inflammatory disease activity is less well understood.

Objective: To investigate the longitudinal relationship of INL volume changes with inflammatory disease activity.

Methods: In this longitudinal multi-center study, spectral-domain optical coherence tomography (OCT) and clinical data were collected in 821 patients with MS, from eleven MS centres between 2010 and 2017. All patients had at least two visits (minimum follow-up of 6 months). Clinical data included EDSS score, occurrence of relapses, including MS-associated optic neuritis (MSON).

At each centre, automated segmentation of OCT scans was performed to obtain data on the pRNFL, GCIPL and INL. Annualized changes were calculated and generalized estimation equations formed to obtain data on the pRNFL, GCIPL and INL. Volume changes were calculated and generalized estimation equations were used to analyze longitudinal changes and associations with clinical measures.

Results: In total, 1596 eyes from 798 patients (68.2% female), with a disease duration of 9.4 (±8.9) years, were included. Mean follow up duration was 2.3 years (range 0.5 to 5.2 years). Microcystic macular oedema (MMO) was present in 1.3% of eyes (20/1299 eyes). Clinical relapses other than MSON were present in 24.9% of patients, and disease progression was observed in 30.1% (20/1299 eyes). Microcystic macular oedema (MMO) was present in 1.3% of eyes (20/1299 eyes). Clinical relapses other than MSON were present in 24.9% of patients, and disease progression was observed in 30.1% (20/1299 eyes). Microcystic macular oedema (MMO) was present in 1.3% of eyes (20/1299 eyes). Clinical relapses other than MSON were present in 24.9% of patients, and disease progression was observed in 30.1% (20/1299 eyes).

At each centre, automated segmentation of OCT scans was performed to obtain data on the pRNFL, GCIPL and INL. Annualized changes were calculated and generalized estimation equations were used to analyze longitudinal changes and associations with clinical measures.

INL volume changes were calculated and generalized estimation equations were used to analyze longitudinal changes and associations with clinical measures.

Conclusions: Our data demonstrate that an increase of the INL volume is associated with inflammatory disease activity, but not with global physical disability. Therefore INL volume changes may be considered as a secondary outcome measure for anti-inflammatory treatment in MSON trials.

Disclosure

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P. Villoslada: is currently an employee of Genentech and this work was done before and independently of the company; holds stocks in Bionure Inc, Spire Bioventures, Mintelab and Health Engineering; is academic editor in Multiple Sclerosis and Demyelinating Diseases; and is in the executive committee of the European Association of Systems Medicine.
P595
Visual evoked potentials are more sensitive than optical coherence tomography in clinically isolated syndrome
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Background: Visual evoked potentials (VEPs) and optical coherence tomography (OCT) can detect demyelination and neurodegeneration in the visual pathway, with higher sensitivity of VEPs reported in clinically definite MS and first-ever optic neuritis. Our aim was to compare the sensitivity of VEPs and OCT in patients with Clinically isolated syndrome - CIS suggestive of MS.

Methods: Seventy-one consecutive patients with CIS (43 females, mean age 34.3 ± 9 years) underwent VEPs and OCT with measure of VEP latency and of thickness of the peripapillary retinal nerve fiber layer (RNFL) in both eyes.

Results: Considering all patients, VEPs were abnormal in 43.7%, whereas OCT showed abnormal RNFL values in 15.5% of patients (decreased except for 2 patients with acute ON); 8 patients (11.3%) had both abnormal VEPs and OCT, 23 (32%) had abnormal VEPs only, while 3 patients (4.2%) had abnormal OCT only (McNemar’s Chi squared 13.885, P value 0.0002). When considering patients with optic neuritis at presentation (n=24, 33.8%), VEPs were abnormal in 22 (91.7%) patients and OCT in 7 (29.2%). In patients without ON, abnormal VEPs were found in 9 patients (19.1%) and OCT in 4 (8.5%).

Conclusions: The present findings of a higher sensitivity of VEPs compared to OCT in CIS is consistent with previous literature in clinically definite MS and isolated optic neuritis. OCT adds little to VEPs in detecting involvement of the visual pathway, particularly in patients with optic neuritis presentation. Longitudinal monitoring is required to assess the comparative value of the two methods in proving optic nerve involvement as an indicator of dissemination in space and their prognostic value on the subsequent conversion to MS.

Disclosure
nothing to disclose

P596
Silent retinal atrophy in multiple sclerosis is mainly due to silent optic nerve lesions
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Background: Optical coherence tomography (OCT) is a precise and reproducible imaging tool enabling us to measure retinal axonal loss. In multiple sclerosis (MS), retinal atrophy is observed after clinical episode of optic neuritis (ON) but also without any previous clinical episode of ON. According to the literature, the silent retinal axonal loss in MS may be related to optic radiations lesions by a retrograde transynaptic degeneration process. By this way, retinal OCT may be a window on the brain of MS patients.

Objectives: To evaluate brain and optic nerve imaging parameters associated with retinal atrophy in MS eyes without previous clinical episode of ON.

Materials and Methods: We prospectively recruited MS patients treated by natalizumab (>6months; JCV negative or with JCV index < 1.5) and followed-up in our MS center since the beginning of their disease. Written informed consent was obtained (VWIMS study). We performed optic nerve/brain magnetic resonance imaging (MRI), and optical coherence tomography (OCT) of both eyes. Primary evaluating criteria were temporal peripapillary retinal nerve fiber layer (pRNFL-T) thickness, optic nerve DIR hypersignal lesion length (3D-DIR sequence), bilateral optic radiations lesions volume (3D-FLAIR sequence). Linear regression model was used for statistical analysis.

Results: No patient presented any relapse during the previous 6 months. At the time of this first analysis (April 2017), 35 patients were included in our study. Among these 70 eyes, 52 had no past clinical episode of ON (MS-NON eyes). Among these 52 MS-NON eyes, 23 presented at least one DIR hypersignal on optic nerve (MS-NON-lesion eyes). With statistical adjustments to age, gender, disease duration and lesion volume on optic radiations, pRNFL-T thickness was significantly decreased (p< 0.001) in MS-NON-lesion eyes (48.9µm) vs MS-NON-nolesion eyes (65.6µm). Among MS-NON eyes population, using linear regression model, we found significant association between pRNFL-T thickness and the length of optic nerve DIR hypersignal (β -0.77 [-1.06;-0.48] p< 0.001) but none between pRNFL-T thickness and T2 lesion volume in optic radiations (β -8.10e5 [-0.002;0.002] p=0.941).

Conclusion: Silent retinal atrophy in MS seems to be mainly the consequence of silent optic nerve lesions rather than the consequence of silent lesions on optic radiations and retrograde transsynaptic degeneration. More detailed results will be presented at ECTRIMS 2017-Paris.

Disclosure
Jean-Baptiste Davion, Julien Lannoy, Jean Pierre Pruvo, Xavier Leclerc and Renaud Lopes have nothing to disclose.

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P597
Association of retinal layer architecture and the development of neuropsychological deficits in early multiple sclerosis
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Purpose: To evaluate the association between retinal layer volumes as measured by optical coherence tomography (OCT), and cognitive and affective disorders in patients with early multiple sclerosis (MS).

Methods: A total of 82 patients with early relapsing-remitting MS (RRMS) and eight patients with clinically isolated syndrome (CIS) (both groups: age 33 ± 0.9 years; disease duration 5.8 ± 6.7 months) were enrolled into the study and prospectively followed over 26.4 ± 8.3 months. At baseline, patients underwent clinical assessment and OCT examination, eyes with a history of optic neuritis before baseline or during follow-up were excluded. Every 12 months, Beck’s depression inventory (BDI), fatigue scale for motor and cognitive functions (FSMC) and multiple sclerosis inventory cognition (MUSIC cognition) were evaluated. Kaplan Meyer survival analysis for worsening within the respective disease scores corrected for age, sex, diagnosis, disease duration, disease modifying therapy and other medications were performed.

Results: We found continuous and sustained worsening in BDI in 10% of patients during follow-up. Increased values of peripapillary nerve fibre layer (pRNFL >101.8 µm; p=0.04) and total macular volume (TMV >8.835 mm³; p=0.01) were linked to a higher chance of developing fatigue, as measured by the FSMC score, during follow-up. In contrast, lower volumes of the common ganglion cell and inner plexiform layer at baseline (GCIPL<1.98 mm³) were associated with an increased risk for sustained cognitive decline (hazard ratio HR=5.7; p=0.04) during follow-up as measured by MUSIC cognition test.

Conclusion: MS-associated comorbidities might be associated with changes in retinal architecture in early MS. Atrophy patterns of inner retinal layers seem to be linked to an increased risk for developing cognitive deficits but decreased risk of fatigue or depression. Further studies are required to address whether the retinal architecture can predict long-term cognitive decline and the occurrence of depression and fatigue in the context of CNS autoimmunity.

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C. Wetzlmair: has nothing to disclose
G. Leppeneter: has nothing to disclose
T. Daltrozzo: has nothing to disclose

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V. Biberacher: has nothing to disclose
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B. Hemmer: has served on scientific advisory boards for F. Hoffmann-La Roche Ltd, Novartis, Bayer AG, and Genentech; he has served as DMS member for AllergyCare; he or his institution have received speaker honoraria from Biogen Idec, Teva Neuroscience, Merck Serono, Medimmune, Novartis, Desitin, and F. Hoffmann-La Roche Ltd; his institution has received research support from Chugai Pharmaceuticals and Hoffmann-La-Roche; holds part of two patents; one for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and one for genetic determinants of neutralizing antibodies to interferon β.
T. Korn: has nothing to disclose
B. Knier: has nothing to disclose

P598
A multidisciplinary assessment through OCT and correlations to brain pathology and endothelial factors in multiple sclerosis
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Background: Degeneration of optic nerve in Multiple Sclerosis (MS) can be measured through optical coherence tomography (OCT). A vascular density reduction is also present in MS. High homocystein (Hcy) levels and low Vascular Endhotelial Growth Factor-A (VEGF-A) levels, well-known factors influencing the vascular flow, have been related to MS.

Objective: To analyse the correlations between retinal pathology, assessed by Anglo- and spectral domain (SD)-OCT, homocystein/VEGF-A serum levels and brain pathology by MRI in MS patients.

Methods: Patients with and without history of Optic Neuritis (ON) were included and underwent angio- and (SD)-OCT. We assessed supratentorial white matter lesion (WML) load on 3D-FLAIR images, using a semiquantitative score ranging from 0 (no lesions) to 6 (large and confluent WMLs), and performed quantitative flow-rate measurements of the extracranial internal carotid (ICA) and vertebral arteries (VA) using a 2D axial phase-contrast, ECG-triggered sequence placed just below the skull base. Intracranial volume (ICV) was also automatically measured. Hcy was dosed in 46 patients and VEGF-A in 18 patients.

Results: Fifty patients (31 females, mean age 40.64 ± 12.45 years) with 100 consecutives eyes were included. Twenty-three eyes of MS patients had optic neuritis (ON), EDSS disability mean score was 3.50 ± 1.28, and mean disease duration was 11.06 years. Fifty eyes without history of ON had a mean score was 3.50 ± 1.28, and mean disease duration was 11.06 years. At base. Intracranial volume (ICV) was also automatically measured. ECG-triggered sequence placed just below the skull base. Intracranial volume (ICV) was also automatically measured. ECG-triggered sequence placed just below the skull base. Intracranial volume (ICV) was also automatically measured.
Results: OCT data were available for 112 participants, MUCCA for 146, and both OCT and MUCCA were available for 95. EDSS was moderately correlated with MUCCA (N=146, t: -0.307, p<0.001), but not with the three OCT measures. SDMT was weakly correlated with MUCCA (N=145, t: -0.202, p=0.015), pRNFL and TMV were inversely correlated to homocystein. Moreover, TAF was inversely correlated to homocystein and directly to VEGF-A levels.

Discussion: We confirmed a relation of VD with disease severity in MS. Its increase in patients with decreased extracranial arterial flow might be a compensatory phenomenon (ie the lower the neck flow, the higher the retinal vascular density). Angiogenic VEGF-A induction may explain TAF increase. We confirm that Homocystein levels are related to retinal atrophy, probably due to its negative effect on endothelial functions and vascularisation. These results, taken together, corroborate the use of OCT in understanding endothelial vascular pathology in MS.

Disclosure
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S Cocozza reports personal fees from Sanofi Genzyme.
M Mocca has received salary from Federico II University of Naples, grant from the ECTRIMS-MAGNISIS fellowship program, honoraria and travel support form Almirall, Coloplast, Genzyme, and Merck-Serono.
D Paoloicelli has received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Almirall, Sanofi-Aventis, TEVA, Novartis and Genzyme.
G Lus has received personal compensation for activities with Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis Pharmaceuticals, Teva neuroscience as a consultant and speaker; has received research support from Biogen Idec, Merck Serono, and Novartis.
E has received personal compensation for activities with Biogen Idec, Roche, Merck Serono, Novartis as a consultant; has received support for travelling from Biogen Idec, Merck Serono, Novartis, Teva, Roche, Genzyme.
G Cennamo, E Tedeschi, C Criscuolo, A Carotenuto, F Sparnell, A Cianflone, G Palma, N Frattaruolo, N Velotti have nothing to disclose.

PS99
Examining cross-sectional relationships of optical coherence tomography, cervical cord MRI and disability in secondary progressive MS

Aim: To assess the cross-sectional relationships of OCT, SC-MRI and clinical measures of disability in a large cohort of patients with secondary progressive MS (SPMS).

Methods: MS-SMART (NCT01910259) is an ongoing UK multicentre, multi-arm, double-blind, placebo-controlled phase IIb randomised controlled trial that has enrolled 445 SPMS patients aged 18-65, with EDSS 4.0-6.5. An embedded single-centre study was pre-planned to assess OCT and SC-MRI. For this sub-study, we excluded patients with ocular disease, high refractive errors (>±6.0 dpt), history of bilateral optic neuritis (ON), or possible subclinical ON (i.e. interocular OCT differences >20%). For patients with no previous ON, we averaged the OCT measures from both eyes; with a history of unilateral ON, we only included the fellow eye with no history of ON. We collected Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test (SDMT), MS Functional Composite (MSFC), mean upper cervical cord area (MUCCA), and 3 OCT measures (peripapillary retinal nerve fibre layer [pRNFL], ganglion cell layer [GCL] volume, total macular volume [TMV])). We calculated Kendall’s tau correlation coefficients between the clinical variables, MUCCA, and OCT. Subsequently, we divided the cohort in quartiles and performed multiple linear regression analyses, with adjustment for gender, age, and disease duration.

Results: OCT data were available for 112 participants, MUCCA for 146, and both OCT and MUCCA were available for 95. EDSS was moderately correlated with MUCCA (N=146, t: -0.307, p<0.001), but not with the three OCT measures. SDMT was weakly correlated with MUCCA (N=145, t: 0.202, p=0.015), pRNFL (N=111, t: 0.262, p<0.001), GCL (N=112, t: 0.259, p<0.001), and very weakly with TMV (N=112, t: 0.138 p=0.034). MSFC was moderately correlated with MUCCA (N=146, t: 0.328, p=0.001), but not with the three OCT measures. There was no significant correlation between MUCCA and any OCT measure. Regression analyses confirmed these findings.

Conclusions: This cross-sectional analysis may suggest that MUCCA and OCT measure complementary dimensions of...
neurodegeneration in SPMS. Ongoing longitudinal analysis will clarify these findings.

Disclosure


F.B. serves on the editorial boards of Brain, European Radiology, Journal of Neurology, Neurosurgery & Psychiatry, Neurology, Multiple Sclerosis, and Neuroradiology, and serves as consultant for Bayer Shering Pharma, Sanofi-Aventis, Biogen-Idec, TEVA Pharmaceuticals, Genzyme, Merck-Serono, Novartis, Roche, Synthion, Jansen Research, and Lundbeck.

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J.C. has support from the National Institute of Health Research (NIHR) University College London Hospital Biomedical Research Centres funding scheme and University College London (UCL). In the last 3 years, he has attended advisory boards for Roche, Merck and Apitope. He is local principal investigator for trials in multiple sclerosis funded by Novartis, Biogen, and Receptos.

D.H.M. has received honoraria through payments to UCL Institute of Neurology, for Advisory Committee and/or Consultancy advice in multiple sclerosis studies from Novartis and Mitsubishi Pharma Europe and compensation through payments to UCL Institute of Neurology for performing central MRI analysis of a multiple sclerosis trial from Novartis.

G.G. is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen-Idec, the fingolimod and sipimomin trials for Novartis, the laqmimod trials for Teva, and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck-Serono, Genzyme-Sanofi, and in relation to DSBM activities for Synthion BV, as well as honoraria for speaking at the Physicians’ summit and several medical education meetings. He is also the co-chief editor of Multiple Sclerosis and Related Disorders (Elsevier).

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P600
Retinal changes in aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders: a longitudinal study

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Background: Neuromyelitis Optica Spectrum Disorders (NMOSD) are frequently associated with retinal damage caused by optic neuritis (ON). NMOSD are characterized by antibodies against aquaporin-4 (AQP4-Ab) in the majority of cases. Most patients with NMOSD show a relapsing-remitting disease course and very rarely develop progressive disease. We recently reported microstructural retinal changes as detected by optical coherence tomography (OCT) in AQP4-Ab seropositive patients in eyes without previous ON.

Objective: To longitudinally investigate retinal changes in patients with AQP4-Ab seropositive NMOSD independent of ON attacks.

Methods: Longitudinal observational study of 28 AQP4-Ab seropositive NMOSD patients (51 eyes, age 47.7 ± 14.9 years, 23 female / five male patients, time from first attack 6.2 ± 5.5 years) and matched healthy controls (HC). Median follow-up time from first OCT assessment was 2.2 years (range: 1.0 - 3.5 years; 2 - 4 OCT assessments per patient). 22 eyes of 17 patients had an ON before baseline, with last ON at least 5 months before inclusion. Ganglion cell and inner plexiform layer (GCIP) and inner nuclear layer (INL) volumes were calculated within a 3 mm diameter cylinder around the fovea from a macular volume scan. Foveal thickness (FT) was measured in a 1 mm diameter cylinder around the fovea. Peripapillary retinal nerve fibre layer (pRNFL) was measured using a 3.4 mm diameter ring scan around the optic nerve head.

Results: During follow-up six eyes of five patients developed ON and were excluded from analysis.

The remaining 45 patient eyes showed a thinning of GCIP (ΔGCIP = -0.02 ± 0.03 mm3, p = 0.012) and pRNFL (ΔpRNFL = -1.5 ± 4.0 µm, p=0.018). This effect remained significant when excluding unaffected eyes from those five patients who suffered from ON during follow-up (GCIP p = 0.015, pRNFL p = 0.031). Eyes with previous ON showed lower absolute GCIP and pRNFL loss over time than eyes without previous ON. FT reduction was not significant (p = 0.217) and INL remained unchanged (p = 0.553).

Conclusion: AQP4-Ab positive NMOSD patients experience retinal neuro-axonal loss in absence of clinically overt. The functional relevance as well as the underlying cause of this finding need to be further investigated. Potential causes include prolonged neuro-axonal damage after ON, retinal affection during non-ON attacks, and a progressive primary retinopathy due to Müller cell damage.

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P601
Spectrum of stiff person syndrome expands with presence of retinal pathology
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Objective: To assess structural and functional changes in the afferent visual system of patients with Stiff-Person Syndrome (SPS).

Background: SPS is a rare neuroimmunological disorder characterized by progressive rigidity and painful muscle spasms. The majority of patients exhibit autoantibodies directed against glutamic acid decarboxylase (GAD). SPS can be misdiagnosed as multiple sclerosis due to overlapping symptoms and demographics which delays appropriate diagnosis. SPS patients often have visual complaints which are often under-recognized and therefore have not been fully characterized in SPS.

Methods: Forty SPS patients and matched healthy controls underwent Cirrus HD-OCT, and a subset of 30 patients and matched controls underwent 100%, 2.5% and 1.25%-contrast letter-acuity testing. An automatic macular segmentation method was used to compute the combined thickness of the ganglion cell+inner plexiform layer (GCIP). Mixed effects linear regression models were used to investigate whether retinal layer thicknesses and visual function differed between SPS and controls.

Results: The SPS cohort was slightly older than controls, although not significantly (mean difference = 3 years; p = 0.17), and had a mean modified Rankin scale of 2.0 (SD = 0.66). Adjusting for age and a history of diabetes, the mean retinal thickness values were significantly lower in the SPS cohort (mean difference = 5.1 µm; p = 0.004), which appears to be driven by a thinned GCIP layer thickness (mean difference = 1.9 µm; p = 0.012). SPS patients exhibited lower visual acuity on 100%, 2.5% and 1.25% contrast letter-acuity charts (mean difference = 4.3 letters, 5.8 letters and 5.0 letters; p = 0.002, p = 0.009 and p = 0.031, respectively). Moreover, SPS patients without a history of diabetes exhibited significantly thinner GCIP layer thicknesses (p = 0.05), and significantly worse visual acuity on high contrast, 2.5% contrast and 1.25% contrast charts (mean differences = 6.2, 6.4 and 5.4 letters; p = 0.001, p = 0.003, p = 0.026, respectively) compared to controls.

Conclusions: SPS patients have mild visual dysfunction compared to healthy controls, as well as thinned GCIP layers. These findings suggest that SPS may cause retinal neuronal pathology, possibly resulting from an autoimmune retinopathy. Therefore SPS may share a common pathway(s) for retinal degeneration with MS. Clinicians should be aware of the expanding spectrum of SPS to help prevent misdiagnosis as more common conditions like MS.

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P602
Retinal ganglion cell layer thickness predicts disease activity in clinically isolated syndrome
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Background: Clinically isolated syndrome (CIS) describes a first clinical attack suggestive of multiple sclerosis (MS), however does not always lead to further MS-related disease activity and...
Objective: To investigate the value of retinal optical coherence tomography (OCT) to predict disease activity in CIS.

Methods: In this prospective, longitudinal cohort study, we recruited 92 patients with CIS between 2010 and 2015 from two centres in Germany and followed them over 722 days (median, IQR: 587-903 days). Patients (age 18-60 years) were included within 12 months after a first clinical event and underwent neurological examination, cerebral MRI and retinal OCT. Outcomes were failing the No Evidence of Disease Activity (NEDA-3) criteria and MS diagnosis according to the 2010 McDonald criteria by MRI (MRI-MS) or a second clinical attack (clinically definite MS, CDMS). OCT analysis included ganglion cell and inner plexiform layer thickness (GCIP), peripapillary retinal nerve fibre layer thickness (pRNFL), and inner nuclear layer thickness (INL) from eyes without history of optic neuritis.

Results: Kaplan-Meier statistics showed a significant probability difference in failing NEDA-3 criteria for predictors GCIP (p=0.001) and pRNFL (p=0.017), but not for INL (p=0.893). Patients with GCIP at baseline in the lowest tertile (< 69.3 µm) were almost four times more likely to fail NEDA-3 criteria than patients in the highest tertile (> 74.3 µm, hazard ratio 3.87, CI: 1.85-8.11, p< 0.001). A multi-state survival analysis showed that a follow-up diagnosis of MS was more likely for patients with low GCIP as well: The lowest GCIP tertile showed higher risk compared to the highest tertile for MRI-MS diagnosis (hazard ratio 3.29, CI: 1.36-7.95, p< 0.008) and a trend for increased risk for CDMS diagnosis (hazard ratio 4.66, CI 0.97-22.49, p=0.055). Low pRNFL, albeit to a lesser extent, indicated risk of not meeting NEDA-3 and of later MS diagnosis. INL was not predictive for NEDA-3 violation or MS diagnosis.

Conclusion: Retinal GCIP and to a lesser extent pRNFL are valuable parameters for predicting future disease activity and diagnosis of MS in patients with a CIS.

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P603

Optical coherence tomography as a marker of disease severity and disability in pediatric multiple sclerosis

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Background: Optical Coherence Tomography (OCT) is a non-invasive modality used to quantify the thickness of the retinal nerve fiber layer (RNFL). Studies have shown that both adult and pediatric patients with Multiple Sclerosis (MS) have decreased RNFL thickness compared to healthy controls. In adult MS patients, RNFL thickness correlates with disability and disease severity measures.

Objective: To determine whether OCT values correlate with markers of disability and disease severity in pediatric MS patients.

Methods: Data was collected via retrospective chart review of 120 patients with MS at Texas Children’s Hospital. Inclusion criteria consisted of MRI, OCT and MS clinic visit performed within 12 months of each other. 32 patients met these criteria, 9 with a history of optic neuritis (ON). Correlation of average RNFL,
temporal Disability Status Scale (EDSS), Visual Functional System Score (VFSS), and annualized relapse rate (ARR) was measured. Patients were divided based on the presence or absence of new T2 lesions on MRI brain and spine and OCT data was compared between the two groups. In the 17 patients with 2 sets of OCT data, correlation between change in OCT values and measures of disease severity was obtained.

**Results:** Patients with history of ON had statistically significant lower average RNFL thickness (p: 0.03) compared to those without history of ON. Thickness of the RNFL was negatively correlated with VFSS ($r^2$: -0.39, p: 0.04). No significant correlation was found between OCT values and EDSS, ARR, or the presence of new T2 lesions. In patients with 2 OCTs, degree of change in the OCT values did not correlate with the above measures.

**Conclusions:** As in previous studies, our data shows that pediatric MS patients with a history of ON have RNFL thinning. Our data importantly shows that decreased RNFL is correlated with higher VFSS, indicating more severe visual disability. However in our cohort of patients, OCT data was not predictive of disease severity or disability as measured by EDSS, ARR, or new T2 lesions. Furthermore, change in OCT values over time did not correlate with these measures. Therefore, though adult literature suggests using OCT data as a surrogate for disease severity and overall disability, our data thus far does not support a similar use of OCT data in the pediatric MS population. Our data does however support the use of RNFL thickness as a surrogate for visual disability.

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**P604**

**An investigation into the relationship between Optical Coherence Tomography (OCT) and cognitive fatigue in people with multiple sclerosis**

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**Objective:** To explore the potential relationship between objective OCT outcomes and fatigue and depression in people with Multiple Sclerosis (PwMS).

**Background:** Multiple Sclerosis is characterized by relapses and progression and disease burden is quantified by EDSS/MRI. Fatigue and depression frequently reported in PwMS can be severe/disabling but is not addressed by either measure. Patient reported outcomes (PRO) are utilized to evaluate/track such PwMS symptoms. Objective analysis of disease impact by MRI lesion burden/changes has improved treatment decisions but does not track with PwMS PRO and EDSS. OCT provides additional objective information about disease in PwMS. A relationship between OCT and PRO in PwMS might provide additional proxy measurements to better understand/predict disease impact.

**Methods:** Retrospective review of PwMS who prospectively completed both OCT testing and PRO Modified Fatigue Impact Scale (MFIS) and Beck’s Depression Index (BDI). Linear regression modeling was used to analyze significant relationships between BDI, Rasch-corrected global (MFIS-G), physical (MFIS-P) and cognitive (MFIS-C) fatigue scores, and OCT outcomes [retinal nerve fiber layer-global (RNFL-G) and nasal/tem- poral ratio (RNFL-N/T), Perimacular Bundle (PMB) and Macular Volume (MV)] for each eye and inter-ocular asymmetry. Significance was set at p< 0.01.

**Results:** PwMS N=103, 76.9% female, average age = 50.4±10.3. PRO MFIS-C in PwMS significantly correlated (p< 0.01) with: RNFL-G OD (p=0.004, r=0.28), and PMB OS (p=0.005, r=0.28). MFIS-G, and MFIS-P, and Depression scores were not significantly associated with any OCT outcome measurement (although depression correlations approached significance with RNFL-G OD and PMB OS).

**Conclusions:** OCT findings related to the degree of axonal damage identified significantly correlated with PRO cognitive fatigue in PwMS. No OCT outcomes were found to be correlated with either MFIS-G, MFIS-P, or BDI. “Fatigue” as a construct should not be exclusively measured as a global outcome, as fatigue subtypes can manifest independently and likely impact PwMS Quality of Life differently.

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**P605**

**Cognitive impairment as prognostic factor in pediatric and juvenile multiple sclerosis**

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**Background:** Cognitive impairment (CI) is frequent in pediatric and juvenile multiple sclerosis (MS) onset patients. In adult onset MS, it predicts a worse clinical outcome. We aimed at evaluating the role of CI as predictor of disease severity in early-onset MS.
Methods: This is a 5-year longitudinal retrospective study including pediatric (< 18 years) and juvenile (< 25 years) onset RR-MS. Socio-demographic and clinical data (age, sex and education level, age at onset, disease duration, expanded disability status scale [EDSS], disease modifying therapy, DMT) were collected at baseline. Patients were assessed through the Brief Repeatable Battery (BRR) and the presence of CI has been defined when patients failed in 1 or more tests. Clinical outcomes were the occurrence of a relapse, a therapeutic switch, the achievement of EDSS 4.0, the sustained increase in the EDSS of at least 1 point and the conversion to SP over 5 years of follow-up. The time to the occurrence of each of these clinical outcomes was collected. Binary logistic models and Cox models were run to explore the presumptive role of CI as predictor for each of the clinical outcomes.

Results: We included 51 subjects (26 females), 33 paediatric and 18 juvenile onset RRMS, with a mean age at baseline of 19.8 ± 3.8 years, and a mean age at onset of 17.2 ± 3.9 years. Median baseline EDSS was 2.5 (1 - 6) with a median disease duration of 2 (0 - 12) years. At NPS evaluation 32/51 (62.75%) patients were CI. After 5 years, 11.8% experienced an increase of 1 point in the EDSS and 12.5% patients reached EDSS 4. Twenty-seven patients experienced at least one relapse over the follow-up period after 32.2 ± 22.5 months. The clinical outcomes were not related to the presence of CI at baseline nor to any single NPS score.

Discussion: In the short-medium term the presence of CI does not predict clinical outcomes in early-onset MS patients. These results seem to confirm the previous findings for adult MS patients, in which CI began to influence clinical outcome only after 5 years from baseline evaluation. However, we can not exclude that juvenile MS patients could experience a more marked inflammatory process than neuro-degeneration, which is strictly related to cognitive functions. Cognitive follow up and extension of observation time is on-going.

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Neurophysiology

P606 Neurophysiological measures of fatigue in multiple sclerosis
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Objectives: Fatigue is a common symptom in patients with multiple sclerosis (MS). Despite its invalidating nature, its physiopathology remains ill-defined and seems to be multifactorial [1]. Transcranial magnetic stimulation (TMS) is an emerging technique that allows, through double pulse paradigm, the exploration of cortical inhibitory and excitatory mechanisms. The alteration of the latter could underlie various neuropsychiatric disorders. In the context of MS fatigue, few studies have addressed these measures and their results remain controversial.

Methods: 38 MS patients were recruited and divided into two groups: non-fatigued (n = 17) and fatigue (n = 21) according to the Modified Fatigue Impact Scale (MFIS) score. The neurophysiological evaluation consisted in testing the following parameters: resting motor threshold, amplitude of motor evoked potentials, short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), cortical silent period and interhemispheric inhibition [2].

Results: SICI was significantly higher in fatigue compared to non-fatigued patients, especially for the 2 ms inter-stimulus interval (35.0 ± 40.8 vs. 63.9 ± 20.9, p = 0.04). SICI at 2 ms was significantly correlated with MFIS scores (total score: r = 0.4, p < 0.01, cognitive subscale score: r = 0.4, p < 0.01, psychosocial subscale score: r = 0.3, p = 0.04).

Conclusion: Fatigued MS patients had increased intracortical inhibition compared to non-fatigued patients. This could reflect an alteration of the GABAergic/glutamatergic balance at the detriment of the facilitatory mechanisms [3]. In other words, there is an apparent link between the integrity of the facilitatory mechanisms and the ability to cope with functional decline and subsequent generation of fatigue in these patients.

References


Keywords: Multiple sclerosis, cortical excitability, intracortical inhibition, transcranial magnetic stimulation, TMS.
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P607
The triple stimulation technique: a potential surrogate marker for motor axonal loss in multiple sclerosis
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The triple stimulation technique (TST) enables a functional quantification of the central motor conduction failure through the resynchronization of the motor neurones discharges along the corticospinal pathway. Unlike classical motor evoked potentials (MEP), TST is rarely used in the clinical setting of multiple sclerosis (MS), despite a likely strong link with the central axonal loss.

Central motor conduction of 28 consecutive MS patients (median EDSS 4) was prospectively and transversely assessed, on classical motor evoked potentials (four limbs) and TST (upper limbs). In the same time, disability (Expanded Disability Status Scale), grasping strength (JAMAR dynamometer) and motor components of the multiple sclerosis functional composite (MSFCm) clinical scale, consisting of the hand dexterity (9-hole peg test) and the walking speed (Timed 25 foot walk), were evaluated. The Spearman correlation (rS) was used to evaluate the relationship between MEP, TST and clinical findings.

Central motor conduction time and amplitude of MEP (upper and lower limbs) significantly correlated with MSFCm (0.43 ≤ rS ≤ 0.61) and EDSS (0.57 ≤ rS ≤ 0.64). Correlations between TST and MSFCm (0.59 ≤ rS ≤ 0.69), TST and grasping strength (rS = 0.51) or TST and EDSS (rS = 0.75) were even higher.

The good correlations observed with the EDSS and clinimetry underline the value of classical MEP parameters as a quantitative tool for the functional assessment. The TST, focused on the upper limbs, appears to reflect a global disability since it is correlated not only to the hand dexterity and grasping strength but also to the walking capacity. The TST allows a quantification of the central motor conduction failure, which could be a key surrogate marker in MS, but need further validation through a confrontation with quantitative metrics provided by magnetic resonance imagery.

Keywords: Triple stimulation technique, Motor evoked potentials, Multiple sclerosis, Axonopathy, Disability, Multiple sclerosis functional composite

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P608
Fatigue in multiple sclerosis: Is it related to cytokines and hypothalamic-pituitary-adrenal axis?
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Background: Fatigue is a common symptom of Multiple Sclerosis (MS) that diminishes the quality of life of patients, but its exact mechanism remains poorly understood. There is not a generally adopted scale to determine MS fatigue. Studies that investigated physiopathology of fatigue symptom have shown dysregulation of hypothalamic-pituitary-adrenal (HPA) axis. In the current study, we aimed to compare the results obtained with two separate scales, namely the Fatigue Severity Scale (FSS) and the Neurological Fatigue Index-Multiple Sclerosis (NFI-MS), and assess the relationship between fatigue and serum IL-1β, TNF-α, IL-35, IL-2, IL-10, ACTH, cortisol, α-MSH, β-MSH, γ-MSH and CLIP (Corticotropin-like intermediate lobe peptide) in MS patients categorized as fatigued and non-fatigued on the basis of FSS scores.

Methods: For the study, a total of 54 (29 females, 25 males) patients diagnosed with RRMS including 26 with fatigue symptom (48.1%), and 26 healthy controls (13 females, 13 males) were enrolled. A FSS score ≥36 was considered as cut-off score to separate fatigued patients from non-fatigued patients.

Results: A significant positive correlation was determined between FSS score and NFI-MS scale, NFI-MS 1, NFI-MS 2, NFI-MS 3 and NFI-MS 4 scores. IL-1β, IL-10 and TNF-α levels did not differ between patient and control groups. IL-35 and IL-2 levels were significantly higher among MS patients (p< 0.01). However, no difference was observed between fatigued and non-fatigued patients in the cytokines and HPA parameters studied. ACTH, cortisol and α-MSH were significantly higher in MS group (p=0.02, p< 0.01 and p< 0.01, respectively). CLIP level was significantly low in MS patient group (p< 0.01).

Conclusion: NFI-MS scale is equally sensitive as FSS scale for assessment of MS fatigue; thus, it may also be widely used to evaluate that symptom. Generally HPA axis is hyperactive in MS patients, but it is not correlated with fatigue in our study. For the first time, levels of CLIP (a type of melancortin) are studied, and determined to be lower among MS patients. Elevated levels of IL-35 and IL-2 suggest that these cytokines may have a prominent role in MS pathophysiology.

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P609
Cognitive impairment in multiple sclerosis is associated with slowing of resting state oscillatory activity on magnetoencephalography
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Background: Fatigue is a common symptom of Multiple Sclerosis (MS) that diminishes the quality of life of patients, but its exact mechanism remains poorly understood. There is not a generally adopted scale to determine MS fatigue. Studies that investigated physiopathology of fatigue symptom have shown dysregulation of hypothalamic-pituitary-adrenal (HPA) axis. In the current study, we aimed to compare the results obtained with two separate scales, namely the Fatigue Severity Scale (FSS) and the Neurological Fatigue Index-Multiple Sclerosis (NFI-MS), and assess the relationship between fatigue and serum IL-1β, TNF-α, IL-35, IL-2, IL-10, ACTH, cortisol, α-MSH, β-MSH, γ-MSH and CLIP (Corticotropin-like intermediate lobe peptide) in MS patients categorized as fatigued and non-fatigued on the basis of FSS scores.

Methods: For the study, a total of 54 (29 females, 25 males) patients diagnosed with RRMS including 26 with fatigue symptom (48.1%), and 26 healthy controls (13 females, 13 males) were enrolled. A FSS score ≥36 was considered as cut-off score to separate fatigued patients from non-fatigued patients.

Results: A significant positive correlation was determined between FSS score and NFI-MS scale, NFI-MS 1, NFI-MS 2, NFI-MS 3 and NFI-MS 4 scores. IL-1β, IL-10 and TNF-α levels did not differ between patient and control groups. IL-35 and IL-2 levels were significantly higher among MS patients (p< 0.01). However, no difference was observed between fatigued and non-fatigued patients in the cytokines and HPA parameters studied. ACTH, cortisol and α-MSH were significantly higher in MS group (p=0.02, p< 0.01 and p< 0.01, respectively). CLIP level was significantly low in MS patient group (p< 0.01).

Conclusion: NFI-MS scale is equally sensitive as FSS scale for assessment of MS fatigue; thus, it may also be widely used to evaluate that symptom. Generally HPA axis is hyperactive in MS patients, but it is not correlated with fatigue in our study. For the first time, levels of CLIP (a type of melancortin) are studied, and determined to be lower among MS patients. Elevated levels of IL-35 and IL-2 suggest that these cytokines may have a prominent role in MS pathophysiology.

Disclosure
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Background: Neurophysiological measures of brain function, such as magnetoencephalography (MEG), are widely used in clinical neurology and have strong relations with cognitive impairment and dementia, but are presently still underdeveloped in multiple sclerosis (MS). This study aims to assess the value of clinically applicable quantitative MEG measures of neuronal activity in evaluating and predicting cognitive impairment in MS.

Methods: Eyes-closed resting-state MEG measurements of 83 patients with long-standing, clinically definite MS and 34 healthy controls (HC) were analyzed and related to neuropsychological evaluations, based on an expanded brief repeatable battery of neuropsychological tests (BRB-N). “Cognitive impairment” (CI) was defined as Z-scores (using HC as reference) of ≤-2 on two or more domains; Z-scores > -1.5 on all domains as “cognitively preserved” (CP) and all scores in between as “mildly cognitively impaired” (MCI). Time series were estimated using a beamforming approach, for 78 cortical regions of interest (ROIs) based on an automated anatomical labeling atlas (AAL). For each subject five artifact-free epochs (~13 seconds, sample frequency 1250Hz) were selected; peak frequencies and relative power were calculated for each of six frequency bands and each ROI. Subsequently, global relative power and peak frequency were averaged over all 78 ROIs. Associations with cognitive impairment were performed using linear modelling correcting for age, gender and educational level where appropriate.

Results: Of all 83 patients, 37 were labeled as CP, 18 as MCI, and 28 as CI. The CI-MS group had a significantly lower peak frequency (β-0.266; P=0.049) than HCs, indicating higher relative alpha1-power and overall slowing of neuronal activity. Increased global relative alpha1-power was associated with impaired overall cognitive performance (β-0.304; P=0.005) but specifically with attention (β-0.408; P<0.001), working memory (β-0.388; P<0.001 and verbal memory (β-0.257; P=0.020). Increased global relative theta-power was associated with worse performance on verbal memory tasks (β-0.333; P=0.003).

Conclusion: These findings indicate a clinically relevant global slowing of neuronal activity in MS patients, affecting cognition, and hold promise for the application of resting-state MEG in a clinical setting as a biomarker for cognitive disturbances. Future studies are warranted to assess the prognostic value of these neurophysiological changes in MS.

Disclosure

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P610 Chronic 4-aminopyridine treatment enhances intracortical glutamatergic transmission in progressive multiple sclerosis

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Background: 4-aminopyridine (4AP) is widely used in people with multiple sclerosis (MS) to improve walking performance and fatigue. Despite its action on K+ channels of demyelinated axons, some of its effects might be dependent on synaptic transmission modulation.

Objectives: To investigate the chronic effects of 4AP on motor cortex excitability in people with progressive MS (PwPMS) using transcranial magnetic stimulation (TMS).

Methods: We enrolled 31 consecutive PwPMS (16 females, age 48.52 ± 8.18, EDSS 5.85 ± 0.58, range 4-6.5) participating in a randomized trial on repetitive TMS coupled with neurorehabilitation, and 11 healthy controls-HC (6 females, mean age 52.31 ± 4.34). Eleven PwPMS were under chronic 4-AP treatment for fatigue. Motor evoked potentials (MEPs) to the right first dorsal intersosseus were tested to measure resting motor threshold (RMT), input-output (IO) curve slopes, short interval intracortical inhibition (SICI) (double-pulse interstimulus interval - ISI 1 and 3ms) and facilitation (ICF, ISI 10 and 15 ms).

Results: A significant difference in IO-curve slopes was found comparing the 3 groups (Kruskall-Wallis; p=0,036), with increasingly higher values respectively in untreated PMS, HC and treated PMS (Jonckheere-Terpstra; p=0.09). However, MEP amplitude at 120% of RMT was significantly higher in HC compared to both treated and untreated PwPMS (p=0.047; p=0.02). MEP at maximum stimulator output, instead, were significantly higher in HC compared with untreated PwPMS (p=0.01), but no significant difference was found with treated PwPMS. Decreasingly lower ICF values for both ISI tested were found respectively in untreated PMS, HC and treated PMS (Jonckheere-Terpstra; ISI 10 p=0.015; ISI 15 p=0.022).

Conclusions: Our findings suggest that 4AP treatment modulates motor cortex excitability in PMS, enhancing glutamatergic tone and may facilitate corticospinal recruitment, leading to a ceiling effect on motor cortex excitability. Enhanced corticospinal transmission might reflect a better exploitation of motor cortex functional reserve in PwPMS treated with 4AP and might explain the effects on walking performances.

Disclosure


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Neuropsychology

P611
Are we underestimating the severity of cognitive dysfunction in MS?

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Background: Our primary source of knowledge of cognitive dysfunction in MS is derived from research studies that require voluntary consent (VC), a requirement that may result in selected samples not fully representative of MS clinic populations. For the past 1.5 years, patients at the Cleveland Clinic Mellen Center for MS Treatment and Research completed the MS Performance Test (MSPT), a self-administered iPad®-based neurological performance assessment tool, as part of their routine clinical care. The sole MSPT cognitive measure is the Processing Speed Test (PST), a measure of information processing speed. We recently published (Rao et al., 2017) a validation study of the PST based on VC.

Goals: To determine if processing speed test performance derived from a validation study based on voluntary consent (VC group) differs from a registry of MS patients who were administered the PST as part of their routine clinical care (REG group).

Methods: The VC and REG groups consisted of 164 and 1,031 MS patients, respectively. The groups were comparable in education, sex, and race; the REG group was older than the VC group by 3.6 years (p=0.0001). PST raw scores were converted to z-scores using regression-based norms derived from a sample of healthy subjects, thus minimizing potential group differences based on demographic variables (age, education, sex). Significant VC vs. REG group differences were observed for relaxing-remitting and secondary progressive MS patients; no group difference was observed for primary progressive MS patients, probably due to small sample sizes. Significant VC vs. REG group differences were observed only for patients >10 years post-diagnosis.

Conclusions: The PST was completed on consecutively treated MS patients, thus providing an accurate representation of a large MS center population. The results indicate that cognitive impairment was more severe in the MS clinic population than estimated from the comparison VC sample. These results raise the possibility that literature reports of cognitive impairment in MS patients have underestimated its prevalence in real world settings. The data strongly support the need to routinely assess cognitive function in clinical practice to tailor and monitor treatment and to properly counsel patients.

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M. Weber, L. Mourny, G. Losinski, C. Reece have nothing to disclose.

P612
Gray matter atrophy and microstructural white matter abnormalities underlying cognitive impairment in benign MS

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Background: The definition of benign multiple sclerosis (BMS) is based on the long disease duration and low level of disability of subjects, without taking into consideration other features, such as cognitive deficits.

Objectives: To investigate whether cognitive impairment in BMS patients is associated with specific patterns of regional gray matter (GM) atrophy and white matter (WM) microstructural abnormalities and whether these measures could be useful to identify those MS patients with a really favorable course.

Methods: Using a 3.0 Tesla scanner, high-resolution 3D T1-weighted, diffusion tensor (DT) and dual-echo images were acquired from 38 BMS patients (Expanded Disability Status Scale score ≤ 3.0 and disease duration > 15 years) and 50 matched healthy subjects (HC). All patients underwent neuropsychological assessment through the Rao Brief Repeatable battery. Regional GM atrophy was estimated using a voxel-based morphometry analysis, while WM microstructural abnormalities were investigated with tract based spatial statistical analysis.

Results: Sixteen (42%) BMS were classified as cognitively impaired (CI). Compared to HC, cognitive preserved (CP) BMS patients had significant GM atrophy of thalami, left precuneus and left middle cingulum. Additional areas of significant GM atrophy in CI patients were found in the anterior and posterior cingulate gyrus, left caudate nucleus, and right precentral gyrus. Compared to HC, CP and CI BMS patients had decreased fractional anisotropy (FA) of supratentorial and infratentorial WM tracts and increased mean (MD), axial (AD) and radial (RD) diffusivity of...
the main supratentorial WM tracts. CI patients had additional increased MD and RD of several infratentorial regions located in the cerebellum and brainstem. No areas were significantly more damaged in CP vs CI BMS patients.

**Conclusions:** Distinct regional patterns of GM atrophy and WM microstructural abnormalities, functionally relevant for cognitive processing, are associated with CI in MS patients with a benign course. These findings support the need for a new clinical definition of BMS, including cognitive features.

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**P613**

**Cognitive impairment in multiple sclerosis: the contribution of cognitive reserve and regional gray matter volumes**

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**Background:** Cognitive impairment (CI) is a common and disabling symptom in multiple sclerosis (MS) and has been related to lower patients’ quality of life, in particular to lower vocational status. Cognitive performance have shown moderate-to-strong correlations with a series of global and regional brain magnetic resonance imaging (MRI) markers of tissue damage. Previous studies in MS have hypothesized a protective role of (CR) on CI in MS. The working hypothesis of the present study is that CR and regional volumes of cognitively relevant gray matter (GM) structures are able to predict cognitive status of MS patients.

**Objective:** To determine the possible effect of cognitively relevant GM regions (cortical gray matter, thalamus, cerebellum), T2 lesion volume (T2-LV) and CR on cognitive functions in MS patients.

**Methods:** Ninety-five Relapsing-Remitting MS (RRMS) patients were included in the study. Cognition was assessed by the Brief Repeatable Battery of Neuropsychological Tests (BRB) and Stroop Test (ST). CR was assessed by vocabulary-based estimate of lifetime intellectual enrichment (VOC). All patients underwent a 3T MRI to assess T2-LV and GM regional measures, including cortical GM, thalamic and cerebellar volumes. To assess the role of GM measures, T2-LV and CR on CI, we performed a separate hierarchical linear regressions in which z-scores of each cognitive test of BRB and of ST was entered as the dependent variable, whereas the independent variable were entered as follows: T2-LV, cortical GM, thalamic GM and cerebellar volumes in block 1; residual scores for VOC in block 2.

**Results:** CR was an independent predictor of performance on tests assessing all cognitive functions examined. Cortical GM volume and CR were predictors of performance on tests assessing verbal and visual memory, attention and information processing speed; thalamic volume and CR were independent predictors of performance on verbal and visual memory and inhibitory control.

**Conclusions:** CR seems able to independently predict cognitive performance in RRMS patients. Cortical GM and thalamic atrophy, together with CR, contributes to explain deficits in specific cognitive functions in MS patients.

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**P614**

**Neuroticism is linked to smaller hippocampal volume and worse memory in early multiple sclerosis**

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**Background:** Memory impairment affects about 50% of multiple sclerosis (MS) patients, and identifying risk and protective factors is an important step toward developing targeted treatments. Neuroticism (tendency toward psychological distress) is related to worse memory in MS (Leavitt et al, 2017), but the neural basis of this relationship has not been described. Informed by preclinical work on stress and hippocampal dysfunction, we

- investigated links among neuroticism, hippocampal volume, and memory; and
- tested a mediation model to determine whether reduced hippocampal volume explains the relationship of neuroticism to worse memory.

**Methods:** 100 MS patients (83 RRMS, 17 CIS) within 5 years of diagnosis received 3D T1 MRIs in a 3.0T scanner and completed...
the NEO Five-Factor Inventory (a 60-item scale yielding scores for neuroticism, extraversion, openness, agreeableness, conscientiousness) and a memory test (CANTAB Paired Associates Learning test). Hippocampal volumes were measured with FreeSurfer. Partial correlations (controlling for age, sex, education, IQ, and intracranial volume) evaluated relationships of 1) neuroticism to hippocampal volume, 2) neuroticism to memory, 3) hippocampal volume to memory.

Mediation analysis tested hippocampal volume as a mediator of the relationship of neuroticism to memory. 

Results: The only personality factor related to hippocampal volume was neuroticism (r = -0.213, p = 0.034); the relationship was specific to hippocampus, (i.e., no relationship to any other subcortical gray matter structures, cortical gray matter, or cerebral white matter). Higher neuroticism was associated with worse memory (r = -0.288, p = 0.004). Smaller hippocampal volume was associated with worse memory (r = -0.251, p = 0.014). The mediation model (Sobel test) revealed a trend whereby hippocampal volume partially mediated the relationship of neuroticism to worse memory (full model, p = 0.084).

Conclusions: We show for the first time that neuroticism is linked to smaller hippocampal volume in MS, which may help to explain the relationship of neuroticism to memory impairment in MS. This is consistent with preclinical research on stress, memory, and the hippocampus, and supports neuroticism as a potentially important treatment target for memory impairment in MS.

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P615    Dissociable neural correlates of speed and memory in early multiple sclerosis: a latent variable approach

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Background: Slowed processing speed and memory decline are widely studied MS cognitive deficits; however, measurements of speed and memory are limited by (a) poorer reliability of single tasks relative to composite measures, and (b) unwanted influence of ancillary processes during idiosyncratic tasks (e.g., visual scanning on the Symbol Digit Modalities Test, SDMT). We used principal components analysis (PCA) with eight measures of processing speed or memory to derive purer measures of each construct. We then investigated neuroanatomical correlates of these purer measures of speed and memory, which should yield more precise neural correlates.

Methods: Persons with early RRMS (87) or CIS (18) completed four speed [SDMT, Stroop, Pattern Comparison (PC), Decision Speed (DS)] and four memory [Selective Reminding Test (SRT), Brief Visuospatial Memory Test, Revised (BVMT), CANTAB Paired Associate Learning (PAL), Verbal PAL (vPAL)] tasks. PCA was performed (oblique rotation, eigenvalues >1). Patients underwent 3.0T 3D T1 MRIs. FreeSurfer derived cortical thickness (CT) for left and right frontal, parietal, temporal, occipital, and cingulate cortices, and normalized volumes of left and right thalamus, caudate, hippocampus, and amygdala. Pearson correlations were performed between cognitive component scores and neuroanatomy, controlling for age, sex, education.

Results: Two principal components / latent variables: SPEED (1st loading) / MEMORY (2nd loading): SDMT (.62/.41), Stroop (.71/.19), PC (.78/.06), DS (.93/.14), SRT (.04/.78), BVMT (.02/.71), PAL (.10/.84), vPAL (.04/.77). SPEED was positively linked with CT in parietal (left: r = .330, p < .001; right: r = .345, p < .001) and temporal (left: r = .276, p = .005; right: r = .251, p = .011) lobes, and greater thalamic volume (left: r = .353, p < .001; right: r = .415, p < .001). MEMORY was related to greater volumes of left hippocampus (r = .275, p = .006) and right thalamus (r = .404, p < .001).

Conclusion: PCA-derived SPEED was uniquely related to temporal-parietal cortical thickness, whereas MEMORY was uniquely related to left hippocampal volume. Both SPEED and MEMORY were related to thalamic volume. Derivation of purer measures of cognitive constructs allows greater precision when identifying neural correlates of separable functions. For instance, SDMT is mostly a measure of speed (loading=.62), but also has a memory component (.41: likely incident learning), thereby leading to imprecision when speed is measured by SDMT alone.

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P616    Evolution of cognitive function in MS and its relationship to physical disability and MRI metrics

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Objective: To assess the course of cognitive function of MS patients from a single centre and the relationship to clinical disability and MRI metrics.

Patients and Methods: 116 patients with MS who had undergone clinical and cognitive assessment up to ten years ago were invited to attend a cognitive follow-up testing in 2016. Disability was measured using the Expanded Disability Status Scale (EDSS). Cognition (verbal learning and memory, visuospatial learning and memory, processing speed, attention, verbal fluency) was assessed by the “Brief Repeatable Battery of Neuropsychological Tests”. T2-lesion load, normalized brain,
Results: 30 MS patients (26% of the baseline cohort) consented to follow-up cognitive assessment after a mean follow-up of seven years (1.6 SD; range 4-10 years; 17 female, 56.7%; 5 clinically isolated syndrome, 22 relapsing-remitting MS, 3 secondary-progressive MS at baseline). Their mean age at baseline was 37 years (10 SD). At baseline, half of these patients had a cognitive deficit in at least one domain and 13% (N=4) showed deficits in at least 3 domains (defined by 1.5 SDs below standardized mean). Processing speed was the most affected domain (47%). Despite a significant increase in the median EDSS (2.0 vs. 3.3, p< 0.05), patients did not change regarding their cognitive function in any domain. Mean T2-lesion load did not significantly increase. Annualized mean percent brain volume change was -0.35%. Higher lesion load and lower brain volume at baseline correlated with higher EDSS scores at baseline ($r=0.37$ -0.58, respectively) and worse cognitive function at baseline and follow-up. Lower thalamic or hippocampal volume correlated with worse cognitive function at baseline and follow-up.

Conclusions: In this small cohort of MS patients we found no evidence of further cognitive deterioration over 7 years of follow-up despite a high prevalence of cognitive deficits at baseline. Interestingly this was paralleled by MRI changes likely not exceeding normal ageing although overall disability as measured with the EDSS deteriorated. This discrepancy needs further exploration.

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P617 Basal ganglia structural and functional abnormalities in multiple sclerosis are related to cognitive impairment
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Introduction: Although role of subcortical gray matter (GM) structures such as thalamus and hippocampus in cognitive performance in Multiple Sclerosis (MS) patients has been previously demonstrated, influence of basal ganglia has not been fully addressed. Very little is known about the independent contribution of basal ganglia structural and functional abnormalities to cognitive impairment in MS.

Objective: We aimed to examine specific basal ganglia volume and functional connectivity (FC) changes in two groups of MS patients according to their cognitive status.

Methods: Basal ganglia volume and FC changes were compared in 36 relapsing-remitting (RR) MS patients and 18 Healthy Controls (HC). MS patients were classified as cognitive preserved (CP, $n=18$) and cognitive impaired (CI $n=18$) according to their scores in Brief Repeatable Battery of Neuropsychological Tests, (BRB-N). Basal ganglia atrophy was assessed through VBM 8 while FC was assessed with resting-state seed-based analysis. All results were presented at whole brain level and FWE cluster corrected.

Results: A widespread reduction of GM volume was found in MS patients compared to HC, especially in CI subgroup. Compared to CP, CI patient showed a significant GM reduction in two clusters corresponding to bilateral basal ganglia (left cluster size: 1146 voxels, MNI coordinates: -30 -17 -3, right cluster size: 1329 voxels, MNI coordinates: 30 3 -6). Neuropsychological global z score was correlated with left putamen ($r=0.44 p< 0.001$), right putamen ($r=0.43 p< 0.001$) and right caudate ($r=0.42 p< 0.001$) volumes in patients group. Furthermore, seed-based FC analysis showed enhanced connectivity in CI patients between right caudate and bilateral medial orbitofrontal cortex (cluster size: 34 voxels, MNI coordinates 3 57 -3), which was also inversely correlated with global z score ($r=-0.66 p< 0.001$).

Conclusions: Cognitive impairment in MS patients is related with GM and FC abnormalities in basal ganglia.

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P618 Cognitive status of patients with multiple sclerosis is associated to cognitive reserve better than conventional MRI measures
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Background: Cognitive Impairment (CI) in multiple sclerosis (MS) has been related to lower patients’ quality of life, in particular to lower vocational status. Therefore, the identification of possible protective factors against cognitive decline in MS might be relevant. Previous studies on MS revealed that patients with greater cognitive reserve (CR) maintain better cognitive performance than patients with lower CR and that CR also moderates the negative effect of brain atrophy on cognition. Although available cross-sectional and longitudinal studies suggested that CR might play a role against CI associated with MS, they seem to be characterized by some methodological limitations.

Objective: To investigate the association between Cognitive Reserve (CR), Brain Reserve (BR) and cognitive functions and to evaluate whether CR might attenuate/moderate the negative impact of brain atrophy and lesion load on cognitive functions in Multiple Sclerosis (MS).

Methods: Ninety-eight Relapsing-Remitting MS (RRMS) patients were included in the study. Cognition was assessed by the Brief Repeatable Battery of Neuropsychological Tests (BRB) and Stroop Test. CR was assessed by vocabulary-based estimate of lifetime intellectual enrichment. All patients underwent a 3T MRI to assess T2-lesion load (T2-LL) and atrophy measures, including normalized gray matter (nGMV) and white matter (nWMV) volumes. The BR was evaluated by maximal lifetime brain volume expressed by intracranial volume (ICV). Hierarchical regressions were used to investigate whether higher BR and/or CR is related to better cognitive performances after controlling for factors affecting cognitive performance in such a disease (i.e., depression, fatigue, disability and brain damage measures).

Results: The ICV was not associated with any cognitive test of BRB and Stroop Test. As for CR, intellectual enrichment was positively associated with performance on tests assessing verbal and visual memory, attention and information processing speed, verbal fluency and inhibitory control. Significant relationship between nWMV and Stroop test was moderate by intellectual enrichment.

Conclusions: While BR does not seem to impact cognitive performances, CR seems able to independently mitigate cognitive dysfunction in RRMS patients. Moreover, CR can reduce the negative impact of brain atrophy on inhibitory control, relevant for social competence, emotional regulation and integrity of instrumental activities of daily living.

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P619

Intensive neurorehabilitation is associated with improved fatigue and depression in patients with progressive MS

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Introduction: Motor disability, depression and fatigue often coexist in people with progressive Multiple Sclerosis (PMS), with negative consequences on their quality of life. We explored the effect of pre-existing depressive symptoms on the outcome of intensive motor neurorehabilitation treatment in PMS.

Methods: Consecutive patients with PMS (40, 22 F, age 48.52+8.18; EDSS 5.85 ± 0.58) entering our Neurorehabilitation department and participating in a randomized trial on repetitive TMS coupled with neurorehabilitation were recruited. They underwent testing with MS walking scale (MSWS); fatigue severity Scale (FSS); 6 minutes walking test (6MWT), numerical rating scale (NRS) for spasticity and pain, expanded disability status scale (EDSS), functional independence measure (FIM), 10 meter walk test (10MW), Beck depression inventory (BDI) and paced auditory serial addition test (PASAT), at baseline (T0) and at T3, after an intensive neurorehabilitation program twice a day, 5 days/week for 3 weeks.

Results: Patients with mild/severe depression at baseline (BDI >14, n=11, 28%) significantly improved in fatigue (delta FSS 1.48 vs 0.16; p=0.036) and depression (delta BDI 9.4 vs 1.7; p=0.025). They also had a tendency to improvement at T3 in 6MWT (55.3 vs 19 mt; p = 0.06), MSWS (35.2 vs 9.6; p = 0.054). These measures did not significantly differ between the two groups at baseline.

Conclusions: We found a better improvement in fatigue and depression and a trend for motor and physical scales in people with MS with higher depression scores at the start of an intensive neurorehabilitation program. These data are consistent with the view that underlying depression may confound motor and fatigue measures and underline the importance to address psychological factors to enhance the positive outcome of rehabilitation treatment and its maintenance.

Disclosure

Congiu M, Pisa M, Gelihter S, Fichera M, Comola M: nothing to disclose
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P620

Specific rehabilitation improves information processing speed and attention in MS: a randomized trial against non-specific training with semi-ecological evaluation

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Introduction: Motor disability, depression and fatigue often coexist in people with progressive Multiple Sclerosis (PMS), with negative consequences on their quality of life. We explored the effect of pre-existing depressive symptoms on the outcome of intensive motor neurorehabilitation treatment in PMS.

Methods: Consecutive patients with PMS (40, 22 F, age 48.52+8.18; EDSS 5.85 ± 0.58) entering our Neurorehabilitation department and participating in a randomized trial on repetitive TMS coupled with neurorehabilitation were recruited. They underwent testing with MS walking scale (MSWS); fatigue severity Scale (FSS); 6 minutes walking test (6MWT), numerical rating scale (NRS) for spasticity and pain, expanded disability status scale (EDSS), functional independence measure (FIM), 10 meter walk test (10MW), Beck depression inventory (BDI) and paced auditory serial addition test (PASAT), at baseline (T0) and at T3, after an intensive neurorehabilitation program twice a day, 5 days/week for 3 weeks.

Results: Patients with mild/severe depression at baseline (BDI >14, n=11, 28%) significantly improved in fatigue (delta FSS 1.48 vs 0.16; p=0.036) and depression (delta BDI 9.4 vs 1.7; p=0.025). They also had a tendency to improvement at T3 in 6MWT (55.3 vs 19 mt; p = 0.06), MSWS (35.2 vs 9.6; p = 0.054). These measures did not significantly differ between the two groups at baseline.

Conclusions: We found a better improvement in fatigue and depression and a trend for motor and physical scales in people with MS with higher depression scores at the start of an intensive neurorehabilitation program. These data are consistent with the view that underlying depression may confound motor and fatigue measures and underline the importance to address psychological factors to enhance the positive outcome of rehabilitation treatment and its maintenance.

Disclosure

Congiu M, Pisa M, Gelihter S, Fichera M, Comola M: nothing to disclose
Comi G has received compensation for consulting services and / or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Roche, Almirall, Celgene, Forward Pharma
Leocani L. has received compensation for consulting services and / or speaking activities from Novartis, Merck, Biogen, Roche, Admiral
Part of this work was supported by FISM-Fondazione italiana Sclerosi Multipla (project FISM 2012/R/9)
Background: The effect of a specific cognitive rehabilitation program (SCR) dedicated to information processing speed (IPS) and attention impairment versus non-specific training (NST) is unknown in persons with multiple sclerosis (PwMS).

Objective: to demonstrate that SCR improves IPS and attention as compared to NST in PwMS.

Methods: A single-blind randomized controlled trial was conducted to compare SCR versus NST in a sample of PwMS. PwMS complaining of discomfort in their daily life due to cognitive problems, aged 18-55, with disease duration ≤15 years and right handedness, were eligible if they had at least 2 scores <1 standard deviation on tests from a neuropsychological (NP) battery including several tasks of the Test of Attentional performance (TAP). They were randomized between SCR or NST groups. SCR includes 50 individual sessions 3 times a week during 4 months and NST includes non-specific cognitive individual training. The primary end-point was NP assessment of IPS and attention after 4 months. Secondary end-points included NP assessment 4 months after the end of treatment, patient-related outcomes about depression, anxiety, fatigue, quality of life and daily functioning and semi-ecological assessment by tasks in a virtual reality environment (Urban Daily Cog®) (Lamargue-Hamel et al., 2015). Statistical significant differences were assessed by non-parametric tests (Wilcoxon test between 2 times in each group and Mann-Whitney test the change over 4 months between groups).

Results: 18 PwMS completed the SCR program and 17 the NST. A significant improvement was observed after 50 sessions in the SCR group but not in the NST group (Wilcoxon) for several reaction times (RT) at tasks of the TAP assessing IPS (alertness, phasic arousal, visual and auditory simple attention, dual task visual and auditory attention but also 3 out of 4 RT of the urban daily Cog®). Some other NP tests were improved. Mann-Whitney analyses confirmed superiority of SCR to NST for alertness, phasic arousal and auditory attention RT. Other outcomes will be presented.

Conclusion: SCR improves significantly IPS and attention in both classical NP tests and semi-ecological assessment by tasks in a virtual reality environment.

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Problem solving in patients with multiple sclerosis - analysing information and optimising strategies under different conditions

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Problem solving is an umbrella term that comprises cognitive aspects like logical thinking, planning, and decision making. Whilst inconsistent results regarding problem solving ability were found, literature indicates that MS-patients need more execution time during such tasks (Azcarraga-Guirola et al., 2017; Hankomäki et al., 2014; Owens et al., 2013, Preston et al., 2013; Rogers & Panegyres, 2007; Simoni et al., 2008). Aim of the study was to investigate problem solving under different conditions. Thirty-eight MS-patients (22 females, 16 males; age 22-62 years [M=40.6+-9.7 years]; disease-duration: M=11.2+-6.1 years; EDSS: Median=1.5; 35 relapse-remitting, 3 secondary-progressive) and 38 gender-, age-, and education-matched healthy controls were examined regarding logical thinking (Intelligenz-Struktur-Test-2000-R, verbal: Analogies (AN), non-verbal: Matrices (MA)), planning (Tower-of-London), and decision making (Iowa-Gambling-Task).

Non-significant differences between groups were found regarding logical thinking (AN: t=-.73, df=37, p=.47; MA: t=-.11, df=37, p=.94). Regarding planning non-significant differences were found regarding solved items (t=.16, df=37, p=.88) and total planning time (t=-.57, df=36, p=.57) whilst significant results were found regarding pausing during most difficult items (t=2.1, df=37, p=.046) and planning time during the most easy items (t=2.8, df=37, p=.009).

MS-patients with a disease-duration of approx. 11 years show preserved problem solving ability in terms of logical thinking, decision making and planning performance. In this context, patients showed significantly more pauses and longer planning time during crucial parts of the planning task. These results indicate that overall problem solving performance is preserved in MS whilst they probably need more time and opportunities to analyse and re-analyse conditions so as to optimise their strategies.

Disclosure
The authors of the study have nothing to disclose.

The symbol digit modalities test and the frontal systems behaviour scale: a one-year follow-up study

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Background and Objective: Anxiety, disinhibition, irritability, apathy, depression, are frequent in multiple sclerosis (MS)
patients. Cognitive impairment is also common in these patients and it has been correlated with neuropsychiatric symptoms. The Frontal Systems Behaviour Scale (FrSBe) is a reliable measure of apathy, disinhibition and executive dysfunction. In the other hand, the Symbol Digit Modalities Test (SDMT) may be used as a screening tool for neuropsychological impairment in MS. The aim of the present study is to assess the correlation between the SDMT and self and family reported measures of the FrSBe.

**Method:** Multiple Sclerosis patients were assessed with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), which includes within other cognitive tests, the SDMT. Patients also answered the Beck Depression Inventor -BDI, as well as the FrSBe, that was also answered by a patient’s relative. The current assessment of behaviour of the FrSBe was used. The same evaluation was performed one year later. Patients who have had a relapse within the last month, who were in treatment with corticosteroids or those with any medical or psychiatric condition that could affect cognitive performance, were excluded.

**Results:** A group of 162 patients (55 males), mean age of 39.75 (SD:10.81) years were included. Mean time of evolution of the disease was 9.25 (SD:7.1) years. A total of 146 patients (48 males) were assessed a year later.

In the first assessment, data analysis showed a significant negative correlation (p<0.01) between the SDMT and the self and family questionnaires of the FrSBe, except for the self-reported disinhibition subscale (p=0.94). A negative and significant correlation was also observed between the SDMT and the BDI score (p<0.01). In the second evaluation, a negative significant correlation (p<0.01) was observed between the SDMT and all the self and family FrSBe subscales and the depression questionnaire. For both assessments, the SDMT showed a positive and significant correlation (p<0.01) with all the BRB-N’s subtests.

**Conclusions:** The results of this one-year follow-up study, support the use of the SDMT as a single screening test to assess MS patients, as it may not only give information regarding cognitive status, but also about possible changes in behavioural symptoms. This test, that is easy to administer, can give us the opportunity to select the patients who will benefit from a comprehensive assessment.

**Disclosure**

Authors have nothing to disclose.

**References:**


**Disclosure**

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**P623**

Neuropsychological and anatomical correlates of theory of mind in patients with multiple sclerosis

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**Objectives:** Theory of Mind (ToM) is a social cognitive domain implying one’s ability to understand and predict mental states of others based on their feelings, thoughts, intentions and beliefs. ToM brain networks include several cerebral regions such as the cingulate cortex, orbitofrontal cortex, as well as temporal and parietal regions. In multiple sclerosis (MS), the neuropsychological and anatomical correlates of ToM were only the subject of few works [1].

**Methods:** ToM was assessed in a cohort of MS patients by the means of the revised version of Reading the Mind in the Eyes test (RMET). Clinical and socio-demographic data were obtained. Patients underwent a neuropsychological evaluation that included scales for mood, fatigue, sleep, alexithymia, as well as cognitive measures (Symbol Digit Modalities test (SDMT) and 60-item empathy quotient (EQ)). They also had a 3 Tesla T1-MRI on which a fully automated volume-based morphometry algorithm (MorphoBox) was applied. Correlation analysis was performed to assess the relationship between RMET scores on one side, and the remaining data on the other side.

**Results:** 34 MS patients completed the study. The RMET mean was 22.91 ± 4.83. A positive correlation was found between RMET and each of SDMT (r=0.50; p<0.01) and EQ (r=0.40; p<0.01). Concerning MRI measures, RMET scores were positively correlated with volumes of several cerebral areas, namely the temporal (left side: r=0.40, p=0.02; right side: r=0.40, p<0.01), parietal (left side: r=0.40, p<0.01; right side: r=0.50, p<0.01), and deep white matter (left side: r=0.40, p=0.03; right side: r=0.40, p=0.04), as well as the right cingular gray matter (r=0.40, p=0.02).

**Conclusion:** In MS patients, visuospatial abilities and information processing speed seem to be linked to ToM. In addition, the abilities to mentalize would impact the individual’s capacity to empathize with others which explains the relationship between RMET and EQ scores. Importantly, ToM performance in MS patients is associated with volumes of areas which are key components in social cognitive networks. A frequent involvement of these regions during the course of MS, screening for ToM deficits is crucial to improve the patients’ quality of life.

**Keywords:** Theory of mind; multiple sclerosis; social cognition; magnetic resonance imaging.

**References:**

Rationale: Behavioural evidence in patients with clinically manifest multiple sclerosis (MS) suggests changes in the processing of emotional information. However, it is

- unclear if and to what extent emotional experience is affected,
- if these changes are related to depressed mood and
- if they are present even in patients with clinically isolated syndrome (CIS) and early MS.

Aim: Our study aimed to investigate emotional processing in patients with CIS and early relapsing-remitting MS (RRMS) and matched healthy controls (HC).

Materials and Methods: We evaluated 29 patients (21 RRMS, 8 CIS; 14 female) with a mean disease duration of 31 months (SD 21; range 3 - 60), a mean EDSS score of 1.2 (SD 0.9; range 0 - 3) and 30 matched healthy controls (15 female). To prompt emotional experiences, each participant was presented 54 pictures from the International Affective Picture System (IAPS) with either negative or positive emotional content and neutral images (18 per category, 6 seconds presentation duration). Upon presentation of each of the pictures, participants rated the induced emotion regarding valence (positive, negative, neutral) and arousal (high, low) using 9-level Self Assessment Manikin Likert scales. Valence and arousal ratings were analysed by means of separate 2 x 2 Scheirer-Rare-Hare tests for the experimental factors group and IAPS category, controlling for the influence of age, sex and mood (Beck Depression Inventory, BDI-II).

Results: The Analysis revealed a main effect of IAPS valence category, F(2,138) = 30.11 (p < .001), and an interaction group x valence, F(2,138) = 4.01 (p = .020). Patients rated the emotions prompted by positive pictures significantly less positive than HCs; z = 2.24 (p = .025). For arousal ratings, the analyses revealed a main effect of IAPS category, F(2,138) = 3.48 (p < .033), and a main effect of group, F(1,138) = 12.37 (p < .001). Compared with HCs, patients were significantly less aroused watching pictures with emotional content.

Conclusion: Emotional processing changes may be present even in early MS. Disease related flattened emotional experience does not appear to be secondary to mood changes and potentially has an impact on the patients’ quality of life.

Disclosure

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Role of sponsors: The study was conducted independently of study sponsors. There was no sponsor involvement in the design; collection, analysis, and interpretation of the data; in writing of the report; or in the decision to submit for publication.

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HK: Received in the last two years personal compensation for speaking from Novartis, Biogen-Idec, Merck-Serono, Bayer, Teva, Mylan, Roche and Genzyme.

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FP: Serves on the scientific advisory board for Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an academic editor for PLoS One, is an associate editor for Neurology® Neuroimmunology & Neuroinflammation; consulted for Sanofi-Genzyme, Biogen Idec, MedImmune, MedImmune, and Alexion; received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA.

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Biomarkers

P625

Cerebrospinal fluid neurofilament light chain is a marker of disease activity in multiple sclerosis

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Introduction: Biomarkers of disease activity that have reliable prognostic utility in MS are lacking. The aim of this study was to determine whether the level of neurofilament light chain (NFL) in the cerebrospinal fluid (CSF) of MS patients, correlates with disease activity and progression.

Methods: Between June 2015 and April 2016 we analyzed all available CSF samples from patients with clinically isolated syndrome (CIS) or MS, collected up to August 2014 and stored at Verona University Hospital. Clinical and MRI variables were obtained retrospectively from medical records. CSF standard examination and isoelectrofocusing for oligoclonal bands were performed at Verona University Hospital at the time of diagnostic lumbar puncture. NFL concentration was assessed using a commercially available ELISA kit.
**Results:** Of the 111 analyzed CSF samples, 25 were collected from CIS and 86 from MS patients (72 with relapsing-remitting and 14 with progressive course). We observed a significant increase in CSF NFL level in patients with at least one enhancing lesion on brain MRI (3718 ng/L vs. 1589 ng/L; p = 0.009), as well as in patients with at least 10 cells/mm² in CSF (5044 ng/L vs. 2149 ng/L; p = 0.031). Furthermore, we found that NFL level of CIS patients who later developed MS was significantly higher than in patients who remained CIS (3796 ng/L vs. 887 ng/L; p = 0.025). We also observed a significant NFL level increase in patients with at least one clinical relapse after lumbar puncture (3954 ng/L vs. 1597 ng/L; p = 0.001). In addition, patients with NFL level >2211 ng/L (i.e. median of study population) had a significantly shorter time to relapse (median 8.2 years vs 11.6 years; p = 0.048). Finally, we found a significant correlation of NFL concentration with relapse rate (r = 0.344, p = 0.001) and with expanded disability status scale score at one year after lumbar puncture (r = 0.289, p = 0.038).

**Conclusion:** Our findings suggest that CSF NFL is prominently a marker of acute inflammation in MS, as shown by the association with gadolinium-enhancing lesions on MRI, CSF pleocytosis, conversion from CIS to MS, shorter time to first relapse and relapse rate after lumbar puncture. CSF NFL level could be used to stratify CIS and relapsing-remitting MS patients according to disease activity and the correlated risk of subsequent disability, in order to identify cases eligible to early disease-modifying treatment.

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**P626**

Autoantibodies to neurofilament light protein as a potential biomarker of treatment response and disease progression in multiple sclerosis

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**Summary:** We aimed to investigate the levels of antibodies to neurofilament light protein (NFL Ab) in serum samples, in a cohort of MS patients treated with disease modifying therapies (DMTs: injectable DMTs, natalizumab, fingolimod and rituximab) at different stages of disease progression. Besides exploring the value of measuring auto-immune humoral response against NFL; we studied the nature of these antibodies by examining their avidity, which represents a good parameter to define the functional value and specificity to the antigen. We also studied the correlation of these antibodies with the levels of NFL protein.

**Study population:** A longitudinal cohort (n=246) was recruited at the Neurologic Clinic and Policlinic, University Hospital Basel as part of the Swiss MS Cohort Study, a prospective observational study in which demographic and clinical data as well as serum samples were collected at baseline and at follow-up visits 1 (7 +/- 4 months) and 2 (16 +/- 6 months).

**Methodology:** A Simoa NFL assay was developed using the monoclonal antibody (mAb) 47:3 and the biotinylated detector mAb. Levels of NFL Abs were quantified by ELISA using a recombinant human-NFL protein. Avidity was determined by elution assays using sodium thiocyanate as a chaotropic agent to disrupt immune complexes. The associations between clinical parameters and NFL protein level, NFL Ab level, NFL Ab avidity and NFL Ab avidity index, respectively were modeled with linear generalized estimating equation and multivariable models.

**Results:** The multivariate model indicates that NFL Ab level is higher in progressive patients (PPMS/SPMS vs RRMS p = 0.01). The NFL Ab levels are higher after a recent EDSS increase (p = 0.012) and tend to drop with increasing EDSS. There is no significant association between NFL protein and NFL Ab levels. NFL Ab levels tend to decrease during treatment (DMT treated vs untreated, p = 0.058). The level of high avidity of NFL Abs is higher in untreated patients (p = 0.028).

**Conclusions:** Level of NFL Ab and avidity is higher in progressive patients and tend to decrease during treatment with DMTs. These results support the usefulness of NFL Abs as potential markers of neurodegeneration. Combination of markers like NFL Ab and NFL protein might have additional diagnostic potential for the identification of practical biomarkers in MS. Future studies are encouraged to investigate whether changes in auto-antibodies / avidity at an early stage can predict successful treatment.

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**P627**

Differential gene expression in stable and active MS patients treated with fingolimod

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**Introduction:** Fingolimod is a sphingosine 1-phosphate receptor modulator that inhibits the egress of lymphocytes from the lymph nodes into the peripheral circulation and the central nervous system, and reduces relapses and MRI activity in relapsing-remitting multiple sclerosis (RRMS). However, some patients continue to experience disease activity while on treatment.

**Objective:** The primary objective of this study was to identify clusters of genes, which are differentially expressed in stable and active MS patients treated with fingolimod and may be used as predictive biomarkers.
Methods: In this study we included 47 untreated and 40 fingolimod-treated RRMS patients of which 20 were stable and 20 active with at least one relapse during the first year of treatment and matched on previous treatment, sex and age. RNA was extracted from whole blood and gene expression measured by Affymetrix Gene 2.0 ST array. Data normalization and analyses were performed in Partek Genomics Suite and the enrichment of annotated genes was investigated using the database DAVID. Unadjusted p-values and Benjamini-Hochberg (false discovery rate) q-values are reported.

Results: We observed a distinct separation between untreated and treated MS patients by primary component analysis. 282 genes had lower expression in treated patients (+2-fold: ANCOVA, q<10^{-11}) corresponding to the peripheral reduction of lymphocytes. More discrete gene expression differences were observed between stable and active fingolimod-treated patients with 27 differentially expressed genes (+1.3-fold: ANCOVA, p<0.01, with adjustment for age, sex, scan-date and treatment). Functional annotation clustering identified one cluster with an enrichment score of 1.31 having five significantly enriched pathways (q<0.0082) centered around six genes. The score of these genes correlated significantly with number of relapses in active patients (Spearman: rho=-0.48, p=0.034) but not with MRI activity (new T2 lesions). ROC-curve analyses of the score could discriminate stable and clinically active patients with an area under the curve of 0.76 (p=0.005).

Conclusion: As expected a clearly defined gene expression signature was observed in fingolimod-treated compared with untreated MS patients. Six genes of the 27 differentially expressed genes in clinically active patients correlated with the number of relapses. This gene expression signature should be tested in an independent cohort for its value as predictive biomarker.

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Finella Seileberg has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva, has been on the steering committee of a clinical trial sponsored by Merck Serono, and served as a consultant for Biogen Idec and Novo Nordisk; has received support for congress participation from Biogen Idec and Novo Nordisk; has received support for congress participation from Biogen Idec, Novartis, Sanofi Aventis and Teva; has received speaker honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Schering-Plough.

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Background: Reliable prognostic markers of primary progressive (PP) multiple sclerosis (MS) evolution are needed.

Aims: We investigated the added value of conventional and diffusion tensor MRI measures of brain and cervical cord damage in predicting the long-term clinical evolution of PPMS in comparison to simple clinical assessment.

Methods: In 54 PPMS patients, conventional and DT MRI scans of the brain and T1-weighted scans of the cervical cord were acquired at baseline and after a median follow-up of 15 months. Clinical evaluation was performed after 5 and 15 years of follow-up in 49 patients. Measures of lesion load, brain and cord atrophy were obtained. Histograms of the mean diffusivity (MD) and fractional anisotropy values from the normal-appearing white matter and gray matter (GM) were analyzed. Linear regression models were used to screen the clinical and MRI variables as independent predictors of 15-year expanded disability status scale (EDSS) change.

Results: At 15-year follow-up, 90% of the patients had disability progression. When models including clinical variables only were built, the best model identified baseline EDSS and 5-year EDSS worsening as independent predictors of 15-year EDSS deterioration (R²=0.57; discriminating ability: 74%). When MRI variables were included into the models, the best model identified baseline EDSS and 1-year change of EDSS, T1-hypointense lesions, brain volume and GM MD as independent predictors of 15-year EDSS deterioration (R²=0.61; discriminating ability: 78%).

Conclusions: In PPMS, MRI measures allow an earlier identification of patients at risk of disease progression after 15 years than clinical assessment.

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Disclosure

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D. Caputo: nothing to disclose.
P629 Serum neurofilament light levels at the time of a clinically isolated syndrome are associated with long-term clinical and radiological outcome

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Background: There is an unmet need for prognostic biomarkers to facilitate treatment decision-making in multiple sclerosis (MS) patients. Recently, increased levels of neurofilament light (NfL) in CSF and serum of MS patients were shown to be associated with higher levels of disease severity and a worse long-term clinical and paraclinical outcome. However, the long-term prognostic value of serum NfL at first MS presentation remains largely unknown.

Objectives: To evaluate serum NfL as a prognostic biomarker for long-term clinical and radiological disease outcome measures in patients with clinically isolated syndrome (CIS).

Methods: Serum NfL levels were measured using a sensitive Single Molecule Array (SIMOA) assay in 319 patients (308 at baseline, 139 at year 2) originally recruited in the CHAMPS study, a 36-month randomized placebo-controlled trial of intramuscular interferon beta-1a in CIS patients. The 5- and 10-year open-label extension of this study, CHAMPIONS, comprises data on conversion to clinically definite MS (CDMS), number of relapses, EDSS milestones and various MRI measures, including brain parenchymal fraction (BPF). Statistical analyses were performed using Spearman correlation, ANOVA, chi-squared tests, and multivariate logistic regression.

Results: Serum NfL levels at CHAMPS baseline were significantly associated with number and volume of Gd+ lesions (p< 0.00001) and T2 lesion volume (p< 0.00001) at the time of sampling. Serum NfL levels at baseline were also associated with the number of new T2 lesions and T2 lesion volume at 5 years (p< 0.00001 for both) and 10 years (p< 0.01 and p< 0.00001, respectively), BPF change over 5 years (p< 0.00001), number of relapses over 10 years (p< 0.05), and time to CDMS over 10 years (p< 0.05). Additionally, serum NfL levels at baseline were associated with the risk of reaching EDSS≥3.5 at 5 years (p< 0.05). Similar observations were noted for NfL serum levels assessed at year 2.

Conclusions: Serum NfL levels in CIS patients are significantly associated with various long-term clinical and paraclinical outcome measures up to 10 years of follow-up. Our findings support the view that serum NfL represents a promising candidate biomarker for disease stratification already in early MS. Additional studies are warranted to corroborate these observations.

Disclosure

Study was sponsored by Biogen.

TP, CMS, DS, CDM, BE, EF, AS, BCK, RAR are employees of Biogen and hold stock/stock options in the company.

JG was an employee of Biogen at the time of the study conduct.

RPK reports personal fees from Genzyme, a Sanofi Corp., from Biogen Idec, from Novartis, and grants from Accelerated Cure Project.
in multiple sclerosis (MS). A promising biomarker for axonal damage early in the disease course of MS is neurofilament light chain (NfL). A correlation has been found between CSF NfL in adult patients with clinically isolated syndrome (CIS) and disease progression. Whether NfL is also increased at disease onset in children is still unknown.

Our first aim was to compare CSF neurofilament light chain (NfL) levels between children and adults at a time of a first demyelinating event. The second aim was to explore the predictive value of NfL in pediatric and adult CIS patients. Finally, we investigated the association between NfL and T1-hypointense lesions on MRI.

**Methods:** We included 88 adult and 65 pediatric patients with follow-up since a first attack of demyelination and 30 controls. NfL levels were determined in CSF using a commercially available ELISA. COX regression analyses were used to calculate univariate and multivariate hazard ratios (HR) for clinically defined MS (CDMS) diagnosis.

**Results:** Patients with a first demyelinating event had higher CSF NfL levels than controls (geometric mean 2040 pg/mL vs 444 pg/mL; p< 0.001). For CIS patients with a future CDMS diagnosis, children showed higher NfL levels than adults (geometric mean 4888 pg/mL vs 2110 pg/mL; p=0.006). After adjustments for age at onset, oligoclonal bands, and T2-lesions on baseline MRI, increased NfL levels in both pediatric and adult CIS patients were associated with a shorter time to CDMS diagnosis (children HR 3.5; p=0.035, adults HR 2.1; p=0.033).

Additionally, NfL was higher in patients with T1-hypointense lesions than in patients without T1-hypointense lesions on baseline MRI in adults (geometric mean 3051 pg/mL vs 1798 pg/mL; p=0.024) and children (geometric mean 7073 pg/mL vs 1890 pg/mL; p=0.020).

**Conclusions:** CSF NfL levels are associated with CDMS diagnosis in children and adults with CIS. This makes NfL a promising predictive marker for disease course with potential value in clinical practice.

**Disclosure**

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Rinze F. Neuteboom: Nothing to disclose
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**P631**

**Serum glial fibrillary acidic protein correlates with disease severity and neuroaxonal demise in multiple sclerosis: a pilot study using Simoa technology**

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**Background:** Investigating neurochemical markers in body fluids of multiple sclerosis (MS) patients is a promising approach to monitor different pathophysiological aspects of the disease. The novel single molecule array (Simoa) technology allows due to its high sensitivity the detection of brain derived proteins in the serum. While serum neurofilaments (sNfL) is an established marker of neuroaxonal damage, little is known about the application of Simoa technology to measure levels of glial fibrillary acidic proteins (sGFAP) in serum of MS patients.

**Methods:** GFAP and NfL were measured in serum with the Simoa technology and the available GFAP Discovery and NfL Early Access assays (Quanterix Corporation, Lexington, MA, USA) of patients with different clinical courses of MS and of healthy controls (HCs). Clinical data like age, disease duration, Extended disability status scale (EDSS) and treatment were retrieved from electronic case report forms.

**Results:** In total 51 MS patients were included (13 RRMS in relapse, 12 without relapse, 8 SPMS and 17 PPMS patients) as well as 22 patients with other neurological diseases (OND, e.g. facial palsy, migraine, etc.). Levels of sGFAP in different MS subtypes were higher than HCs (p< 0.005). Similar to sGFAP, sNfL levels were higher in MS compared to OND (p=0.005). GFAP levels correlated with disease severity in the whole MS group and in PPMS (Spearman correlation = 0.5, p< 0.001) while NfL did not. sGFAP levels correlated with sNfL (Spearman correlation = 0.5, p<0.001).

**Discussion:** Our study applies for the first time the Simoa technology to measure the levels of sGFAP in MS patients. We report higher levels in MS patients, especially patients with progressive clinical course, than HCs. Furthermore, sGFAP correlated with disease severity and sNfL indicating a possible role of the astrocytes in the neuroaxonal demise. The unique correlation between sGFAP and the disease severity in PPMS may highlight a unique role of the astrocytes in PPMS.

**Disclosure**

AA has no conflict of interest to declare.
AH has no conflict of interest to declare.
FB has no conflict of interest to declare.
SH has no conflict of interest to declare.
PO has no conflict of interest to declare.
HT has no conflict of interest to declare.

**P632**

**Relationship between different cerebrospinal fluid biomarkers in multiple sclerosis: meaning and use in clinical practice**

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**Background:** In the past years, several biomarkers of axonal damage have been investigated in multiple sclerosis (MS). A promising biomarker for axonal damage early in the disease course of MS is neurofilament light chain (NfL). A correlation has been found between CSF NfL in adult patients with clinically isolated syndrome (CIS) and disease progression. Whether NfL is also increased at disease onset in children is still unknown.

**Methods:** We included 88 adult and 65 pediatric patients with follow-up since a first attack of demyelination and 30 controls. NfL levels were determined in CSF using a commercially available ELISA. COX regression analyses were used to calculate univariate and multivariate hazard ratios (HR) for clinically defined MS (CDMS) diagnosis.

**Results:** Patients with a first demyelinating event had higher CSF NfL levels than controls (geometric mean 2040 pg/mL vs 444 pg/mL; p< 0.001). For CIS patients with a future CDMS diagnosis, children showed higher NfL levels than adults (geometric mean 4888 pg/mL vs 2110 pg/mL; p=0.006). After adjustments for age at onset, oligoclonal bands, and T2-lesions on baseline MRI, increased NfL levels in both pediatric and adult CIS patients were associated with a shorter time to CDMS diagnosis (children HR 3.5; p=0.035, adults HR 2.1; p=0.033).

Additionally, NfL was higher in patients with T1-hypointense lesions than in patients without T1-hypointense lesions on baseline MRI in adults (geometric mean 3051 pg/mL vs 1798 pg/mL; p=0.024) and children (geometric mean 7073 pg/mL vs 1890 pg/mL; p=0.020).

**Conclusions:** CSF NfL levels are associated with CDMS diagnosis in children and adults with CIS. This makes NfL a promising predictive marker for disease course with potential value in clinical practice.

**Disclosure**

Roos M. van der Vuurst de Vries: Nothing to disclose
Yu Yi M. Wong: Nothing to disclose
Julia Y. Mescheriakova: Nothing to disclose
E. Daniëlle van Pelt: Nothing to disclose
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Johnny P. Samijn: Received honoraria for serving on advisory boards for Merck-Serono and Genzyme. Received travel grants from Merck-Serono. He participated in trials with BiogenIdec, Merck-Serono, Roche and Genzyme
Rinze F. Neuteboom: Nothing to disclose
Rogier Q. Hintzen: Received honoraria for serving on advisory boards for Biogen Idec, Roche, Sanofi. He participated in trials with BiogenIdec, Merck-Serono, Roche, Genzyme and Novartis

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**Objective:** To explore the relationship between three cerebrospinal fluid (CSF) biomarkers of poor prognosis (IgM Oligoclonal Bands -OCMB-; Light Neurofilaments -NFl-; and of Chitinase 3-like 1 -CHI3L1-) and the clinical phenotype of multiple sclerosis.

**Methods:** The CSF of 153 MS patients (94 with relapsing-remitting MS -61.4%; 36 with secondary progressive MS -23.5%; and 23 with primary progressive MS -15.0%-) has been studied, in 40 of them the CSF was obtained during a relapse. OCMB was analyzed by isoelectric focusing and immunodetection in membranes preincubated with the lipids of interest. Determination of levels of light chain Neurofilaments (NF-L) and of Chitinase 3-like 1 (CHI3L1) were quantified by enzyme immunoassay and are detected by absorbance. The disability was measured by the EDSS and the Multiple Sclerosis Severity Score (MSSS).

**Results:** OCMB were present in 72 patients (47.1%); the EDSS was no different between patients with or without OCMB, but the MSSS was higher in patients with OCMB (4.5 vs. 5.6, p=0.01).

The mean CHI31L was 168 ng/ml, significant higher in patients with OCMB (p=0.003); the mean NFl concentration was 991 pg/ml, with no no differences in patient with or without OCMB. CHI31L correlated with the EDSS and the MSSS (p=0.013, and p=0.000, respectively); but NFl shown only a modest correlation only with the MSSS (p=0.04). The correlation between CHI31L and NFl was high (Spearman correlation 0.439). CHI31L was significant higher in progressive MS (p=0.002, Kruskal-Wallis), and independent of relapses; NFl was higher in the CSF obtained during a relapse (1765 pg/ml, p=0.003).

**Conclusions:** A relationship between the presence of OCMB and CHI31L has been proved, as the expression of a subset of more aggressive patients, according to the high MSSS observed and the evolution to the progressive MS. In respect to NFl, our work underlying the relationship between the acute axonal destruction and the elevation of NFl, and demonstrate a correlation between the axonal destruction and the microglial activated biomarker CHI3L1. Take together our results reinforced the role of the innate immune system in the developing progressive MS.

**Disclosure**

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**P633**

Lower baseline levels of vitamin D are associated with a higher risk of new lesion development in patients with relapsing multiple sclerosis


1Data Clarity Consulting, Ltd, Stockport, United Kingdom, 2Receptos, a wholly owned subsidiary of Celgene, San Diego, 3Steinman Lab, Neurology & Neurological Sciences, Stanford Medicine, Stanford, CA, United States

**Background:** Prior studies have established vitamin D as an immunomodulator that affects gene expression, regulates the production of cytokines, as well as lymphocyte proliferation and maturation in many auto-immune diseases, and may be associated with protection of the central nervous system in relapsing multiple sclerosis (RMS) patients. A genetically lowered vitamin D level has been strongly associated with increased susceptibility to MS (Mokry et al, *PLoS Med*, 2015). The virtual twins approach (Foster et al, *Stat Med*, 2011) was used to identify whether baseline biomarkers, including 25-OH vitamin D [25-OH] and 1,25-OH vitamin D [1,25-OH], could be used as prognostic indicators.

**Methods:** Baseline plasma samples were collected and assayed. Data were analysed in accordance with a pre-specified statistical analysis plan. Univariate analysis was used to relate baseline values of 25-OH and 1,25-OH to the number of gadolinium-enhancing (GdE) lesions at Week 24 as the primary endpoint, consistent with the planned primary endpoint of the original trial for the placebo dose group.

**Results:** Baseline assay data, for the 88 placebo patients were analysed in the intend-to-treat population. In the placebo group, the measured baseline levels of both 1,25-OH and 25-OH, reflected an inverse relative risk with the occurrence of new GdE lesions being approximately three-fold lower (75% to 25%) as a function of higher baseline Vitamin D levels. All patients with GdE lesions at baseline in the placebo group subsequently developed new lesions.

**Conclusion:** This is the first time in a randomized and longitudinal clinical study that a numerical relationship for the relative risk has been established between baseline levels of vitamin D and new GdE lesions in RMS patients. Moreover, this study is the first to conclude that the measurement of 1,25-OH vitamin D versus 25-OH vitamin D provides no difference in prognostic power. Finally, the prognostic value of vitamin D levels appears to impact on the natural course of disease.

**Disclosure**

Opiteck, Aranda, Frohna, Scott, Taylor Meadows, Shareholder: Celgene.

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**P634**

Neuroinflammation and neuroaxonal damage in multiple sclerosis: a cross-sectional cerebrospinal fluid-based proteomic study

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**Background:** Prior studies have established vitamin D as an immunomodulator that affects gene expression, regulates the production of cytokines, as well as lymphocyte proliferation and maturation in many auto-immune diseases, and may be associated with protection of the central nervous system in relapsing multiple sclerosis (RMS) patients. A genetically lowered vitamin D level has been strongly associated with increased susceptibility to MS (Mokry et al, *PLoS Med*, 2015). The virtual twins approach (Foster et al, *Stat Med*, 2011) was used to identify whether baseline biomarkers, including 25-OH vitamin D [25-OH] and 1,25-OH vitamin D [1,25-OH], could be used as prognostic indicators.

**Methods:** Baseline plasma samples were collected and assayed. Data were analysed in accordance with a pre-specified statistical analysis plan. Univariate analysis was used to relate baseline values of 25-OH and 1,25-OH to the number of gadolinium-enhancing (GdE) lesions at Week 24 as the primary endpoint, consistent with the planned primary endpoint of the original trial for the placebo dose group.

**Results:** Baseline assay data, for the 88 placebo patients were analysed in the intend-to-treat population. In the placebo group, the measured baseline levels of both 1,25-OH and 25-OH, reflected an inverse relative risk with the occurrence of new GdE lesions being approximately three-fold lower (75% to 25%) as a function of higher baseline Vitamin D levels. All patients with GdE lesions at baseline in the placebo group subsequently developed new lesions.

**Conclusion:** This is the first time in a randomized and longitudinal clinical study that a numerical relationship for the relative risk has been established between baseline levels of vitamin D and new GdE lesions in RMS patients. Moreover, this study is the first to conclude that the measurement of 1,25-OH vitamin D versus 25-OH vitamin D provides no difference in prognostic power. Finally, the prognostic value of vitamin D levels appears to impact on the natural course of disease.

**Disclosure**

Opiteck, Aranda, Frohna, Scott, Taylor Meadows, Shareholder: Celgene.
Introduction and aim: Neuroaxonal damage is strongly related to disease progression in multiple sclerosis (MS). In MS, axonal loss is considered the detrimental consequence of central nervous system (CNS) inflammation. While several treatments are effective in reducing the inflammatory activity of the disease, no therapy is available to directly counteract axonal damage. The study of cerebrospinal fluid (CSF) inflammatory markers closely related to axonal damage can help to identify novel immunological pathways responsible for a more severe neuronal injury. The aim of this study was to explore the correlations between a panel of CSF inflammation-related proteins (IRPs) and CSF neurofilament light (NfL) as a marker of neuro-axonal damage.

Patients and Methods: The levels of NfL and of 92 IRPs were determined in the CSF of patients with radiologically isolated syndrome (RIS, n=6), clinically isolated syndrome (CIS, n=32), relapsing remitting MS (RRMS, n=51), progressive MS (PMS, n=8) and in the CSF of patients with other neurological diseases (OND, n=36). NfL was assessed through a newly developed in-house ELISA while the 92 IRPs were determined with a proximity extension assay (PEA) using the Proseek Multiplex Inflammation kit (Olink Bioscience, Uppsala, Sweden).

Results: CSF NfL levels were significantly higher in RIS, CIS, RRMS and PMS patients compared to controls (p<0.001). No significant differences in CSF NfL levels were found between RIS, CIS, RRMS and PMS patients. Out of the 92 IRPs, 41 were excluded from the analysis because of a call rate <75% (>75% of the patients had values below the lower limit of detection). Of the remaining 51 proteins, 44 were not significantly different between patients and controls. On the contrary, 7 proteins (listed according to p-values from p<0.0001 to p=0.049: CD5, IL12b, TNFβ, MIP1α, TNFSF14, TNFRSF9, CXCL11) were significantly increased in MS patients. Moreover, 15 proteins (including the 7 proteins with higher concentrations in the CSF of MS patients plus CXCL1, CXCL6, CXCL9, CXCL10, CCL23, CCL28, CST5, EIF4EBP1) correlated positively with CSF NfL in MS patients.

Conclusions: Our results suggest that in MS patients several IRPs are increased as compared to controls and positively correlate with the degree of neuro-axonal damage. The IRPs we have found to be increased in MS and to correlate with neuroaxonal damage reflect different immunological pathways including B cell activity and lymphoid neogenesis.

Disclosure
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Zetterberg Henrik is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg.
Di Filippo Massimiliano participated to advisory boards of Biogen Idec, Teva and Bayer, received travel grants from Bayer Schering, Biogen-Dompé, Biogen-Idec, Merck-Serono, Novartis and Sanofi-Aventis to attend national and international conferences and speaker and writing honoraria from Biogen Idec, Novartis and Sanofi-Genzyme.

P635
Neurofilament light chain in CSF and serum in relation to disease activity and brain volume loss during four years of follow-up in a cohort of patients with CIS and RRMS
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Background: Improved biomarkers are needed to facilitate clinical decision-making and as surrogate endpoints in clinical trials in multiple sclerosis. We assessed the correlation between levels of neurofilament light chain (NFL) in cerebrospinal fluid (CSF) and serum in patients with clinically isolated syndrome (CIS) and relapsing remitting multiple sclerosis (RRMS) and in healthy controls. We also assessed NFL levels in relation to disease activity during one, two and four years of follow-up and brain volume loss over time.

Methods: In 191 samples from 41 patients with CIS or RRMS and 22 healthy controls, NFL was analysed in CSF using an enzyme-linked immunoabsorbent assay and in serum using a single-molecule array (Simoa) method. No evidence of disease activity 3 (NEDA-3) status in patients was recorded during four years of...
follow-up in this prospective longitudinal cohort study and repeated measurements of brain volume, calculated as brain parenchymal fraction (BPF) using SyMRI 8.0 (SyntheticMR), were obtained from 37 patients. All patients were treatment-naive at baseline.

**Results:** NFL levels in CSF and serum correlated significantly (Spearman’s r 0.59, p < 0.001). Receiver operating characteristics (ROC) curves for baseline NFL levels and separation of patients with regard to NEDA-3 status during one, two and four years of follow-up showed a significantly higher area under curve (AUC) for CSF-NFL than for S-NFL at two years (0.85 compared to 0.65, p 0.03), but not at one year (0.81 compared to 0.75, p >0.05) or four years (0.73 compared to 0.69, p >0.05). Linear regression modeling of BPF decrease during the study showed that combining baseline CSF-NFL and mean CSF-NFL during the study resulted in a significant model (adjusted R2 0.28, p 0.002), as did combining baseline number of T2 lesions in brain MRI and number of new T2 lesions in brain MRI during follow-up (adjusted R2 0.20 p 0.008). Among these four variables and baseline BPF, the highest adjusted R2 was achieved by combining baseline CSF-NFL, mean CSF-NFL and baseline number of T2 lesions (adjusted R2 0.33, p 0.001).

**Conclusions:** NFL levels in CSF and serum correlate, but baseline CSF-NFL may perform better than baseline S-NFL at predicting disease activity during follow-up. Brain volume loss over time seems to be associated with both NFL levels in CSF and T2 lesions in brain MRI and may be best explained in linear regression by a combination of NFL data and MRI data.

**Disclosure**
IH, AT, PC, PL and JE have no conflicts of interest to declare.
HZ is one of the founders of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg and has served on advisory boards of Roche Diagnostics, Eli Lilly and Pharmasum Therapeutics.
KB has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujiirebio Europe, IBL International, Pfizer and Roche Diagnostics and is also a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg.
CD has received honoraria for lectures from Biogen Idec, Teva, Sanofi Genzyme and Novartis and served at advisory boards of Roche Diagnostics, Novartis and Biogen Idec.
MV has received unrestricted research grants from Biogen and Novartis, honoraria for lectures from Biogen and Genzyme and for advisory boards from Roche and Novartis.

**P636**

**Serum neurofilament light chain correlates with disease activity and predicts clinical and MRI outcomes in MS**

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**Background:** Neuronal degeneration is a key factor in the development of permanent disability in multiple sclerosis (MS). Neurofilament light chain in CSF and more recently also peripheral blood has emerged as a biofluid marker reflecting neuronal damage in MS.

**Objective:** To compare serum neurofilament light chain (sNFL) levels in MS and healthy controls (HC) and to determine their association with measures of disease activity and their ability to predict future clinical and MRI outcomes.

**Methods:** sNFL was measured by Single Molecule Array assay in repeated serum samples from 257 MS patients (188 CIS/RMS and 69 PPMS/SPMS) and 258 HC collected as part of the international cohort study “GeneMSA” (Genetic MS Associations). Standardized clinical assessment, serum sampling and MRI were conducted yearly; median follow-up time was 6.5 (interquartile range 2.1-9.1) years. Brain volumes and volume change between baseline and years 2 and 5 were quantified by SIENA and SIENAX. Analysis was performed by linear and Poisson regression models using generalized estimating equations and Cox regression.

**Results:** sNFL was higher in CIS/RMS and in SPMS/PPMS than in HC (p< 0.001 for both after age adjustment). In a multivariable model, age (p< 0.001), EDSS (p< 0.001) and a recent relapse (< 120 days, p< 0.001) were all positively associated with sNFL concentration, while MS treatments in general were associated with lower sNFL levels (p=0.001). Similarly, sNFL levels were increased in patients with lower normalized brain volume (p< 0.001), higher number of contrast enhancing T1-weighted lesions (CEL, p< 0.001) and more new/enlarging T2-weighted lesions (T2w, p< 0.001) over time. sNFL levels above the 80th HC percentile were associated with risk of subsequent relapses (hazard ratio: 1.66 (95% CI: 1.15-2.38), p=0.006), new/enlarging T2w lesions (incidence rate ratio, IRR: 2.46 (95% CI: 1.67-3.63), p< 0.001) and CEL (IRR: 4.38 (95% CI: 2.18-8.81), p< 0.001) in the yearly follow-up scan. Finally, baseline sNFL was an independent predictor of brain atrophy rate at year 2 (p=0.035) and 5 (p< 0.001).

**Conclusion:** sNFL levels were increased in MS and correlated with concurrent and future clinical and MRI measures of disease activity and severity. Highly sensitive NFL measurements may open the option for reliable measurements of neuronal damage in real time from a fluid compartment that is readily accessible in routine clinical practice.

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Neurofilament light chain in human blood is a predictor of disease worsening in relapsing-remitting multiple sclerosis

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Objective: To assess the prognostic value of blood NfL for relapses and disability progression in patients with RRMS in a placebo-controlled phase 3 study of fingolimod (FREEDOMS).

Methods: A retrospective analysis of blood NfL levels in patients with RRMS (n=164) treated with fingolimod or placebo. Patients who consented and had 4 or 5 serial blood samples available, including baseline and month 24 samples, were selected. NfL levels at baseline were measured using Single Molecule Array (SIMOA) technology and grouped in 3 categories (low: < 30, medium: 30-60, high: >60 pg/mL; n=97, 47, 20, respectively). High and low baseline NfL categories were compared using Chi-square and Wilcoxon rank sum tests for binary outcomes, and Cox regression for time to confirmed relapse and time to 3-months confirmed disability progression (CDP).

Results: In the overall analysis population, ‘high’ compared with ‘low’ NfL levels at baseline were associated with higher MRI and clinical disease activity at Month 24: proportion of patients with new or enlarging T2 lesions (88.9% vs 54.7%, p<0.0069), average number of Gd+ lesions (0.9 vs 0.3, p=0.1165), annualised rate of brain atrophy (−1.11% vs −0.42%, p=0.0003), annual relapse rate (ARR, 0.65 vs 0.22, p=0.0011), and CDP (40.0% vs 18.6%, p=0.0365). Patients with high baseline NfL levels were at a 2.8-fold higher risk of experiencing confirmed relapses (95% CI: 1.45, 5.43; p=0.0022) and had a 3.6-fold higher risk for CDP (1.48, 8.74; p=0.0047) than patients with low baseline NfL. Fingolimod, compared with placebo, reduced the risk of relapses and disability progression (both p<0.01), in NfL-defined low- and high-risk patients. The proportion of patients with new/enlarging T2 lesions in high/low NfL groups: 80%/46% for fingolimod and 100%/64% for placebo; ARR in high/low NfL groups was 0.5/0.14 in fingolimod and 0.84/0.32 in placebo.

Conclusion: NfL in blood qualifies as a mid-term prognostic marker of future relapses and disability worsening in RRMS. Fingolimod reduced disease activity and worsening in both high and low blood NfL groups.

Disclosure

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Jens Kuhle and Harald Kropshofer contributed equally to this work.

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Methods:

In the overall analysis population, ‘high’ compared with ‘low’ NfL levels at baseline were associated with higher MRI and clinical disease activity at Month 24: proportion of patients with new or enlarging T2 lesions (88.9% vs 54.7%, p<0.0069), average number of Gd+ lesions (0.9 vs 0.3, p=0.1165), annualised rate of brain atrophy (−1.11% vs −0.42%, p=0.0003), annual relapse rate (ARR, 0.65 vs 0.22, p=0.0011), and CDP (40.0% vs 18.6%, p=0.0365). Patients with high baseline NfL levels were at a 2.8-fold higher risk of experiencing confirmed relapses (95% CI: 1.45, 5.43; p=0.0022) and had a 3.6-fold higher risk for CDP (1.48, 8.74; p=0.0047) than patients with low baseline NfL. Fingolimod, compared with placebo, reduced the risk of relapses and disability progression (both p<0.01), in NfL-defined low- and high-risk patients. The proportion of patients with new/enlarging T2 lesions in high/low NfL groups: 80%/46% for fingolimod and 100%/64% for placebo; ARR in high/low NfL groups was 0.5/0.14 in fingolimod and 0.84/0.32 in placebo.

Conclusion: NfL in blood qualifies as a mid-term prognostic marker of future relapses and disability worsening in RRMS. Fingolimod reduced disease activity and worsening in both high and low blood NfL groups.

Disclosure

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P638 Intrathecal B-cell inflammation influences CSF macrophage activity and the degree of cortical pathology in multiple sclerosis

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Introduction: Diffuse meningeal inflammation in cerebral sulci of MS patients, particularly rich in B-cell infiltrates, was found associated with a gradient of microglia activation in the adjacent grey matter (GM). It was suggested that molecules released by meningeal infiltrates within the cerebrospinal fluid (CSF) may influence the gradient of cortical pathology, but currently the underlying cellular and molecular mechanisms remain poorly understood.

Aims: In order to understand how intrathecal inflammation mediates differential GM macrophage activity, we analysed the correlation between meningeal/CSF B-cell-related inflammation, microglia/macrophage activity and GM pathology. Neuro-pathological study of meninges and GM of 30 post-mortem SPMS and 10 control cases was performed. In addition, combined CSF proteomic analysis and 3D double inversion recovery MRI imaging at 3T of 60 MS patients and 20 individuals with non-inflammatory neurological conditions has been performed at time of diagnosis.

Results: High level of meningeal inflammation and GM lesion (GML) in post-mortem SPMS cases was found associated with preponderance of CD163+ and CD68+ cells in the meningeal infiltrates and in the adjacent external cortical layers; opposite prevalence of CD14+ cells have been detected in the meninges and GM of SPMS cases with low level of meningeal inflammation and GML. High protein CSF levels of B-cell mediators, including CXCL13, CXCL12, BAFF, IL6, IL10, GM-CSF and TNF, were strongly linked to the high number and volume of GML in a subgroup (56.25%) of MS patients at time of diagnosis. Elevated protein levels of sCD163 found in the CSF of the same MS subgroup correlated (p<0.001) with the correspondent levels of BAFF (r=0.4), IL10 (r=0.5), CXCL13 (r=0.5), CXCL12 (r=0.5) and TNF (r=0.5). Furthermore, CSF sCD163 levels correlated (r=0.4; p=0.004) with the CSF levels of free hemoglobin in the same MS patients. Conversely, increased sCD14 levels were detected in CSF of MS patients with lower GML load and correlated (r=0.5, p=0.0006) with high protein levels of IFN-α2.

Conclusions: Intrathecal B-cell activity may play a key role in GML in MS by influencing different intracerebral macrophage activity in a subgroup of MS patients at the diagnosis. Combined CSF analysis of sCD14/sCD163/hemoglobin, B-cell biomarkers and MRI profiling may represent a potential tool to predict and monitor intrathecal inflammation and cortical pathology early in the disease.

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P639 MS treatment effects on plasma cytokine receptor levels

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Genetic variants within some cytokine receptor genes have been associated with multiple sclerosis (MS) susceptibility, including interleukin 7 receptor (IL7RA) and interleukin 2 receptor alpha (II2RA). As these genes are expressed by cells targeted by immune-modulatory drugs, we explored the potential role of their gene products as biomarkers in monitoring MS treatment. Here we specifically assessed the impact of natalizumab and fingolimod on the intra-individual changes of soluble protein levels of sIL-7Ra and sIL-2Ra. In addition, we included protein levels of soluble interleukin-6 receptor (sIL6R) and the soluble glycoprotein 130 (sgp130) in the study. Analysis of serial plasma samples from patients during natalizumab and subsequent fingolimod treatment revealed a decline in the plasma levels of sgp130 and sIL-7Ra. In addition, we included protein levels of soluble interleukin-6 receptor (sIL6R) and the soluble glycoprotein 130 (sgp130) in the study. Analysis of serial plasma samples from patients during natalizumab and subsequent fingolimod treatment revealed a decline in the plasma levels of sgp130 and sIL-7Ra during natalizumab treatment (P= 0.009 and 0.006, respectively). During fingolimod treatment the plasma levels of sIL-2Ra declined while sgp130 and sIL-7Ra increased (P= 6x10-11, 2.2x10-5 and 8x10-4, respectively). We replicated the previous observation that patients with the MS associated genotype of rs6897932 in the IL7RA gene have higher plasma levels of sIL-7Ra. Furthermore, the plasma levels of sIL-7Ra during fingolimod treatment were increasing significantly more in patients homozygous for the MS risk genotype than in patients from the other genotype groups (P=0.0007). In addition, we observed a protein quantitative trait locus effect of the MS associated SNP rs71624119 on the levels of sgp130. Monitoring the changes in the plasma levels of these soluble cytokine receptors...
in a well-defined cohort of MS patients during treatments will determine the possibility of using these proteins as biomarkers for treatment response. By exploring the MS associated risk variants in the context of clinical information one may elucidate the pharmacodynamics of treatments with the eventual aim to identify biomarkers for MS outcomes.

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Serum neurofilament light chain as a biomarker for acute and chronic neuronal damage in early relapsing-remitting multiple sclerosis
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Background: Monitoring of acute and chronic axonal damage remains one of the main challenges in early relapsing-remitting multiple sclerosis (RRMS) patients. Upon axonal damage, neurofilament-a major component of the neuro-axonal cytoskeleton- is released into the cerebrospinal fluid (CSF) and subsequently the peripheral blood. Serum neurofilament light chain (sNfL) was recently suggested as a novel biomarker for MS patients according to first observations in small patient groups.

Objective: To investigate the relevance of sNfL for acute and chronic neuronal damage in early RRMS and evaluate its potential as a biomarker.

Methods: 74 patients with early MS were investigated. Serum NfL was determined in 63 therapy naïve patients with recently diagnosed clinically isolated syndrome (CIS) or RRMS by Single Molecule Array technology; standardized 3 tesla MRI protocol was also performed at baseline. Of these 63 patients, 42 had 1-3 consecutive standardized MRI follow-ups (6-37 months). Brain parenchymal atrophy was calculated and correlated with baseline sNfL. Correlation between sNfL levels and gadolinium (Gd)-enhancing lesions was evaluated in all 74 patients.

Results: Median sNfL level in the therapy-naïve cohort at baseline was 36.3 pg/ml. Baseline sNfL correlated significantly with T2 lesion volume (r = 0.555, p < 0.0001). There was no correlation between baseline sNfL and disease duration, EDSS score or other MRI measurements (white matter volume, grey matter volume, brain parenchyma and total volume). However, brain parenchymal volume decreased more rapidly in patients with higher baseline sNfL (r = -0.623; p = 0.0004). In patients with Gd-enhancing lesions at baseline, sNfL levels were 63.2 pg/ml versus 28.1 pg/ml in patients without acute inflammation (p < 0.0001). There was a positive correlation between the number of Gd-enhancing lesions and sNfL levels (r² = 0.64). Initiation of disease-modifying treatment lead to a significant decrease in sNfL levels (p = 0.045).

Conclusion: Serum NfL indicates acute inflammation as demonstrated by correlation with Gd+ lesions. Moreover, it is a promising biomarker to predict acute neuro-axonal damage in early RRMS patients, since higher baseline sNfL levels predicted future brain atrophy within 3 years. Prospective studies with standardized MRI protocols in larger early MS cohorts are needed for further validation.

Disclosure
Anna Glaser: nothing to disclose.
Clinical measures included the Multiple Sclerosis Functional Composite (MSFC), evaluated at baseline and 6, 12, and 24 month follow-up evaluations. A hierarchical multiple linear regression analysis was performed to assess the relationship among baseline T2 hyperintense and Gd-enhancing lesion number, GMF, cerebellar GM volume and clinical disability at baseline and follow-ups, adjusted for age, gender, disease duration and acquisition center.

**Results:** The regression model including T2 and Gd-enhancing lesion number, GMF and cerebellar GM volume, significantly correlated with the clinical impairment at baseline ($R^2 = 0.17, p = 0.02$), and predicted subsequent impairment 6 ($R^2 = 0.26, p = 0.001$), 12 ($R^2 = 0.27, p = 0.002$) and 24 months ($R^2 = 0.24, p = 0.01$), with cerebellar volume being an independent predictor of MSFC at all time points (respectively, Beta = 0.32, p = 0.009; Beta = 0.37, p = 0.002; Beta = 0.26, p = 0.03; Beta = 0.31, p = 0.03).

**Conclusions:** These preliminary results suggest that cerebellar volume is an independent predictor of short- and longer-term clinical disability in MS patients as measured by MSFC. The study is ongoing and results from the entire trial population will be presented.

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**Serum exosomes expression of myelin proteins is a biomarker of the multiple sclerosis activity**

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In keeping with increasing evidence that cell-to-cell communication may be mediated by exosomes, we have investigated serum exosomes for the presence of myelin proteins outside the central nervous system. We studied 40 patients with relapsing-remitting multiple sclerosis (RRMS), 25 secondary progressive multiple sclerosis (SPMS) and 40 control. With the polymer formulation method, exosomes were isolated from sera and CSF and from peripheral blood mononuclear cell (PBMC) cultures. Exosome size, concentration, marker and CNS myelin protein content were measured by a nanoparticle tracking analysis method, enzyme-linked immunosorbent assays and Western blot. Exosomes of similar size were found in sera from all groups with a trend for higher frequency in multiple sclerosis patients. Exosomes from multiple sclerosis patients and controls displayed the three major myelin proteins, myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein (MOG). The serum and CSF exosomal content of MOG strongly correlated with disease activity and was highest in RRMS and SPMS patients. The sera exosomes induced proliferation of MOG - T cell receptor (TCR) transgenic T cells thus confirming that serum exosomal MOG maintained its immunogenicity. To exclude the generation of MOG-containing exosomes in the peripheral immune system we examined exosomes from PBMC and showed that they did not express myelin proteins. These data provide compelling evidence that exosomes outside the CNS compartment express myelin peptides and exosomal MOG, the presence of which correlated strongly with disease activity. Thus, exosomes might enhance and/or perpetuate anti-myelin immune reactions in multiple sclerosis and may provide a novel marker of disease activity.

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Intrathecal immunoglobulin synthesis as a predictive marker for disability progression in multiple sclerosis

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Serum and CSF levels of immunoglobulins were evaluated in 40 multiple sclerosis (36 RRMS, 4 SPMS) patients and 40 controls. An increased CSF IgG index was observed in RRMS and SPMS patients, whereas an increased CSF IgA index occurred in RRMS only. A lower CSF IgG index was associated with a more severe disability. Moreover, a significantly higher IgG index was observed in patients with an annualized relapse rate (ARR) of at least 1.0 when compared to patients with an ARR of less than 1.0. Moreover, CSF IgG index correlated negatively with the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) scores. These preliminary results suggest that intrathecal immunoglobulin synthesis may be a predictive marker for disability progression in multiple sclerosis.

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Introduction: Course, progression of disability and response to treatment are highly variable in multiple sclerosis (MS). Several cerebrospinal fluid (CSF) parameters have been suggested as possible prognostic markers to predict disease activity and progression. Intrathecal immunoglobulin (IG) synthesis is frequently seen in patients with MS and clinically isolated syndrome (CIS) and may reflect the extent of humoral immune response in the CNS. The aim of this study was to investigate the association between intrathecal IG synthesis and EDSS progression in the national German MS cohort, a large prospective cohort of patients with newly diagnosed relapsing remitting MS (RRMS) or CIS.

Methods: 375 CIS and RRMS patients from the national German MS cohort with available detailed CSF data and a clinical follow-up over two years were included in the analysis. The association between intrathecal IG synthesis (synthesis of at least one of the IG subclasses IgG, IgA and IgM) and risk of expanded disability status scale (EDSS) progression within two years was tested by binomial regression with adjustments made for age and sex. Additionally, Kaplan-Meier analysis with a log-rank test was used to assess intrathecal IG synthesis as a prognostic factor for time to EDSS progression.

Results: The presence of intrathecal IG synthesis was significantly associated with higher risk of EDSS progression within two years (p=0.01). This effect was even more pronounced for patients who had not been treated with disease modifying drugs (p=8E-3). Additionally, intrathecal IG synthesis was associated with a shorter time to EDSS progression (p=0.035). Subanalyses showed that the effect was mainly driven by intrathecal IgG synthesis.

Conclusion: In this study newly diagnosed MS or CIS patients with intrathecal IG synthesis had a higher risk of and shorter times to EDSS progression within two years. This demonstrates a potential predictive value of a standard CSF parameter for disease progression in MS. Follow-up studies will address whether CSF parameters also predict long-term outcome in newly diagnosed CIS and MS patients.

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**P644**

Decreased cerebrospinal fluid antioxidative capacity is associated with disease severity and progression in early multiple sclerosis

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**Introduction:** Oxidative stress (OS) is a major feature of multiple sclerosis (MS) and promotes damage to proteins, lipids and DNA, and finally neuronal death. OS induced toxic effects may be limited by the antioxidative capacity (AOC) in body fluids, which acts as an important defence mechanism. An imbalance of OS and AOC may therefore facilitate tissue damage in MS. Various reactive oxidative species have been investigated so far; however, the relation of AOC in body fluids to clinical outcome measures in MS remains inconclusive.

**Objective:** To compare AOC in serum and cerebrospinal fluid (CSF) between MS patients and controls, and assess its relation with clinical measures in MS.

**Methods:** We included patients with a clinically isolated syndrome (CIS) or MS (n=57/13; 68.6% female; age median 32.3, IQR 26.6-40.0 years; disease duration median 0.5, IQR 0.3-4.9 months; Expanded Disability Status Scale (EDSS) score median 1.5, IQR 0.0-3.0) and controls with other non-inflammatory neurological diseases (n=67; 67.2% female; age median 32.7, IQR 25.2-44.9 years). All subjects underwent diagnostic CSF and serum sampling. AOC was determined for all CSF/serum samples with dihydrorhodamine dihydrochloride (AAPH) induced oxidation of dihydrorhodamine, and finally neuronal death. OS induced toxic effects may be limited by the antioxidative capacity (AOC) in body fluids, which acts as an important defence mechanism. An imbalance of OS and AOC may therefore facilitate tissue damage in MS. Various reactive oxidative species have been investigated so far; however, the relation of AOC in body fluids to clinical outcome measures in MS remains inconclusive.

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**Objective:** To compare AOC in serum and cerebrospinal fluid (CSF) between MS patients and controls, and assess its relation with clinical measures in MS.
higher EDSS (≥3, n=19) vs. EDSS < 3 (p=0.001) or controls (p=0.01). CSF AOC was further negatively correlated with EDSS at time of sampling (clinically active (r=−0.4, p=0.003) and non-active patients (r=−0.6, p=0.001)). CIS patients who later converted to clinically definite MS (n=16) had lower CSF AOC compared to non-converters (n=41) (p=0.01).

**Conclusion:** Decreased CSF AOC is associated with disease activity and progression in MS patients. The AOC thus seems to be a critical factor to counteract MS pathology. Further research is warranted to investigate the potential role of AOC as a treatment target in MS.

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**Objective:** To prospectively assess the development of olfactory function in multiple sclerosis over time and its correlation with occurrence of relapse and disability progression.

**Methods:** In this prospective, 3-year longitudinal study on 151 MS patients and 30 healthy controls, three different qualities of olfactory function (threshold, discrimination and identification) were quantified using the Sniffin’ Sticks test. The influence of occurrence of relapses and expanded disability status scale (EDSS) on olfactory function was analyzed at different time-points. We conducted a multivariate logistic regression model including baseline covariates (age, sex, disease duration, EDSS, cognitive dysfunction and disease modifying treatment) to assess the association between olfactory function at baseline and occurrence of relapse and EDSS progression.

**Results:** Odor discrimination and identification capability significantly worsened over three years in MS patients, while olfactory threshold did not. Threshold was markedly impaired in patients with relapse activity within 12 months, recovered in the absence of relapse and was associated with a 2.5-fold increased risk of relapse within three years when measured at baseline. Deterioration of discrimination and identification was irreversible and was both strongly associated with and predictive of EDSS progression.

**Conclusions:** Olfactory function changes over time in MS. Impairment of threshold is transient and a predictor of inflammatory disease activity, while odor identification and discrimination are associated with disability progression. Olfactory dysfunction might be a useful and easily obtainable parameter to monitor patients with regard to inflammation and neurodegeneration in MS.

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**P646**

**Multiple sclerosis: structure-function correlations in the cerebral cortex**

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**Background:** Cortical grey matter (GM) atrophy correlates with worsening physical and cognitive disability in patients with relapsing-remitting multiple sclerosis (RRMS). While transcranial magnetic stimulation (TMS) provides evidence of cortical dysfunction in patients with motor disability and progressive MS,
this technique has not been explored extensively in patients with RRMS.

**Objective:** To perform cortical structure-function correlations in a cohort of real-world patients with RRMS.

**Methods:** Sixteen RRMS patients were prospectively recruited. Magnetic resonance imaging (MRI), threshold tracking-TMS (TT-TMS), neuropsychological testing (Minimal Assessment of Cognitive Function in MS [MACFIMS]) and clinical assessment (including the Expanded Disability Status Scale [EDSS]) were performed. Lesion masks were semi-automatically delineated with JIM and volumetrics obtained using Freesurfer. The worse affected hemisphere (defined as larger T2 lesion volume) was used for comparisons. Pearson correlations were used to compare cortical structure and function measures, and the Benjamin-Hochberg procedure applied for multiple comparisons.

**Results:** The cohort was mostly female (11 female, 5 male) with mean age (SD) 42.83(10.74) years, mean disease duration 5.96(5.16) years and mean EDSS 2.25(1.45). Statistical significance was considered at p < 0.05 (corrected for age, disease duration and multiple comparisons). Normalised brain volume (NBV) significantly correlated with normalised cortical GM (cGM) volume (r=-0.959) and cGM thickness (r=-0.869); normalised cGM volume and cGM thickness correlated significantly (r=0.842). Resting motor threshold (RMT) negatively correlated with NBV (r=-0.838) and normalised cGM volume (r=-0.828).

No significant correlations were found between brain volumetric data (NBV, normalised cGM volume, cGM thickness) and other measures, including T2 lesion volume, paired-pulse TMS variables, EDSS, and components of the MACFIMS cognitive battery.

**Conclusions:** Strong negative correlations between resting motor threshold and normalised cortical GM volume link cortical structure and function in this real-world RRMS patient cohort. Furthermore, the correlation of RMT with NBV; and between cortical GM and NBV, supports further investigation of threshold tracking-TMS as a potential biomarker of neurodegeneration in RRMS.

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**P647**

**Conduction velocity in demyelinated cerebral white matter: a structure-function correlation study in optic radiation**

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**Introduction:** Functional impairment in MS reflects a composite of white matter (WM) and grey matter (GM) damage. Estimation of axonal conduction velocity (ACV) within demyelinated white matter (WM) lesions could be used to elucidate the relative contribution of focal structural pathology within WM bundles in the CNS. While an ACV of approximately 2.72mm/ms has been reported in brainstem MS lesions1, cerebral WM tracts have not been similarly interrogated. We used a combination of MRI and multi-focal visual evoked potentials (mVEP) to probe the impact of focal WM pathology on visual pathway function in patients with MS.

**Objective:** To estimate the ACV in demyelinated segments of the optic radiation (OR) in vivo.

**Methods:** Fifty patients with RRMS were enrolled in the study. mVEP recording from eyes without a clinical history of optic neuritis (ON) were included, and analyzed for each visual hemifield, corresponding to left and right ORs. 3DT1, FLAIR and 64-dir dMRI were acquired with a 3.0T MRI scanner. ORs were delineated using probabilistic tractography and lesion length along each OR computed. Patients without lesions in both ORs or with active gadolinium-enhancing lesions (GELs) in either OR were excluded. The onset latency differences (Δτ) and corresponding lesion length differences (Δλ) between visual hemifields were modelled with linear regression, and the absolute ACV calculated based on Δτ/Δλ= 1/ACV lesion -1/ACVnormal, where ACVnormal was assumed starting at approximately 32mm/ms.

**Results:** Twenty patients remained in the study after excluding those with bilateral ON, OR Ga+ lesions, and those without OR lesions on either side. Linear regression predicted lesion length difference between left and right OR based on the onset latency differences (F(1,19)=12.44, p=0.002, R2=0.40). ACV lesion were estimated at approximately 1.70 mm/ms.

**Conclusion:** The estimation of ACV lesion ~ 1.70 mm/ms in demyelinated OR aligns with the ACV previously reported in the demyelinated medial longitudinal fasciculus; and represents a composite MRI-mVEP biomarker that discerns the relative contribution of WM and GM pathology to functional impairment in MS.


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**P649**
Single-cell mRNA marker analysis reveals appearance of t-SNE-defined new B-cell clusters in cynomolgus monkeys in response to ofatumumab treatment

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**Background:** Ofatumumab is the first fully human, highly potent and subcutaneously (s.c.) administered anti-CD20 monoclonal antibody in development for MS. A Phase 2b dose-finding study demonstrated high MRI efficacy and helped to identify an optimal dose for the ongoing Phase 3 trials. An effective depletion of B cells was observed in cynomolgus monkeys treated s.c. with ofatumumab. Here, we analysed single-cell mRNA expression and applied machine learning algorithm to determine the effect of ofatumumab treatment on mRNA expression patterns in B cells isolated from lymph nodes.

**Objective:** To identify novel anti-CD20 therapy markers in response to ofatumumab treatment in cynomolgus monkeys by using single-cell genomics technology.

**Methods:** Cynomolgus monkeys received human equivalent doses of ofatumumab (1mg/kg, s.c.) on Days 0, 7 and 14. Axillary lymph node biopsies were collected at various time points until Day 90. Single-cell mRNA analysis was performed on fluorescence-activated cell-sorted CD20+ B cells. The mRNA expression patterns were analysed with machine learning algorithms (t-distributed stochastic neighbor embedding [t-SNE]), which enables the similarity of cells to be expressed by the proximity of dots in a 2-D graph. A set of 96 detectable lymphocyte RNA markers was selected to generate clusters of related B cells.

**Results:** In cynomolgus monkeys, s.c. injection of low-dose ofatumumab induced a strong depletion of B cells from Days 2-21, followed by a repletion starting 2 weeks after the last injection. Single-cell analysis of mRNA marker expression in 595 isolated CD20+ cells showed five t-SNE-defined cell clusters in untreated monkeys. Ofatumumab induced a new cell cluster and strongly enhanced a second cluster found at baseline. Upon repletion both clusters diminished, approaching cluster properties similar to baseline. No control markers such as CD4 or CD28 were detected in any of the six clusters. Cells in the new cluster expressed mRNA markers linked to the cell cycle/proliferation, such as CBX2, cyclin E1, cyclin A, AURKA, MK167 and FFM2, which were not expressed by the other clusters.

A more refined cluster analysis is under way.

**Conclusions:** Single-cell mRNA expression analysis in small-size samples is a new approach for identifying B-cell subsets, independent of known marker sets. Transcriptional expression analysis in MS and animal models may improve our molecular understanding of ofatumumab treatment effects on B-cell subsets and their role.

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**P650**
The neutrophil-to-lymphocyte ratio is associated with multiple sclerosis

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**Background:** Subtypes of white blood cell counts are known biomarkers of systemic inflammation. A high neutrophil-to-lymphocyte ratio (NLR) is a possible predictor of systemic inflammation in several diseases and a predictor of disease course. Only two previous studies have investigated NLR in MS patients. C-reactive protein (CRP) has also been examined as a predictor of disease course in MS patients, but the results are conflicting.

**Objective:** To examine the differences in levels of NLR between MS patients and healthy controls (HC). Furthermore to assess if levels of NLR or C-reactive protein (CRP) in MS patients correlate with MS severity score (MSSS) at start of first treatment.

**Methods:** This was a retrospective investigation of 746 Danish relapsing-remitting MS (RRMS) patients and 5231 healthy Danish blood donor controls. Information on patient NLR was obtained just before commencement of their very first disease modifying treatment (DMT). Blood samples from the controls were collected at the Danish Blood Donor Study. Clinical information regarding date of first treatment was obtained from the Danish Multiple Sclerosis Register. Information about BMI and smoking was obtained from a comprehensive lifestyle and environmental questionnaire. We investigated the association between NLR and MS by binary logistic regression with MS status as response variable and logarithmic transformed NLR as explanatory variable with adjustment for baseline variables and smoking (regular smoker vs. not). Using linear regression we examined the correlation between log-NLR and MSSS and between CRP and MSSS with age on onset of MS, sex, smoking status and BMI as covariates.
**Results:** The mean NLR was 2.45 for patients and 1.85 for controls (p < 0.0001). The binary logistic regression analysis of logarithmic transformed NLR, when controlling for sex, year of birth, BMI, and smoking showed highly significant effect of log-NLR (p < 0.001) with an odds-ratio (OR) of 3.34, which corresponds to an OR of 2.45 for each doubling of NLR. MSSS proved to be weakly although statistically significantly associated with log-NLR (r²=0.09; p = 0.039). CRP was not associated with MSSS (p = 0.58).

**Conclusion:** Based on investigation of NLR, we found that patients with early MS, just before their very first DMT, have increased systemic inflammation, compared to controls, and that NLR was weakly correlated with MSSS. These results are in line with previous findings from studies on NLR in MS.

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Finn Sellebjerg has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva; has been on the steering committee of a clinical trial sponsored by Merck Serono, and served as consultant for Biogen Idec and Novo Nordisk; has received support for congress participation from Biogen Idec, Novartis, Sanofi Aventis and Teva; has received speaker honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Schering-Plough.

Annette Bang Oturai has served on scientific advisory boards for Biogen and Genzyme; has received support for congress participation from Biogen, Novartis, Genzyme, and TEVA; has received speaker honoraria from, Biogen, Novartis, and TEVA.

**P651**

**Delay-release dimethyl fumarate demonstrated no evidence of difference in clinical outcomes vs fingolimod in patients with RRMS: a propensity-matched comparative effectiveness analysis of the German NeuroTransData registry**

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**Background:** There are no head-to-head, randomized controlled trials comparing the efficacy of delay-release dimethyl fumarate (DMF) vs fingolimod (FTY) in patients with relapsing-remitting multiple sclerosis (RRMS).

**Objective:** To assess the comparative effectiveness of patients initiating DMF vs FTY in a pair-wise propensity-score matched (PSM) cohort from the NeuroTransData (NTD) MS registry, a German network >130 practice-based neurologists and including >25,000 out-patients with RRMS. Patients meeting either the EU fingolimod label patient population (EUF) or an all-comer population (ALL) were assessed for the primary outcome of time to first relapse (TTFR) and secondary outcomes of annualized relapse rate (ARR), time to treatment discontinuation (TTD) and time to 3- and 6-month expanded disability status score (EDSS) confirmed disability progression (TTCDP3, TTCDP6).

**Methods:** Data were sourced from the NTD MS registry on 01 October 2016, including patients with RRMS aged ≥18 years at therapy initiation with ≥1 relapse or EDSS assessment on-therapy. The EUF population required 1 relapse on prior treatment with interferons, glatiramer acetate or teriflunomide. DMF patients were matched to FTY ALL and EUF patients respectively using 1:1 pair-wise PSM. TTFR, TTD, TTCDP3, and TTCDP6 were analyzed using a Kaplan-Meier approach and Cox marginal regression model. ARR was analyzed using a GEE Poisson regression model. The clustered nature of the matched design was taken into account. Non-pairwise censoring was applied.

**Results:** DMF patients were 1:1 matched to FTY ALL (n=457) and FTY EUF (n=99) patients. In the ALL population, >77% had ≥1 prior disease-modifying therapy, whereas 100% of the EUF population were pre-treated. There was no evidence of difference in TTFR between DMF vs FTY ALL (Hazard Ratio [HR] 0.91; 95% confidence interval [CI] 0.68, 1.22; p=0.5316) and FTY EUF (HR 1.10; 95% CI 0.66, 1.85; p=0.714). Consistent results were observed for ARR, TTCDP3, and TTCDP6. FTY ALL and FTY EUF patients had significantly longer TTD vs DMF: HR 1.76; 95% CI 1.34, 2.31; p< 0.0001 and HR 3.31; 95% CI 1.75, 6.24; p=0.0002, respectively.

**Conclusions:** In the German NTD registry of patients with RRMS, PSM analyses of DMF vs FTY revealed no evidence of difference across all clinical effectiveness outcomes assessed, however, patients on FTY had a significantly longer time to TTD compared to DMF in the ALL and EUF populations

**Disclosure**

Braune S, Bergmann A and most of the members of NTD study group receive royalties from many pharmaceutical companies for participation in clinical trials, lecturing, consultancy. For this NeuroTransData own project there is no conflict of interest.

van Hövell P, Grimm S are fulltime employees of PwC and have no conflict of interest.

Hyde R and Freudensprung U are fulltime employees and stockholders in Biogen.

**P652**

**Sustained disease remission in multiple sclerosis after autologous haematopoietic stem cell transplantation. The Italian experience**

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Background: Despite the advent of new highly-active therapies for multiple sclerosis (MS), long-term disease remission remains elusive and only a small percentage of patients achieves the so-called no evidence of disease activity (NEDA) status. This is particularly relevant for patients with aggressive MS with suboptimal response to conventional treatment. Against this scenario, autologous haematopoietic stem cell transplantation (AH SCT) has recently demonstrated the potential to maintain long-term disease remission in aggressive MS patients.

Objective: To evaluate the long-term outcomes of a large multicenter cohort of aggressive MS patients treated with AH SCT.

Methods: Data were obtained in a multicenter, observational, retrospective cohort study including patients treated with AH SCT with the same conditioning regimens in Italy from 1996 to 2016. EDSS progression was defined as 1 EDSS point increase (0.5 if baseline EDSS≥5.5) confirmed at 6 months. Demographic, disease-related and treatment-related data and reports of adverse events were collected.

Results: 122 consecutive MS patients were included, with a median follow-up of 4.7 years (range, 0.5-17 years), 59% of patients had relapsing-remitting (RR) MS. The median EDSS score was 5 (range 1-8.5) 1 year before AH SCT and 6 (range 1-9) at AH SCT. One death (0.8%) was reported within 100 days of transplant. Stem cell were mobilized with cyclophosphamide and G-CSF; 102 patients (84%) were conditioned with carmustine- etoposide-melphalan (BEAM) plus anti-thymocyte globulin (ATG) whilst 20 patients (16%) with cyclophosphamide plus ATG. Only patients who underwent the BEAM protocol were included in the long-term analysis. The 5-year probability of progression-free survival were 91% for RRMS and 62% for SPMS respectively (p=0.001). NEDA status (defined as no relapses, no EDSS progression and no MRI activity) at 5 year was maintained by 72% of RRMS patients and by 55% of SPMS patients (p=0.07).

Conclusion: Our data demonstrate that AH SCT is reasonably safe and extremely effective for inducing long-term disease remission in aggressive MS patients.

Disclosure

GB, DC, EC, FG, MC, MLR, MDG, CI, AM, BC, AB have nothing to disclose.

MPS: MPS received consulting fees from TEVA, Biogen, Merck Serono, Genzyme, Roche, GeNeuro, Novartis, Medday.

GLM: GLM has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Sanofi Aventis, Teva, Genzyme, and Merck Serono Pharmaceuticals.

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P653 Naturally or induced immunization against CCL20 confer protection against experimental autoimmune encephalomyelitis

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Objective: The study the effect of immunization against CCL20 in EAE and MS.

Background: Th-17 type immune response was implicated in the pathogenesis of MS and is linked to chemokine receptor CCR6 and its ligand CCL20. The CCR6-CCL20 axis was found to be important in introduction of inflammation into the CNS via the choroid plexus.

Design and Methods: EAE was induced with MOG35-55 in C57BL/6 mice, in CCR6 +/- mice, in mice that were pre-immunized with hCCL20 or were adoptively transferred with sera from immunized mice with hCCL20 and the severity of EAE was studied. Production of anti-CCL20 was induced by immunization of Balbc/c mice against CCL20. Levels of anti- CCL20 studied in sera of MS patients and healthy controls (HC) - tested by ELISA.

Results: EAE severity was reduced by up to 70% with a significantly reduced accumulating score (AS) in CCR6+/- mice with EAE vs. wild type mice with EAE (p< 0.001). Vaccinating of mice with human CCL20, but not with mouse CCL20, produced autoantibodies against murine CCL20, and protects mice against MOG 35-55 induced EAE (AS = 2.2 vs. 89.6, p< 0.001). Protective effect was LV adoptively transferred with sera from hCCL20 immunized mice to non-immunized mice (AS=36.8, p=0.019).
Anti mCCL20 levels were negatively correlated with degree EAE severity (R2=0.7667). Using bioinformatics search, we identified a novel peptide sequence - LQDYTDRI, comprising an epitope conserved among bacterial capsular outer membrane protein A (ompA) containing homologic sequence with hCCL20. Pre-immunization with ompA or with the LQDYTDRI peptide ameliorated EAE vs. control EAE (AS=25.2 and 31.2 vs. 42.9; p=0.03 and 0.04, respectively). We found a significantly lower levels of anti CCL20 in sera of 103 relapsing remitting MS patients (0.22±0.03 O.D405 vs. 44 matched HC (0.43±0.08 O.D405, p=0.016).

Conclusions: Naturally or induction blockade of CCL20 may confer protection against autoimmune disease such as MS, probably by preventing the trafficking of Th17 CCR6+ cells to the central nervous system. Active or passive immunization against CCL20 may confer protection against MS.

Disclosure
Dr. Karni, Dr. Abraham, Dr. Fainberg, Dr. Weiss and Dr. Peled have noting to disclose.

P654
Ocrelizumab reduces disability progression independent of relapse activity in patients with relapsing multiple sclerosis

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Background: Ocrelizumab (OCR) showed superior efficacy vs interferon beta-1a (IFNβ1a) in the Phase III OPERA I and OPERA II trials in relapsing multiple sclerosis (RMS). Confirmed disability progression (CDP) based on a composite of the Expanded Disability Status Scale (EDSS), timed 25-foot walk (T25FW) and 9-hole peg test (9HPT) may better characterise aspects of disability progression, such as ambulation and hand/arm function, than EDSS alone and has improved sensitivity for assessing progression in secondary progressive multiple sclerosis (SPMS).

Objective: To assess OCR vs IFNβ1a on composite CDP independent of relapse activity (CCDP-IRA) in patients with RMS.

Methods: RMS patients, including SPMS patients with relapses, in OPERA I and OPERA II (NCT01247324/NCT01412333) received OCR 600 mg IV q24w or IFNβ1a 44 μg SC tw over 96 weeks. CDP was defined as disability progression measured by EDSS (increase of ≥1.0 or 0.5 if baseline >5.5) or ≥20% increase in T25FW or ≥20% increase in 9HPT confirmed after ≥12 or ≥24 weeks. For Definition 1 of CCDP-IRA the reference EDSS/T25FW/9HPT was re-baselined at first available assessment ≥30 days after each relapse and no relapse should occur between baseline and initial disability progression (IDP), as well as within 30 days after IDP and 30 days prior to IDP confirmation. Definition 2 included a period of no relapse for 30 days after IDP confirmation. A subgroup analysis included patients at potentially higher risk of SPMS based on baseline EDSS ≥4.0 and pyramidal Kurtzke Functional Systems Score ≥2.

Results: In the pooled intention-to-treat (ITT) cohort (N=1,656), the risk reduction (RR; OCR vs IFNβ1a) for 12- and 24-week CDP was 34% (30.7% vs 21.5%; p<0.001) and 31% (22.6% vs 16.1%; p=0.002). The 12- and 24-week CCDP-IRA RRs for Definition 1 were 24% (25.4% vs 19.6%; p=0.010) and 22% (19.2% vs 14.9%; p=0.046); and for Definition 2 were 25% (25.4% vs 19.5%; p=0.008) and 23% (19.2% vs 14.8%; p=0.039). In the subgroup at higher risk of SPMS, 12- and 24-week RRs for CCDP-IRA (Definition 2) were 40% (31.2% vs 19.1%; p=0.022) and 36% (26.9% vs 16.6%; p=0.064). All components of CCDP-IRA in the ITT and subgroups followed similar trends.

Conclusions: The results show that considerable disability progression in RMS occurs independently of protocol-defined relapses. Ocrelizumab significantly reduced this progression vs IFNβ1a in the OPERA ITT population of RMS patients and more so in the subgroup at higher risk of SPMS.

Disclosure
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F. Lublin reports personal fees for consulting from Actelion, Almirall, Biogen, Canbex Therapeutics, Five Prime Therapeutics, Genzyme, GSK, GW Pharma, Merck, Merck Serono, Mitsubishi, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; licence fees for Neurostatus products; and research grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, the Novartis Research Foundation and the Roche Research Foundation. F. Lublin reports funding of research from Biogen Idec, Novartis, Novartis Research Foundation, the Novartis Research Foundation, Genentech, Merck, Mitsubishi, Novartis, Roche, Takeda and Teva Pharmaceuticals; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation.
Long-term lymphocyte counts in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets 3.5 mg/kg: total lymphocytes, B and T cell subsets

Objective: To investigate absolute lymphocyte counts up to 312 weeks and B and T cell subsets up to 240 weeks after the first administered dose of CT, in patients with RRMS receiving 2 annual courses of CT (3.5 mg/kg) followed by no further active treatment.

Methods: Data from patients randomised to CT 3.5 mg/kg over 2 years in CLARITY or CLARITY Extension including time spent in the PREMIERE registry (N=685) were pooled to provide long-term follow-up data.

Results: At baseline, median absolute lymphocyte count (ALC) was 1.86×10^9/L. During Year (Y)1, ALC reached nadir at 9 weeks post-treatment with CT 3.5 mg/kg (1.00×10^9/L) and then gradually increased. During Year (Y)2, ALC reached nadir at Week (Wk) 55 (0.81×10^9/L), recovered to the normal range (≥1.00×10^9/L) by the end of Y2 (Wk96), and continued to increase thereafter. ALC had returned to the normal range in 75% of patients by Wk144. Median CD8+ lymphocytes at baseline were 378 cells/µL. CD8+ reached Y1 nadir at Wk16 (239 cells/µL), then gradually increased, and Y2 nadir was reached at Wk72 (232 cells/µL). CD8+ recovered quickly after treatment and never dropped below the threshold of 200 cells/µL at any time in the 240-week observation period. Median CD19+ lymphocytes were 205 cells/µL at baseline. After Y1 treatment, CD19+ reached nadir at Wk9 (18 cells/µL) and after Y2 treatment at Wk52 (31 cells/µL). CD19+ then gradually recovered, reaching the threshold of 100 cells/µL by the end of Y2 (Wk96), continuing to improve thereafter.

Conclusion: Lymphocyte recovery begins soon after CT treatment, with ALC, CD19+ B cells and CD4+ T cells reaching threshold values by 7.5 months, 12 months and 18 months, respectively, after the last dose in Y2. CD8+ cells never dropped below the threshold value.

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PS-S: has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme.

FD: is an employee of EMD Serono, Inc., Billerica, USA, a business of Merck KGaA, Darmstadt, Germany.

CH: is an employee of Merck KGaA, Darmstadt, Germany.

GG: has received speaker honoraria and consulting fees from Abbvie, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood.

Characterization of the efficacy of ORY-2001, a novel epigenetic drug for the treatment of multiple sclerosis, during the effector phase of the EAE model

Background: Lysine specific demethylase 1 and histone deacetylase (HDAC) 1 and 2 are histone modifying proteins involved in transcription regulation. ORY-2001, a clinical stage LSD1/M AO-B inhibitor, reduces the clinical score in a mouse model of experimental autoimmune encephalomyelitis (EAE) at doses ranging from 0.05 to 3 mg/kg. ORY-2001 reduced lymphocyte egress and infiltration of immune cells in the spinal cord, preventing demyelination. Importantly, the therapeutic effects of ORY-2001 could be achieved at doses that do not significantly affect
hematology, a common side effect in multiple sclerosis (MS) drugs, and in absence of gastro-intestinal toxicity. Interestingly, several FDA-approved drugs for MS including S1P receptor modulators and fumarates, were reported to target HDAC complexes in addition to their primary targets.

**Objectives:** To compare the mechanism of action of ORY-2001 and fingolimod in the effector phase of the EAE model.

**Methods:** Mice were immunized with MOG35-55 and treated orally during 2 weeks following onset of symptoms with 0.5 mg/kg ORY-2001 or 1 mg/kg fingolimod/day. The clinical score was assessed daily and animals were sacrificed on D17 after immunization (maximum clinical score). Spleen and lymph nodes were harvested for cell count and cytokine analysis; medulla and brain were used for gene expression (GE), cytokine and morphological analysis.

**Results:** ORY-2001 and fingolimod reduced the clinical score in the model, but ORY-2001 was more effective (60 vs 22% reduction) and/or acted faster under the described test conditions. Both compounds induced IL2 and MOG-induced cell proliferation; and increased anti-inflammatory cytokines (IL-4 and IL-10) and chemokines (IP-10 and MCP1). ORY-2001 and fingolimod increased cellularity in lymph nodes but only ORY-2001 increased it in spleen and modulated the B cell compartment, reducing the IgG2a/IgG1 ratio. GE profiling confirmed that:

- a) ORY-2001 reduced S100a9 expression in the spinal cord;
- b) considerable overlap exists between the GE profiles of ORY-2001 and fingolimod;
- c) ORY-2001 but not fingolimod induced Translthyretin (Ttr), a gene potently downregulated in a progressive EAE model; and lowered the demyelination marker Cystatin F, elevated in MS.

**Conclusion:** ORY-2001, a novel epigenetic drug finalizing a Phase I clinical trial, is a compound with distinct immune modulatory and expression profile, to be evaluated in clinical trials in multiple sclerosis.

**Disclosure**

Tamara Maes is executive director and shareholder of Oryzon Genomics S.A. and member of the ADDF Scientific Review Board.

Fernando Cavalcanti is employee of Oryzon Genomics S.A.

Elena Gonzalez-Rey has nothing to disclose.

Manuel Delgado has nothing to disclose.

Michelo Lufino is employee of Oryzon Genomics S.A.

Jordi Xaus is employee of Oryzon Genomics S.A.

Cristina Mascaró is employee of Oryzon Genomics S.A.

Carlos Buesa is executive director and shareholder of Oryzon Genomics S.A.

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**P657**

Subcutaneous low dose ofatumumab in cynomolgus monkeys induced changes in lymphocyte subsets and reversible cytoarchitectural changes in lymph nodes


Novartis Pharma AG, Basel, Switzerland

**Background:** Ofatumumab is the first fully human, subcutaneous, anti-CD20 monoclonal antibody in Phase 3 development for MS. In cynomolgus monkeys, treatment with human equivalent subcutaneous (s.c.) doses of ofatumumab resulted in potent B-cell depletion in both blood and tissues. Studies in this model allow parallel comparison of blood and tissue effects. Ongoing immunophenotyping focuses on ofatumumab mode of action.

**Objective:** To compare changes of lymphocyte subsets in blood and lymph nodes (LN) and changes in lymph node morphology and distribution of lymphocyte subsets in ofatumumab-treated cynomolgus monkeys.

**Methods:** Axillary LN and blood were collected on Days 0, 21, 62 and 90. Further tissues were collected upon termination on Day 90. Fluorescence-activated cell sorting (FACS) analysis enabled quantitation of lymphocyte subsets in blood, spleen and various LN. Morphological evaluation and quantitative imaging-based immunophenotyping of LN were performed using immunohistochemistry (IHC) or in-situ hybridisation (ISH) for individual B- and T-cell markers or imaging mass cytometry (IMC) for the detection of multiple markers on the same tissue section.

**Results:** Various subsets of B-cells were differentially affected by low dose ofatumumab s.c. in cynomolgus monkeys, while the total number of B cells was potently and rapidly reduced. Absolute numbers of marginal zone (MZ) B cells in axillary LN increased with ofatumumab treatment. All B-cell subsets in blood and tissues were BAFFR positive which may be relevant to B-cell depletion kinetics. In addition, there was a sharp decline in CD20+CD3+ T cells followed by full recovery in the treatment-free period. Preliminary IMC results confirmed that the CD8 T cells in blood and LN decreased early after treatment initiation but recovered by Day 90. At Day 21, B-cell IHC revealed depletion of the perifollicular and interfollicular area of axillary LN, while the core of CD20+CD21+ cells LN follicles was detectable. At Day 62, the perifollicular and interfollicular areas became abundantly infiltrated by CD21+ B cells. At Day 90, LN showed high expression of CD27 mRNA and a return to baseline cytoarchitecture arrangement.

**Conclusions:** Low dose s.c. ofatumumab potently depleted both B cells and CD20+ T cells in blood and LN. However, MZ B cells, a subset relevant for immune defence, were spared from depletion.

**Disclosure**

This study was funded by Novartis Pharma AG, Basel, Switzerland. All authors are employees of Novartis. Paul Smith was an employee of Novartis at the time of study conduct.

**P658**

**Rescue therapy with propionic acid reverts the pro-inflammatory effects of a high-fat-diet in neuroinflammation**


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**Background:** Previous studies have shown that a ‘western diet’, rich in salt and saturated long chain fatty acids (LCFA) enhances the pro-inflammatory immune responses in experimental autoimmune encephalomyelitis (EAE). The LCFA lauric acid (LA) leads
to an enhanced differentiation/proliferation of Th1/Th17 cells and worsened clinical course of EAE. In contrast, the short chain fatty acid propionate (PA) ameliorated EAE, via an increased Treg differentiation in the gut. This study investigated the potential therapeutic effects of PA on the course of EAE during feeding of a LA rich diet.

**Methods:** MOG-EAE was induced in C57BL/6 mice fed a normal diet (ND) or LA-rich diet starting four weeks before immunization. LA-fed mice received PA (150mM per day) or water as a control via oral gavage starting at the day of immunization. Mice were clinically evaluated; spinal cord cross section were stereologically analyzed after staining for demyelination (Luxol Fast Blue), infiltrating immune cells (CD3, Mac3), glial cells (Olig-2, NogoA, GFAP) and neurons/axons (NeuN, Bielschowsky silver staining) at the maximum of disease. Treg cells within the spinal cord and the gut were analyzed by flow cytometry (FACS).

**Results:** Mice fed a LA-diet showed a more severe EAE course compared to ND-fed mice. The deleterious clinical effect of LA diet was reversed by oral gavage of PA after immunization (mean EAE scores ± SEM: ND 4.1 ± 0.8, LA 5.7 ± 0.4, LA+PA 4.4 ± 0.5, p< 0.05, n=7-10 per group). This clinical effect was paralleled by a significantly reduced T cell infiltration (ND 289.5 ± 13.4, LA 422.5 ± 16.9, LA+PA 330 ± 13.3, p<0.001) and reduced number of macrophages in the spinal cord at the maximum of EAE. In addition, PA-treated mice showed less pronounced demyelination (ND 5.6 ± 0.8, LA 12.3 % ± 1.39, LA+PA 7.94 % ± 1.3, p< 0.05) and reduced axonal loss (ND 12.5 ± 0.3, LA 9.6 ± 0.3, LA+PA 10.7 ± 0.3, p< 0.05). Additionally, PA feeding prevented the pronounced neuronal loss on a LA-rich diet. FACS analysis further showed increased Treg frequencies in the spinal cord and the gut of PA treated mice as compared to sham-treatment (spinal cord: ND 21.7 % ± 1.2, LA 14.8 % ± 0.6, LA+PA 20.5% ± 0.3, p< 0.01).

**Conclusion:** Our data confirm the beneficial effects of the potent immunomodulator PA in neuroinflammation with the potential to revert the deleterious effects of a high-fat diet. PA treatment may serve as a safe and effective immune-regulatory add-on therapy in multiple sclerosis.

**Disclosure**

JM and SI have nothing to disclose.
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**P659**

Ocrelizumab does not modulate peripheral T cell functionality or prevalence in a small subset of relapsing MS patients enrolled in OPERA I, a phase III double-blind double-dummy interferon beta-1a-controlled study

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**Rationale:** Ocrelizumab is a humanized, anti-CD20 specific, cytolytic antibody that depletes B cells, and is indicated for the treatment of relapsing and primary progressive forms of multiple sclerosis in the US. B cells modulate T cell activity through antigen presentation, cytokine production, and support secondary lymphoid organ structure. We hypothesize that global T cell activity may be altered in patients undergoing ocrelizumab therapy. The goal of these studies was to evaluate the effect of ocrelizumab treatment on peripheral blood T cell prevalence and/or function in a subset of relapsing MS patients treated with ocrelizumab and enrolled in the OPERA I study at the University of California, San Francisco (UCSF).

**Methods:** A novel mass cytometry (CyTOF) assay was developed to immunophenotype a diverse array of B and T cell subsets utilizing 41 separate markers, and used to compare PBMCs from patients before and after ocrelizumab or interferon beta-1a treatment. To test the ability of T cells to elicit polyfunctional cytokine responses, PBMCs before and after treatment were stimulated with phorbol myristate acetate (PMA) and ionomycin and stained for intra-cellular cytokine secretion. The study assessed longitudinal PBMC samples from 7 unique patients that included 1 baseline untreated and 3 other post treatment samples from each patient. The experiments and data analysis were conducted while blinded to the treatment assignment for each patient.

**Results:** Despite dramatic reduction of all B cell subsets in blood after ocrelizumab treatment, no significant modulation in the frequency of T cell subsets was observed. Permutation testing identified that immune subsets significantly differentiated by ocrelizumab were all CD19+ B cell subsets. Furthermore, an unsupervised t-distributed stochastic neighbor embedding (t-SNE) based visualization only revealed B cell depletion and modulation; however, overt changes in T cell populations were not apparent.

**Conclusions:** Our findings suggest that the peripheral blood T cell compartment remains largely unaltered in RMS patients treated with ocrelizumab. The treatment also did not appear to affect the ability of T cells in these patients to elicit a functional cytokine response to stimulation. These results may be relevant for safety purposes.

**Disclosure**

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**P660**

Dimethyl fumarate reduces the frequency of antigen-experienced B cells in patients with multiple sclerosis
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Background: Tecfidera is an oral formulation of Dimethyl fumarate (DMF) used for treatment of relapsing remitting multiple sclerosis (RRMS). Previous studies have shown that DMF affects the absolute number and frequency of peripheral lymphocytes in patients with multiple sclerosis (MS); however, the effects of DMF on circulating B cell subsets have not yet been investigated.

Objective: With this study, we wish to investigate the immunological effect of DMF on B cell subsets from DMF treated patients with RRMS.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from untreated RRMS patients (n=16) and patients treated with DMF > 12 month (n=18). Multi-colour flow cytometry was used to analyse the cellular phenotypes of peripheral B cells: B regulatory/transitional cells, naïve, memory, partly-activated and memory-like B cells defined by their CD19 and CD27/CD38 expression.

Results: We found that DMF treatment reduced the frequency of partly-activated B cells (p < 0.031), memory B cells (p < 0.0001) and memory-like B cells (p < 0.0001). In contrast, the frequency of regulatory/transitional B cells (p < 0.0001) and naïve B cells (p < 0.0001) were increased in DMF treated RRMS patients.

Conclusion: Our data illustrate a preferential depletion of antigen-experienced B cells. Memory B cells are thought to play a role in MS pathogenesis due to their production of proinflammatory cytokines, antigen-presenting abilities and rapid differentiation into antibody secreting plasma cells. The immunological effects of DMF on the B cell subpopulations as observed in this study therefore may underlie the positive treatment effects of DMF in RRMS.

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P661
Efficacy of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing-remitting multiple sclerosis: eight-year follow-up of an integrated analysis of DEFINE, CONFIRM, and ENDORSE

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Background: Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated strong efficacy and a favourable benefit-risk in patients (pts) with relapsing-remitting multiple sclerosis (RRMS) in the Phase 3 DEFINE/CONFIRM studies, and the associated ongoing extension study, ENDORSE (NCT00835770).

Objectives: Report 8-year (yr) clinical efficacy outcomes in newly diagnosed RRMS pts treated with DMF.

Methods: Pts randomized in DEFINE/CONFIRM to DMF 240 mg twice (BID) or three times daily (TID) continued on the same dosage in ENDORSE. Pts randomized to placebo (PBO) or glatiramer acetate (CONFIRM only) were re-randomized 1:1 to DMF BID or TID. In March 2014, all pts were switched to DMF BID with regulatory approval. DMF BID results are reported. “ Newly diagnosed” pts were defined as pts diagnosed with MS ≤1 yr prior to parent study entry and either treatment-naïve or previously treated with corticosteroids alone. As of October 2016, the median total follow-up was ~8 yrs: pts initially randomized to DMF BID in DEFINE/CONFIRM who continued on DMF BID in ENDORSE received ~8 yrs continuous DMF treatment (DMF/DMF); pts initially randomized to PBO who switched to DMF BID in ENDORSE received 2 yrs PBO followed by ~6 yrs DMF (PBO/DMF).

Results: At ~8 yrs (ENDORSE = 6 yrs), 55% (79/144) DMF/ DMF and 48% (41/85) PBO/DMF newly diagnosed pts remained on treatment. Over ~8 yrs, annualized relapse rate (ARR, [95% confidence interval, CI]) was 0.14 (0.10, 0.18) in DMF/DMF and 0.16 (0.11, 0.23) in PBO/DMF pts; rate ratio (95% CI) for DMF/DMF vs PBO/DMF was 0.86 (0.54, 1.37; P=0.5301). In PBO/DMF, ARR (95% CI) was 0.25 (0.18, 0.36) from Yrs 0-2 (DEFINE/CONFIRM) and 0.09 (0.06, 0.14) from Yrs 3-8 (ENDORSE); rate ratio (95% CI) for Yrs 3-8 vs 0-2 was 0.37 (0.25, 0.56; P<0.0001). At baseline, mean (SD) expanded disability status scale (EDSS) score was 2.07 (1.16) for DMF/DMF and 2.20 (1.04) for PBO/DMF. The number of pts with EDSS<3.5 was 129/139 (93%) and 65/72 (90%) at Yr 2, and 56/61 (92%) and 29/31 (94%) at Yr 8, for DMF/DMF and PBO/DMF, respectively. Over ~8 yrs, 52.1% DMF/DMF and 48.2% PBO/DMF pts remained free from relapses and 24-week confirmed disability progression.

Conclusions: Over ~8 yrs, ARR remained low in newly diagnosed DMF/DMF and PBO/DMF pts. ARR was significantly reduced in PBO/DMF pts after switching to DMF. The proportion of pts with EDSS≤3.5 remained stable in both treatment groups.

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P662
Peginterferon beta-1a improves clinical and radiological disease outcomes in patients who are newly diagnosed with relapsing multiple sclerosis: subgroup analysis of ADVANCE
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Background: The pivotal Phase 3 ADVANCE study evaluated the efficacy of subcutaneous peginterferon beta-1a 125 mcg every 2 weeks in patients with relapsing-remitting multiple sclerosis (RRMS), approximately 45% of whom were newly diagnosed and had no prior treatment with a disease-modifying therapy (DMT). While peginterferon beta-1a demonstrated a significant treatment effect vs placebo, the impact of treatment on newly diagnosed patients was not evaluated.

Objectives: Evaluate the effect of peginterferon beta-1a on clinical and radiological disease activity in the subgroup of newly diagnosed, treatment-naïve patients from ADVANCE.

Methods: ADVANCE was a 2-year double-blinded study, in which patients were randomised to receive peginterferon beta-1a every 2 weeks, every 4 weeks, or placebo in Year 1. In Year 2, placebo patients were re-randomised to peginterferon beta-1a every 2 or 4 weeks (delayed-treatment group). Here, the subgroup of patients who were diagnosed ≤1 year prior to study enrolment and had never received a DMT for RRMS were analysed. Annualised relapse rate (ARR), time to first relapse, 24-week confirmed disability worsening (CDW), MRI endpoints, and safety were compared between the every-2-weeks group and the delayed-treatment group.

Results: Over 2 years, the adjusted ARR in newly diagnosed patients was reduced by 32.3% for the peginterferon beta-1a every-2-weeks group (n=231), compared with the delayed-treatment group (n=229; p=0.0352). Time to first relapse was delayed in the every-2-weeks group compared with the delayed-treatment group (p=0.0101), and the proportion of patients with 24-week CDW was numerically lower in the every-2-weeks group compared with the delayed-treatment group. At Year 2 the number of new/newly enhancing T2 lesions was lower in the every-2-weeks vs the delayed-treatment group (p< 0.0001), although there appeared to be no difference between the groups in the number of gadolinium-enhancing (Gd+) lesions. The safety profile in newly diagnosed patients was similar to what was observed in the overall patient population.

Conclusions: Newly diagnosed, treatment-naïve patients displayed significantly reduced disease activity when administered peginterferon beta-1a every 2 weeks compared with delayed-treatment patients. These results are generally consistent with what was observed in the previously reported overall population in ADVANCE, and highlight the benefits of initiating therapy early following diagnosis with RRMS.

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P663
Comparative effectiveness and discontinuation of dimethyl fumarate and fingolimod in two large academic medical centers at 24-month follow-up
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Objectives: To assess real-world effectiveness and discontinuation of dimethyl fumarate (DMF) and fingolimod (FTY) over 24 months in patients with multiple sclerosis (MS) from two large academic centers.

Background: DMF and FTY are approved oral disease modifying therapies (DMTs) for relapsing MS. Previous randomized controlled trials (RCTs) and large observational studies, including our 12-month combined analysis, showed comparable efficacy at 12 and 24 months, but DMF patients were more likely to discontinue DMT earlier compared to FTY-treated patients. Observational studies are valuable when there are multiple available treatments and comparative RCTs are not feasible. Multi-site studies allow investigators to ascertain external validity of previously examined treatment effect differences.

Methods: Patients prescribed DMF (n = 737) and FTY (n = 535) from two large academic MS Centers (Cleveland Clinic and University of Colorado) with 24-month follow-up were identified. Discontinuation rates and measures of disease activity were assessed using propensity score (PS) weighting. Covariates used in the PS model included demographics and baseline clinical and MRI characteristics. Outcomes of interest included proportion of patients discontinuing DMT and proportion with disease activity [clinical relapse, gadolinium-enhancing (GdE) brain MRI lesions, and new T2 lesions]. Odds ratio estimates were calculated as DMF versus FTY.

Results: PS weighting showed excellent covariate balance. Our results showed discontinuation was more common in DMF (44.2%) compared to FTY (34.8%) over 24 months [OR=1.53, 95% CI (1.19, 1.96)].
p<0.001]. Leading cause for discontinuation was intolerability in both DMF (56.1% of all DMF discontinuations) and FTY (46.2% of FTY discontinuations) [OR=1.67, 95% CI (1.22, 2.27), p=0.001]. Primary reason for discontinuation due to intolerability was GI side effects in DMF (57.9%) and headaches in FTY (14.0%). There was no difference in the proportion with clinical relapses [OR=1.29, 95% CI (0.91, 1.82), p=0.15], GdE lesions [OR=1.44, 95% CI (0.94, 2.23), p=0.10], or new T2 lesions [OR=1.13, 95% CI (0.83, 1.55), p=0.43].

Conclusions: This combined analysis suggests similar effectiveness profiles for DMF and FTY in a large clinical population over 24 months. Discontinuation of both DMTs was common and occurred more frequently with DMF, largely driven by intolerability.

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P664

Real life use of natalizumab and fingolimod - data from the nation-wide Austrian Multiple Sclerosis Treatment Registry

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Background: Natalizumab and fingolimod were approved for treatment of active relapsing-remitting multiple sclerosis (RRMS) in Austria in 2006 and 2011, respectively. No randomized head-to-head studies comparing natalizumab and fingolimod are available.

Objectives: To compare patients who started with natalizumab or fingolimod in a nationwide observational cohort using prospectively collected data.

Methods: We included all patients starting treatment with natalizumab or fingolimod documented in the Austrian MS Treatment Registry (AMSTR) from 2011 and staying on therapy for at least 24 months. We used propensity scores for several matching methods and as a covariate in multivariate models to correct for the bias of this non-randomised registry study.

Results: The study cohort includes 588 RRMS patients. 10 patients did not produce a propensity score in the common support region, thus leaving 578 cases for final analyses, 332 in the fingolimod and 246 in the natalizumab group. Mean annualized relapse rates (ARR) during the 24 months observation period were 0.19 under fingolimod and 0.12 under natalizumab treatment (p = 0.005). No statistical significant differences were found analysing the log-transformed ARR, probability for experiencing a relapse, EDSS progression and EDSS regression. The hazard ratio for switching treatment from fingolimod comparing with natalizumab was 0.36 (95% CI: 0.247-0.523), p<0.001.

Conclusions: The generalized linear model (GLM) for relapse count as Poisson distributed dependent variable and propensity score as covariate showed a statistically significant reduction for the mean relapse count in the natalizumab group compared with fingolimod. This effect was smaller in the analyses of log transformed ARR with propensity score matching, loosing statistical significance although showing the same direction for the effect. We assume, that the GLM was the more sensitive model analysing this question.

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P665
Dimethyl fumarate vs. fingolimod in multiple sclerosis: an independent, multi-centre, real world, quasi-randomized study
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Background: Delayed-release dimethyl fumarate (DMF) and fingolimod (FNG) are two approved oral drugs for relapsing-remit-
ting multiple sclerosis (RRMS). Although the European Medicine Agency recommends different indications for DMF and FNG, both drugs are sometime used either as switch strategy in patients who do not respond to self-injectable drugs or as first treatment option. However, real world data reporting direct comparison of their effectiveness are still scarce.

Objective: To directly compare the effectiveness of DMF and FNG in achieving the No Evidence of Disease Activity (NEDA-3) status, defined as absence of relapses, disability worsening and magnetic resonance imaging activity.

Methods: We analyzed data of patients with RRMS regularly attending 7 MS Clinics in Central Italy and who started DMF or FNG as first treatment (naïves) or were switched from a self-injectable drugs (switchers). To be included, patients were required to have had at least one relapse in the year prior to DMF or FNG start, no previous exposure to either monoclonal antibodies or immunosuppressants, minimum 3-month persistence on DMF and FNG. Since patients were not randomized to treatment group, we performed a propensity score (PS)-based nearest neighbour matching within a caliper of 0.05 to select only patients with similar baseline characteristics. Pairwise comparisons were then conducted in matched samples using a Cox proportional hazards model (stratified by Centre) with the NEDA-3 as main outcome. Pairwise censoring was adopted to adjust for difference in length of follow-up among the two treatment groups.

Results: Overall, 426 and 469 patients started DMF and FNG, respectively. There was significant imbalance in pre-matching baseline characteristics across treatment groups, due to the lower EDSS score, fewer pre-treatment relapses and active MRI scans in DMF group (p-values< 0.001). A total of 550 patients (275 per group) was retained by the PS-matching procedure. After a median on-study follow-up of 18 months, we found a trend toward a better outcome (NEDA-3) for FNG over DMF (HR=0.76, p=0.07). Subgroup analyses showed a comparable effectiveness of the two drugs in naïves (n=198; HR=0.88, p=0.96), while FNG was superior to DMF in the achievement of NEDA-3 status in switchers (n=352; HR=0.62, p=0.02).

Discussion: Our study suggests that DMF is as effective as FNG in naïve patients, while FNG could be a better option for patients switching from a self-injectable drug.

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P666
Rates of lymphopenia year-by-year in patients with relapsing multiple sclerosis treated and retreated with cladribine tablets 3.5mg/kg
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Background: The CLARITY and CLARITY Extension studies demonstrated the efficacy of cladribine tablets in patients with relapsing multiple sclerosis. The most common adverse event was lymphopenia, consistent with the mechanism of action of cladribine tablets.

Objective: To evaluate whether lymphopenia persists following treatment and re-treatment with cladribine tablets 3.5 mg/kg.

Methods: Lymphopenia by grade (National Cancer Institute Common Terminology Criteria for Adverse Events v3.0) for patients who were randomised to cladribine tablets 3.5mg/kg in the two-year CLARITY study and re-randomised to cladribine tablets 3.5mg/kg in the two-year CLARITY Extension study (7 mg/kg cumulative dose over 4 years; N=186) are reported. Patients with Grade 0 lymphopenia (≥1.0×10^9 cells/L) before the first course of cladribine tablets and Grade 0 or 1 (≥0.8×10^9 cells/L) prior to administration of all subsequent courses in Years 2, 3 and 4 were included in the analysis, according to re-treatment guidelines.

Results: 176 patients were Grade 0 at the start of CLARITY and 167 patients were Grade 0 at the start of CLARITY Extension. Grade 3 lymphopenia was observed in 1% of patients at Week 13 in Year 1, and in 7%, 11% and 12% of patients at Week 12 in Years 2, 3 and 4, respectively. By Week 24 in each of Years 1, 2, 3 and 4, Grade 3 lymphopenia was observed in 1%, 4%, 4% and 4% of patients, respectively. By Week 36 in each of Years 1, 2, 3 and 4, Grade 3 lymphopenia was observed in 1%, 2%, 2% and 2% of patients, respectively. By Week 48 in each year, Grade 3 lymphopenia was only observed in Year 2 (1% of patients). Occurrence of Grade 3 lymphopenia was reported in <18% of patients at any single time point. No patients had Grade 4 lymphopenia at the end of any of the four treatment years.

Conclusions: In patients who were treated according to re-treatment guidelines i.e. having lymphocyte counts ≥1.0×10^9/L before the first course and ≥0.8×10^9/L before up to 3 subsequent annual courses of cladribine tablets (up to 7 mg/kg cumulative dose), no patients experienced Grade 4 lymphopenia at the end of any treatment year, and Grade 3 lymphopenia was uncommon. Results of this study demonstrate the effectiveness of lymphocyte-based re-treatment criteria in minimising the incidence of severe, sustained lymphopenia during four years’ treatment with cladribine tablets.

Disclosure
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Effects of cladribine tablets on CD4+ T cell subsets in the ORACLE-MS study: results from an analysis of lymphocyte surface markers

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Background: ORACLE-MS demonstrated the efficacy of cladribine tablets 3.5mg/kg (cumulative dose over 2 years) in patients with early multiple sclerosis (MS). Evaluation of lymphocyte subtypes from patients in the cladribine tablets 3.5 mg/kg arm of the study showed that a transient ~32% median reduction in CD19+ B cell count occurred by week 13 with reconstitution from week 24 to 48. CD4+ and CD8+ T cells were also reduced (median reduction between ~40 and ~55%). Because of the durable clinical effects of cladribine tablets, the influence on cells with regulatory immune function is also of interest.

Objective: To examine effects on central and effector memory CD4+ T cells and naturally occurring regulatory CD4+ T cells (nTregs) after the first administration of cladribine tablets in the ORACLE-MS study.

Methods: Peripheral blood T lymphocytes were immunophenotyped at baseline, and weeks 5, 13, and 48 in patients treated with cladribine tablets at week 1 and week 5 in ORACLE-MS (3.5 mg/kg group; n=41) using T lymphocyte surface markers. Absolute numbers and proportions of central memory (CD4+RO+CCR7+), effector memory (CD4+RO+CCR7−), Th1-type (CD4+CXCR3+) and nTregs (CD4+CD25+CD127−), including naïve-like nTregs (CD4+CD25+CD127-RA[HI]+) and memory-like nTregs (CD4+CD25+CD127-RA-) were measured.

Results: Greatest median reductions from baseline in absolute cell numbers occurred at week 13 for effector memory cells (-54%) and week 24 for central memory (-63%) and Th1-type cells (-51%) with similar or slightly increased levels of these CD4+ cell subtypes at week 48. Over time, there was a reduction (~5%) in the proportion of the central memory cells in total CD4+ cells, but no change in proportion for effector memory and Th1-type cells. Absolute numbers of nTregs (-48%), naïve-like nTregs (-67%) and memory-like nTregs (-42%) were decreased at week 48. The proportions of nTregs and naïve-like nTregs in total CD4+ cells were not changed. Memory-like nTregs slightly increased up to 48 weeks after treatment with cladribine tablets (median increase from baseline in the proportion of memory-like nTregs was 11% at week 48).

Conclusion: The first administration of cladribine tablets has a comparable magnitude of effect on CD4+ T cell subpopulations, with no dramatic shifts in their proportions. Further investigation is ongoing to explore the implications for the mechanism of action of cladribine tablets in MS and the effects of retreatment in the second year.

Disclosure
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OS: serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, and Therapeutic Advances in Neurological Disorders. He has served on data monitoring committees for Pfizer and TG Therapeutics without monetary compensation. He has advised Genzyme and Novartis, and has participated in a Teva-sponsored meeting. He currently receives grant support from Teva Pharmaceuticals and Opexa Therapeutics. He is funded by a Merit Review grant (federal award document number (FAIN) 101BX001674) from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development. PS-S: has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK, on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme.

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YH, DD and UB: are employees of EMD Serono, USA.

T-cell population changes and serious infection rates in the controlled periods of the pivotal phase III trials of ocrelizumab in multiple sclerosis

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Background: Variation in T-cell subpopulation levels is multifactorial and was seen in Phase III studies of ocrelizumab (OCR), a humanised, CD20+ B cell-selective monoclonal antibody approved by the FDA for the treatment of relapsing remitting and primary progressive multiple sclerosis.
**Objective:** To evaluate changes in T-cell levels and correlations with serious infections in OCR Phase III studies.

**Methods:** OPERA I (NCT01247324) and OPERA II (NCT01412333) data were pooled; patients received OCR 600 mg intravenous infusions every 24 weeks (N=825) or subcutaneous interferon β1a (IFN β1a) 44 μg three times weekly for 96 weeks (N=826). Patients in ORATORIO (NCT01194570) received OCR 600 mg (N=486) or placebo (PBO; N=239) for ≥120 weeks until the planned number of progression events were seen. Percent change in T-cell levels (calculated using adjusted geometric mean ratios), the proportion of patients with a confirmed (verified at 2 study visits) T-cell drop < lower limit of normal (LLN), and correlation between confirmed drops in T-cells and serious infection rates per 100 patient years were assessed.

**Results:** Compared with baseline, at the end of the controlled treatment periods of the OPERA and ORATORIO studies, the slight decrease seen in T-cell levels with OCR was less than that seen with IFN β1a (CD3+ 4.3 vs 17.3%; CD4+ 0.8 vs 11.8%; CD8+ 8.6 vs 23.9%) while similar changes were seen with OCR and PBO at Week 120 (CD3+ 3.5% decrease vs 3.3% increase; CD4+ 1.0% vs 5.6% increase; CD8+ 12.5% vs 0.7% decrease). The proportions of patients with T-cells < LLN with OCR were lower than with IFN β1a (CD3+ 6.2 vs 15.0%; CD4+ 3.0 vs 7.6%; CD8+ 14.8 vs 24.9%) and higher than with PBO (CD3+ 11.5% vs 9.6%; CD4+ 4.9 vs 4.2%; CD8+ 28.2 vs 17.6%). Serious infection rates were low; during periods of confirmed CD8+ < LLN, rates (95% CI) with OCR and IFN β1a were 3.44 (1.12-8.02) vs 1.29 (0.27-3.76) and with OCR and PBO were 5.08 (2.84-8.37) vs 3.66 (0.75-10.69). Event rates during periods of CD4+ < LLN were too low to make meaningful conclusion.

**Conclusions:** OCR had a lesser impact on T-cell populations (overall and < LLN) than IFN β1a in the OPERA studies but a slightly greater effect than PBO in ORATORIO. Periods of T-cell populations < LLN are not considered an isolated safety risk with OCR. Nevertheless, it cannot be ruled out that an increase in the risk of serious infection may exist when B cells are depleted and T cells are decreased concomitantly. Further follow-up is required.

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C. Harp is an employee and shareholder of Genentech, Inc.

A. Herman is an employee of Genentech, Inc. and shareholder in F. Hoffmann-La Roche.

H. Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd.

C. Li is an employee of F. Hoffmann-La Roche Ltd.

B. Shi is an employee of F. Hoffmann-La Roche Ltd.

S. L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Symbiotix and Bionure. He has also received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

**Objectives:** Aim of this study is to track and evaluate post-marketing Dimethyl fumarate (DMF) safety, tolerability and efficacy profile in a real world setting.

**Materials and Methods:** From January 2015 to January 2017 we enrolled patients receiving DMF in 9 northern Italy MS centres. Patients were prospectively followed, collecting demographic and clinical data as well as laboratory assessment.

**Results:** We included 735 patients (66.7% F; mean age: 38.7±10 years; mean disease duration: 10.5±3.7 years). Mean annual relapse rate (ARR) in the two years before DMF was 0.49±0.52, median baseline EDSS was 2 (range 0-6.5). One-hundred and ninety-four patients (26.4%) were treatment naïve. Four hundred and twenty eight patients (59.5%) switched to DMF from interferon-β (IFN), glatiramer acetate (GA) or teriflunomide (TFU) due to loss of tolerability (40%) or inefficacy (60%). Seventy patients (9%) switched to DMF from fingolimod (FTY), natalizumab (NAT) or rituximab (RTX) because of safety reasons. Median DMF treatment exposure was 15 months (0-36), 554 patients (75%) had at least 12 months of follow-up. Most frequent adverse events (AEs) were flushing/pruritus (37.1%), gastrointestinal side effects (31.4%), urticaria (2.6%) and arthralgia (1.1%). Only 5 severe AEs were reported (malignancies). Most frequent laboratory testing abnormalities were lymphopenia (19%, none grade III or IV severe) and ALT increase (1.8%). DMF was discontinued in 25.8% of patients; among them, 61% stopped treatment due to side effects. AEs were more frequent in patients who stopped DMF treatment than in those who continued (p<0.001).

Among patients completing one year of follow-up, 73.1% were relapse-free. Patients previously on FTY, NAT or RTX had higher relapse rates than those who were treatment-naïve or switchers from IFN, GA or TFU (p<0.001). Median interval between DMF start and first relapse was 12 months (range 0-36).

The overall mean ARR during the observation period (0.21) was reduced compared to baseline.

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Discussion and Conclusion: Although the frequency of some AEs (such as flushing and gastrointestinal side effects) was mildly higher than that reported in previous studies, our observational data confirm the good tolerability and safety profile of DMF, as well as its efficacy in reducing ARR.

Disclosure

G. Pallucco received support to travel to scientific meetings from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva; received speaker honoraria from Biogen Idec and served on the scientific advisory board for Genzyme and Merck Serono
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M. Mota has nothing to disclose.
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A. Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec Pharmaceutical Industries Ltd, has received speaker honoraria from Merck Serono, Biogen Idec, Bayer Schering Pharma and Novartis, Serono Symposia International, served as a consultant for Novartis, and receives research support from Sanofi-Aventis, Biogen Idec and Merck Serono.
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Sclerosis (RRMS) and Primary Progressive MS (PPMS). Since the publication of the results of these trials, rituximab has been increasingly used off-label to treat MS in a heterogeneous cohort of patients.

**Objective:** To investigate the safety and efficacy of rituximab given off-label to MS patients.

**Methods:** Uncontrolled retrospective multicentre observational study including all the patients with MS treated off-label with Rituximab in 16 Italian and 1 Swiss MS centers. Outcome data (relapse rate and EDSS progression, defined as a point increase in EDSS 6-month confirmed) and adverse events (AE) over the follow-up were summarised.

**Results:** 241 patients were included [170 females, mean age (range) 43 (15-79) years, 140 (58%) RRMS, 72 (30%) Secondary Progressive MS, 29 (12%) PPMS]. The mean (range) EDSS pre-treatment was 4.2 (0-8). Before Rituximab initiation, 18 (7.5%) patients were treatment naive, 119 (49%) were treated with first line injectable drug, 30 (12%) with oral drugs, 31 (13%) with natalizumab and 43 (18%) with other therapies. 27 out of 241 patients (11%) had auto-immune co-morbidities at treatment start. Patients were treated with 500 or 1000 mg Rituximab IV every 6-12 months over a median (range) follow-up time of 2 (0.3-11) years. The annualized relapse rate (ARR) in the year before Rituximab start was 0.82 (95% Confidence Interval (CI)=0.68-0.99) in RRMS and 0.41 (95%CI=0.30-0.56) in progressive patients. It was 0.11 (95%CI=0.06-0.19) and 0.17 (95%CI=0.09-0.29) in the first 6 months of treatment, and 0.096 (95%CI=0.06-0.14) and 0.13 (95%CI=0.07-0.20) during the whole follow up in RRMS and in progressive patients respectively. The proportion of patients free from EDSS progression after 2 years was 96% (SE=4%) in the RR group and 76% (SE=8%) in the progressive group. The rate of AE per patient/year was 0.30 (95%CI=0.22-0.42) and the rate of serious AE per patient/year was 0.05 (95%CI=0.02-0.10).

**Conclusions:** The safety and clinical findings in this heterogeneous retrospective real-world study are in line with previous larger observational studies showing that rituximab is efficacious and safe in the treatment of multiple sclerosis and similar to those reported in previous randomized controlled trials on B-cell depletion therapy in MS.

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**Slowing of cortical grey matter atrophy with teriflunomide is associated with delayed conversion to clinically definite MS**

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**Background:** In TOPIC (NCT00622700), teriflunomide significantly reduced risk of conversion to clinically definite MS (CDMS) vs placebo in patients with a first clinical episode suggestive of MS. Teriflunomide also significantly reduced MRI activity, consistent with outcomes in patients with relapsing forms of MS in TEMSO (NCT00134563). Pathologic changes in grey matter (GM) contribute to disease worsening in MS. GM atrophy after a first clinical event is associated with conversion to CDMS and disability accumulation.

**Objective:** To explore the effect of cortical GM volume (CGMV) change on risk of conversion to CDMS in TOPIC.

**Methods:** Patients were treated with placebo (n=197), teriflunomide 7 mg (n=203) or 14 mg (n=214) for ≤108 weeks. Percentage change in CGMV was evaluated using SIENAX (Structural Image Evaluation using Normalisation of Atrophy, Cross-sectional) multi-time point analysis. Placebo and teriflunomide data at Month (M) 6, 12, 18, and 24, standardized for follow-up duration, were analysed relative to baseline. Non-parametric ANCOVA models adjusted for covariates were used to assess treatment effects at each time point separately and cumulatively. Relationship of CGMV loss to CDMS conversion over varying time of follow-up was analysed using Cox proportional hazards models adjusted for covariates.

**Results:** Teriflunomide 14 mg reduced median percentage CGMV change by ≥40% vs placebo at all time points (P<0.05 at each time point; P=0.0052 for cumulative difference over 2 years). Consistent results were observed with teriflunomide 7 mg; ≥40%
redun4tion vs placebo at all time points (P< 0.05 at M18 and M24; P=0.0089 for cumulative difference over 2 years). There was a significant association of CGMV loss with conversion to CDMS at M12 (12.4% increased risk of CDMS conversion for every 1% decrease in CGMV [P=0.0099]), and a significant treatment effect (14 mg vs placebo, risk reduction [RR]: 46.3%, P=0.0166). These significant results were replicated at M18 and M24: association of CGMV loss with CDMS conversion, 14.2%, P=0.0009 and 14.5%, P=0.0005, respectively; treatment effect, RR 42.1%, P=0.0239 and 46.6%, P=0.0093, respectively. Correlation between CGMV and CDMS will be further explored with longer-term data.

Conclusions: Consistent effects of teriflunomide on reducing CGMV loss, together with the correlation between conversion to CDMS and CGMV loss, indicate how teriflunomide may favourably impact early inflammatory and neurodegenerative components of MS.

Disclosure
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EC: Nothing to disclose.
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Confirmed disability improvement in patients treated with fingolimod in phase 3 and extension trial programmes for up to 96 months
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Background Sustained improvement in disability status is an emerging goal of therapy for MS. Disability improvement has been described with high-efficacy therapies and has been used as a secondary outcome in recent MS clinical trials. Definitions of confirmed disability improvement (CDI) have varied in these trials.

Objective To evaluate the proportion of patients with CDI over time while on long-term (up to 8 years) fingolimod treatment in the Phase 3 TRANSFORMS trial and its extensions.

Methods The analysis included patients who had an Expanded Disability Status Scale (EDSS) score ≥2.0 at baseline and were randomised to fingolimod 1.25mg (N=244), fingolimod 0.5mg (the fingolimod-0.5 cohort; N=247), or interferon beta-1a (the IFN-to-fingolimod-switch cohort; N=254) during the 12-month core phase of TRANSFORMS. All patients received fingolimod 0.5mg during trial extensions. Confirmed disability improvement (CDI) was defined as a confirmed ≥1 or ≥0.5 point decrease in EDSS score in patients with baseline scores ≤5.0 or ≥5.5, respectively; CDI plus was defined as a ≥20% improvement in score on the 9-hole peg test (9HPT), a ≥20% improvement in the timed 25-foot walking test (T25FWT), or a ≥1 decrease in EDSS score lasting ≥166 days.

Conclusions In patients with RRMS enrolled in the active-comparator study TRANSFORMS and followed for up to 8 years, 35-52% experienced confirmed improvements in their disability while on fingolimod. Numerically higher improvement rates were observed when the CDI definition included 9HPT or T25FWT improvement.

Results The analysis included a total of 745 patients. Mean (SD) scores for EDSS, 9HPT, and T25FWT were 3.04 (1.01), 24.1 (12.4), and 7.85 (10.43), respectively. A total of 328 patients were observed for 96 months (completers). Completers and non-completers had similar baseline characteristics, apart from 9HPT (23.3 vs 24.7, respectively; p=0.005) and T25FWT (7.58 vs 8.06, respectively; p=0.021). At Month 96, KM estimates (95% CI) for cumulative probability of having CDI were 36.9% (30.0, 44.8) and 35.1% (28.2, 43.1) in the fingolimod-0.5 and IFN-to-fingolimod-switch cohorts, respectively. When using the CDI plus definition to take into account disability measures other than EDSS, the KM estimates were 52.0% (44.4, 60.0) and 48.3% (40.6, 56.6), respectively.

Conclusions In patients with RRMS enrolled in the active-comparator study TRANSFORMS and followed for up to 8 years, 35-52% experienced confirmed improvements in their disability while on fingolimod. Numerically higher improvement rates were observed when the CDI definition included 9HPT or T25FWT along with EDSS.

Disclosure
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P673
Comparison of rituximab and highly effective second line disease modifying therapies after breakthrough disease activity in relapsing-remitting multiple sclerosis

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Introduction: Continued disease activity during first line disease modifying therapy (DMT) in relapsing-remitting multiple sclerosis (RRMS) indicate suboptimal treatment response and should therefore prompt treatment escalation to a second line DMT. In Sweden rituximab (RTX) is used off label as a second line DMT by one third of all treated multiple sclerosis (MS) patients. A retrospective study suggested that RTX had favourable adverse event (AE) profile, efficacy and drug survival compared to fingolimod (FGL) in patients switching from natalizumab (NTZ) due to JC virus positivity (JCV+). There are currently no comparative studies between RTX and other highly effective (HE) DMTs after breakthrough disease on first line therapy.

Objective: To compare the safety and efficacy of RTX, FGL, NTZ and alemtuzumab (ALZ) in RRMS cases who, despite treatment with first line DMTs, experienced clinical relapses and/or had contrast enhancing lesions (CELs) on magnetic resonance imaging (MRI).

Method: At three Swedish MS Centres, the Swedish MS registry was searched for patients with RRMS who had switched from first line DMTs (interferons or glatiramacer acetate) to either RTX, FGL, NTZ or ALZ between 2011-01-01 and 2015-12-31 due to breakthrough disease. Patients with a follow-up period of at least 12 months were included. Data in this retrospective observational study were collected from the MS registry and medical charts.

Result: Preliminary data shows an approximate number of 220 RRMS patients meeting the inclusion criteria. The majority of patients (78%) had switched from interferons, and the most common reason to switch was CELs (65%). The most common HE drug was FGL (44%), followed by NTZ (40%), RTX (15%) and ALZ (< 1%). The annualised relapse rate (ARR) after switch was 0.016 (NTZ), 0.032 (RTX) and 0.058 (FGL). 15% of patients had AQP4-IgG (< 1%). The annualised relapse rate (ARR) after switch was 0.016 (NTZ), 0.032 (RTX) and 0.058 (FGL). 15% of patients had AQP4-IgG (< 1%). The annualised relapse rate (ARR) after switch was 0.016 (NTZ), 0.032 (RTX) and 0.058 (FGL). 15% of patients had AQP4-IgG (< 1%).

Conclusion: The study has the potential to show how the studied drugs perform in a real life setting and data may be used to guide future treatment decisions.

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P674
Relapse rates and disability in the modern treatment era of neuromyelitis optica: data from a specialist UK centre

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Background: Neuromyelitis Optica Spectrum Disorders (NMOSD) have been considered a disease with poor outcomes and a high degree of morbidity and mortality in the past. We have been offering a proactive, early, standardised stepwise escalation protocol of immunosuppressive treatments for NMOSD for 10 years using commonly available and relatively inexpensive drugs, including corticosteroids, azathioprine, mycophenolate and rituximab.

Methods: We compared the annualised relapse rates (ARR) and expanded disability status scale (EDSS) scores of 130 NMOSD patients (95 AQ4-IgG positive, 12 MOG-IgG positive, 23 seronegative) seen in a specialist NMOSD clinic at first presentation to the clinic and at most recent follow-up.

Results: Median disease duration prior to attending clinic was 3.51 years and median follow-up in clinic was 3.68 years (0.33-10.11 years). At last follow up 39 patients (30%) are on treatment with azathioprine, 30 patients on mycophenolate mofetil (23%), 38 patients on rituximab (29%) and 15 patients (12%) on other immunosuppressant medications; 8 patients (6%) are not on treatment. Median ARR was 0.97 (range 0.09-7.77) at presentation and 0 (0-1.63) on final follow-up (p < 0.0001). 62% of all patients (and 61% of AQP4-IgG positive patients) remained relapse-free at last follow-up. Median EDSS score was unchanged at 4.0, at presentation and at last follow-up, with 84% of patients either improving or maintaining their EDSS score. 4 patients (3%) died during follow-up and none of these deaths were directly caused by an NMOSD relapse.

Conclusion: Relapse outcomes of NMOSD have improved remarkably in the last few years using conventional immunosuppressants in a standardized manner in specialist care settings. However improvement in disability is limited, indicating the importance of early aggressive management of relapses and index events with high probability of NMOSD.

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P675
Design of a phase II dose range finding, efficacy and safety study of the Bruton’s tyrosine kinase inhibitor evobrutinib (M2951) in relapsing multiple sclerosis patients

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Evobrutinib (M2951) is a potent, highly specific, irreversible, oral inhibitor of Bruton’s Tyrosine kinase (BTK). Inhibition of BTK is expected to achieve B-cell silencing and interfere with innate immune cell activation. Evobrutinib has been shown to inhibit primary B-cell responses including proliferation, and antibody and cytokine release in a T cell-independent manner. The role of B-cells in the pathogenesis of multiple autoimmune diseases has been underlined by the efficacy of B-cell depleting approaches in rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis (MS). Functional impairment of B-cells without depletion may show similar efficacy and perhaps a more favorable safety profile.

This study (NCT02975349) aims to evaluate the efficacy, safety, dose-response, and pharmacokinetic/pharmacodynamic relationships of evobrutinib in patients with relapsing MS (RMS) who are clinically and radiologically active. The presence of other autoimmune diseases, concomitant medications affecting the immune system, and laboratory evidence of immune system dysfunction are exclusionary. This Phase II design consists of five treatment arms with 50 patients in each arm: three oral (BID) doses of evobrutinib, placebo and an active control arm of dimethyl fumarate. Rescue treatment with corticosteroids is allowed for the treatment of relapses. After a 24-week treatment period, placebo patients will be switched to evobrutinib and all other groups will continue unchanged for a further 24 weeks. Open label extension treatment is planned for treatment beyond 48 weeks.

The primary endpoint is the sum of gadolinium-positive (Gd+) T1 magnetic resonance imaging lesions at Weeks 12, 16, 20, and 24 of treatment. The secondary endpoint is the total number of Gd+ T1 lesions at Week 48. Safety endpoints including immune function measures will be evaluated across the treatment period. The primary analysis will take place when all patients have reached 24 weeks of treatment or prematurely discontinued treatment, at which time the study team, but not the sites, will be unblinded. An interim analysis for futility may be carried out when 50% of patients have reached 24 weeks of treatment. A final analysis will be conducted when all patients complete 48 weeks of treatment. The first patient was randomized to treatment in April 2017 and the study is expected to be completed in early 2019. This will be the first clinical proof of concept study of a BTK inhibitor in RMS.

Disclosure
JB, EM and JM are employees of EMD Serono; a business of Merck KGaA, Darmstadt, Germany. XM has received speaker honoraria and travel expenses for scientific meetings, steering committee member, and advisory board member of clinical trials for Bayer Schering Pharma, Biogen Idec, EMD Serono, Genentech, Genzyme, Novartis, Roche, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall.

P676
Safety of ocrelizumab in multiple sclerosis: updated analysis of patients in relapse and primary progressive multiple sclerosis

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Background: Two identical Phase III trials in relapsing multiple sclerosis (RMS; OPERA I [NCT01247324] and OPERA II [NCT01412333]) and the Phase III trial in primary progressive MS (PPMS; ORATORIO [NCT01194570]) evaluated the safety and efficacy of ocrelizumab. Ongoing safety reporting on disease-modifying therapies for MS is crucial to understanding the long-term benefit-risk profile.

Objective: To report safety data from the follow-up of the clinical trials of ocrelizumab in RMS and PPMS.

Methods: In the OPERA studies, patients with RMS were randomised in a 1:1 ratio to receive intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous interferon beta-1a (IFN β-1a) 44 µg three times weekly for 96 weeks. In the ORATORIO trial, patients with PPMS were randomised in a 2:1 ratio to receive intravenous ocrelizumab 600 mg or placebo every 24 weeks for at least 120 weeks. Following completion of the controlled treatment periods, Phase III patients were eligible to enter the ocrelizumab open-label extension (OLE) phase of the trial. In a Phase II study in relapsing-remitting MS, patients were randomised in a 1:1:1:1 ratio to receive ocrelizumab 600 mg, ocrelizumab 2000 mg, placebo or intramuscular IFN β-1a through Week 24, followed by ocrelizumab every 24 weeks through Week 96. Following a treatment-free period, eligible patients from the Phase II trial entered a long-term OLE in which ocrelizumab 600 mg was administered every 24 weeks. Safety outcomes were reported for all patients administered with ocrelizumab in Phase II and III MS clinical trials, including patients who switched to ocrelizumab from comparators. Long-term safety data will continue to be reported, particularly for serious infections, malignancies and any new signals that could arise.

Results: As of 17 February 2017, 2,301 patients with MS received ocrelizumab, resulting in 7,748 patient-years (PY) of exposure. Reported rates per 100 PY (95% confidence interval) were as follows: adverse events (AEs), 226 (222-229); serious AEs, 7.18 (6.59-7.80); infections, 71.3 (69.5-73.2); and serious infections, 1.86 (1.57-2.19). The incidence rate of malignancy was 0.454 (0.316-0.632).

Conclusions: The updated safety profile in the ocrelizumab MS all-exposure population is generally consistent with that seen during the controlled treatment period in the RMS and PPMS populations. Additional data from the ongoing follow-up will be reported.
**Disclosure**

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L. Kappos’s institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos’s activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; license fees for Neurostatus products; and research grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, the Novartis Research Foundation and the Roche Research Foundation.

X. Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos. C.J. Guitiérrez is an employee of Genentech, Inc.

H. Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd.

C. Li is an employee of F. Hoffmann-La Roche Ltd.

C. Marcillat is an employee of F. Hoffmann-La Roche Ltd.

D. Wormser is an employee and shareholder of F. Hoffmann-La Roche Ltd.

J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaking honoraria from the following entities: AbbVie, Academic CME, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, Forward Pharma A/S, MedDay Pharmaceuticals, Novartis Pharmaceuticals, PRIME, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals and WebMD; royalties are received for outsourced monoclonal antibodies through UTHealth from Millipore Corporation.

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**P677**

**Effectiveness of fingolimod, dimethyl fumarate and teriflunomide in relapsing-remitting multiple sclerosis: a comparative longitudinal study**


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**Background:** Oral immunotherapies are becoming a standard treatment in relapsing-remitting multiple sclerosis. Relapse and disability outcomes have not been directly compared between oral immunotherapies.

**Objective:** To compare relapse and disability outcomes and treatment persistence among patients treated with teriflunomide, dimethyl fumarate and fingolimod.

**Methods:** We identified all patients with relapsing-remitting multiple sclerosis treated with teriflunomide, dimethyl fumarate or fingolimod, with minimum 6-month treatment persistence and research support for Prof Kappos’s activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos. C.J. Guitiérrez is an employee of Genentech, Inc.

H. Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd.

C. Li is an employee of F. Hoffmann-La Roche Ltd.

C. Marcillat is an employee of F. Hoffmann-La Roche Ltd.

D. Wormser is an employee and shareholder of F. Hoffmann-La Roche Ltd.

J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaking honoraria from the following entities: AbbVie, Academic CME, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, Forward Pharma A/S, MedDay Pharmaceuticals, Novartis Pharmaceuticals, PRIME, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals and WebMD; royalties are received for outsourced monoclonal antibodies through UTHealth from Millipore Corporation.

Background: Oral immunotherapies are becoming a standard treatment in relapsing-remitting multiple sclerosis. Relapse and disability outcomes have not been directly compared between oral immunotherapies.

Objective: To compare relapse and disability outcomes and treatment persistence among patients treated with teriflunomide, dimethyl fumarate and fingolimod.

Methods: We identified all patients with relapsing-remitting multiple sclerosis treated with teriflunomide, dimethyl fumarate or fingolimod, with minimum 6-month treatment persistence and disability follow-up in the global MSBase cohort study. Patients were matched using propensity scores. Three pairwise analyses compared annualised relapse rates and hazards of disability accumulation, disability improvement and treatment discontinuation (analysed with negative binomial models and weighted conditional survival models, with pairwise censoring) over a 2-year follow-up. Sensitivity analyses were completed.

Results: The eligible cohorts consisted of 450 (teriflunomide), 599 (dimethyl fumarate) or 1936 (fingolimod) patients. Annualised relapse rates were higher on teriflunomide compared with dimethyl fumarate (0.26 vs. 0.17; p=0.005) and fingolimod (0.24 vs. 0.18; p=0.009) and similar on fingolimod and dimethyl fumarate (0.21 vs. 0.24; p=0.13). No differences in disability accumulation
or improvement were found between the therapies (p<0.1). Patients were less likely to discontinue fingolimod vs. teriflunomide and dimethyl fumarate (p<0.001). Discontinuation rates on teriflunomide and dimethyl fumarate were similar (p=0.9).

Sensitivity analyses, including secondary progressive disease, different matching strategies, different prior disease activity and matching on MRI, largely confirmed the outcomes of the primary analyses.

Conclusion: The effect of fingolimod and dimethyl fumarate on relapse frequency was similar, and superior to teriflunomide. The effect of the three oral therapies on disability outcomes was similar during the initial two years. Persistence on fingolimod was superior to the two comparator drugs.

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Alessandra Lugaresi is a Bayer, Biogen, Genzyme, Merck Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institution received research grants from Bayer, Biogen, Merck, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM).

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Eugenio Pucci served on scientific advisory boards for Merck, Genzyme and Biogen; he has received honoraria and travel grants from Sanofi Aventis, UCB, Lundbeck, Novartis, Bayer Schering, Biogen, Merck, Genzyme and Teva; he has received travel grants and equipment from “Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche”.

Franco Granella served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and received funding for travel and speaker honoraria from Biogen Idec, Merck, and Almirall.

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Patrizia Sola served on scientific advisory boards for Biogen Idec and TEVA, she has received funding for travel and speaker honoraria from Biogen Idec, Merck, Teva, Sanofi Genzyme, Novartis and Bayer and research grants for her Institution from Bayer, Biogen, Merck, Novartis, Sanofi, Teva.

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Claudio Solaro did not declare any competing interests.

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Rana Karabudak did not declare any competing interests.

Helmut Butzkeuven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck, Novartis and Biogen.

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T cell mediated experimental CNS autoimmunity induced by PLP in SJL mice is modulated by Evobrutinib (M2951) a novel Bruton’s tyrosine kinase inhibitor

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Bruton’s tyrosine kinase (Btk) is a member of the Tec family of non-receptor tyrosine kinases expressed in cells of hematopoietic origin, including B cells and myeloid cells, but not T cells. In addition to its well-known effects on diverse B cell functions, BTK mediates signaling in innate immune cells downstream of various receptors including Fc, integrin, chemokine and Toll-like receptors. The goal of this study was to test the clinical efficacy of BTK inhibition in an experimental autoimmune encephalomyelitis (EAE) model not responsive to B cell inhibition, but in which pathogenic T cells and innate immune cells are centrally involved in disease.

Methods: EAE was induced in SJL/J mice by Proteolipic Protein (PLP) 139-151 peptide and Complete Freund’s adjuvant (CFA) on day 0. Mice also received a pertussis toxin injection on day 0 and day 2. Disease severity was scored using a standard scale from 0 - 5. Treatment with the BTKi M2951 (0.3, 1, 3, 10 mg/kg), or vehicle was conducted in 2 separate experiments using both prophylactic and late-therapeutic regimens. The compound Fingolimod (FTY720 1 mg/kg) served as a positive, anti-CD20 AB as a negative control. Blood was collected at the end of the studies for pharmacokinetic and BTK occupancy analysis. Gene expression analysis was performed on spinal cords.

Results: Both prophylactic and therapeutic treatment with M2951 reduced clinical score in a dose dependent manner. While the lowest dose (0.3 mg/kg) exerted a minimal effect, higher doses (1, 3, 10 mg/kg) of the BTKi significantly ameliorated EAE severity when administered before disease onset or after the peak of the disease. M2951 (10 mg/kg) reached comparable efficacy to FTY720 in the therapeutic setting. After M2951 treatment a high degree of BTK occupancy was achieved in peripheral blood early in disease, while BTK occupancy in the brain was found only at later timepoints. Anti-PLP titers were not reduced by M2951 treatment, but myeloid genes in the spinal cord were affected by M2951.

Conclusions: BTK inhibition proved to be effective in limiting CNS inflammation and clinical severity in a T cell dependent EAE model. Given the fact that BTK is not expressed in T cells, further mechanistic experiments are needed to investigate the effect of BTKi on innate immune cells in the context of this disease. Our results suggest that BTK inhibition might have broader therapeutic benefit in MS than seen with B cell depletion alone.

Disclosure

All authors are employees of EMD Serono Inc.

P679

Real world efficacy and safety of teriflunomide in patients with relapsing-remitting multiple sclerosis

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Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS (RRMS). Relapse and disability outcomes have not been directly compared between oral immunotherapies.

Objective: We aimed to compare relapse and MRI outcomes, treatment persistence and safety in patients treated with teriflunomide in real-world clinical settings.

Methods: Using the Imed MS registry, relapsing remitting MS patients who had been prescribed teriflunomide in 12 MS centers in Turkey were retrospectively analyzed.

Results: A total of 532 RRMS (356 females, 176 males; female/male=2.01) patients treated with teriflunomide were included in the study. Mean age at teriflunomide initiation was 40.9 ± 10.8 years (19-76). Before treatment initiation, the mean annualized relapse rates was 0.66 and the median EDSS was 2.2 (0-5.5). Teriflunomide was first line drug in 30% of the patients. Three hundred and seventy-two patients switched to teriflunomide from other treatments (76% switched from injectables and
8% from fingolimode, 5% from natalizumab, 11% from others) due to loss of tolerability or inefficacy. The average duration for drug treatment was 1.4 years (1 month to 10 years). In 295 patients, treatment duration was more than a year and more than 2 years for 77 patients. Annualized relapse rates were 0.26 in year 1 and 0.21 in year 2. MRI’s showed new or gadolinium enhanced lesions in 21% of patients in the first year. Fifty-nine patients (%11.1) stopped teriflunomide mainly due to lack of tolerance (15 patients), lack of efficacy (23), adverse events (18 patients) and 3 for planned pregnancy. Four patients discontinued due to hair loss. No life-threatening adverse events were encountered.

Conclusion: Even with the limitations of an open label observational study, we found that efficacy and safety of teriflunomide in real-life settings were similar to data obtained by the pivotal trials. In this teriflunomide treated patients cohort, the female to male ratio were similar to the MS population treated with other drugs. Relapse rates decreased during the first and second years of treatment with teriflunomide compared to pre-treatment. We conclude that teriflunomide is a well-tolerated and effective option for early RRMS patients as first-line therapy and switch therapy from other medications in patients without high disease activity.

Disclosure
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P680
Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in relapsing-remitting multiple sclerosis in clinical practice at 24-month follow-up
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Objective: To assess real-world efficacy and discontinuation of dimethyl fumarate (DMF) and fingolimod (FTY) over 24 months in relapsing-remitting multiple sclerosis (RRMS) patients.

Background: DMF and FTY are approved oral disease modifying therapies (DMT) for relapsing MS. Our previous 12-month comparative study showed comparable clinical efficacy in RRMS patients, but DMF patients discontinued DMT earlier and had higher likelihood of gadolinium-enhancing (GdE) lesions compared to FTY.

Methods: 293 DMF-treated and 215 FTY-treated RRMS patients completed 24-month follow-up in a large academic MS center.

Discontinuation rates and measures of disease activity were assessed using propensity score (PS) weighting. Covariates used in the PS model included demographics and baseline clinical and MRI characteristics within 12 months of respective DMT initiation. The primary outcome was on-treatment annualized relapse rate (ARR). Secondary outcome measures included the proportion of patients who discontinued therapy, time to first relapse and discontinuation, and proportion with new MRI lesions defined as new T2-weighted and/or GdE lesions.

Results: PS weighting showed excellent covariate balance. By 24 months, the proportion of patients who discontinued therapy was high (DMF = 43.3%; FTY = 32.6%), largely driven by intolerability (of all patients with discontinuation: DMF = 59.8%; FTY = 44.3%). Overall, the proportion with relapses was low (DMF = 17.9%; FTY = 17.7%). DMF-treated patients demonstrated increased likelihood of discontinuation [OR = 1.85, 95% CI (1.16, 2.95)] that was commonly due to adverse effects [OR = 2.29, 95% CI (1.28, 4.09)] and occurred earlier compared to FTY [HR = 1.71, 95% CI (1.29, 2.26)]. DMF- and FTY-treated patients had comparable ARR [rate ratio = 1.33, 95% CI (0.52, 3.43)], time to first relapse [HR = 1.27, 95% CI (0.84, 1.92)], and MRI disease activity [OR = 1.37, 95% CI (0.75, 2.50)]. The 12-month treatment effect difference in new GdE lesions among DMF-treated patients was not seen in our 24-month experience [OR = 1.69, 95% CI (0.75, 3.84)].

Conclusions: RRMS patients treated with DMF and FTY were equally likely to develop clinical relapses and new MRI disease activity including GdE lesions by 24 months. DMF had higher likelihood of early discontinuation due to tolerability compared to FTY.

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P681
An observational study of alemtuzumab-treated relapsing MS patients at the UBC MS Clinic
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Introduction: Clinical trials have established efficacy of alemtuzumab in relapsing-remitting MS (RRMS), but data from non-controlled settings is limited. Here, we report data on alemtuzumab-treated RRMS patients in a British Columbia cohort, and compare their outcome to concurrent RRMS patients that were denied alemtuzumab by their drug insurance coverage and treated with other MS disease modifying therapies (DMTs).

Methods: In a single center (UBC MS Clinic), a retrospective chart review was conducted. Prior to government reimbursement of alemtuzumab, only patients with extended insurance coverage who met clinical criteria were eligible for therapy. The alemtuzumab cohort included those who had at least one cycle of therapy from July 2014-July 2016. Patients with lack of reimbursement were used as a contemporary control cohort. Clinical outcomes included annualized relapse rate (ARR) and change in EDSS. Improvement was defined as a 1-point decrease sustained over 6 months, stability between -1 and 1, and worsening as a 1-point increase.

Results: 73 RRMS patients received alemtuzumab (41 received 2 cycles, 32 had 1 cycle). The comparison group included 51 patients similar in pre treatment ARR, EDSS and demographics. At the time of first data extraction mean follow-up was 13.2 months (ranging from 1 to 24 months). The post treatment ARR was 0.13 (95% CI: 0.04-0.22) for alemtuzumab versus 0.36 (0.17-0.56) for the comparator group, which was significantly different using a two-sample t-test (p=0.0241). Within-group comparisons to pretreatment values showed that mean EDSS improved in the alemtuzumab group by 0.5 at 12 months (SD 1.20; 95% CI: -0.94 to -0.09; p=0.02) by Wilcoxon matched-pairs signed rank test. There was no significant change in EDSS in the control group (mean EDSS decrease of 0.3 (SD 1.12; 95% CI: -0.78 to 0.13; p=0.2). At last follow-up, 39% of alemtuzumab-treated patients improved from pretreatment values on the EDSS Scale, 39% were stable, and 22% worsened. In the comparator group, 26% had improvement, 50% were stable, and 24% worsened. The year 2 (July 2017) follow-up data is being analyzed and will be presented at the meeting.

Conclusion: The effectiveness of alemtuzumab in RRMS in a real world setting is similar to what is reported in phase 3 clinical trials. Alemtuzumab-treated patients had better relapse and disability outcomes than a similar group of RRMS patients denied alemtuzumab that then went on to other MS DMTs.

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Dimethyl fumarate therapy is associated with immune-deviation and anti-inflammatory cytokine profiles in B and T cells in patients with multiple sclerosis

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Introduction: Dimethyl fumarate (DMF) is approved for patients with relapsing remitting Multiple Sclerosis (RRMS). We and others have shown that DMF reduces circulating lymphocytes, mainly CD8 T cells and B cells, and alters the proportions of B cell subsets, reducing memory B cells while increasing transitional B cells. The aim of this study was to assess the effect of DMF therapy on the cytokine profile of B and T cells in RRMS patients.

Methods: Blood was obtained from 23 RRMS patients about to initiate DMF therapy (12 1st line, 11 2nd line patients), before and after treatment initiation. B and T cells were purified and cultured for 40 hours in 3 setups: B cells with/without anti-IgM/antiCD40-stimulation; T cells with anti-CD3/CD28 + ionomycin/Phorbol 12-myristate 13-acetate stimulation; stimulated B cells co-cultured with stimulated baseline T cells used for both baseline and 3.5m setup to focus upon the drug effect on B cells. After 4h Golgistop, cells were stained for IL-10, TNFα, IFNγ, IL-4, TGFβ and Lymphotoxin-α (LTA) and analyzed by flow cytometry. IL-6 secretion from B cells was assessed by Cytometric bead array.

Results: In B cells cultured alone, 3m DMF therapy significantly increased the expression of TGFβ and IL10, mainly in 1st line patients, as well as % IL10+ B cells in 2nd line patients, while in 1st line patients % IL10+ B cells was reduced. % IL4+, LTA+ and TNFα- B cells were reduced in 1st line patients, while % IFNγ+ B cells was increased (2nd line patients only). Furthermore, IL6 secretion was elevated (1st line patients). In B cells co-cultured with T cells, similar effects were found, including an increase in % TGFβ+ B cells (2nd line), while a reduction in % LTA+ and IL4+ B cells (1st line). A reduction in % IL10+ B cells was found in 1st line patients, but their IL10 expression level was elevated (trend). In T cells cultured alone, 3m DMF therapy significantly reduced % TNFα+ and IFNγ+ as well as double-positive IFNγ+TNFα+ CD4 T cells. The expression levels of both LTA+ and TGFβ+ in CD4 T cells were increased, while no effect was found on IL10 or IL4. Baseline T cells co-cultured with B cells from DMF-treated patients, showed no change.

Conclusion: DMF therapy is associated with modulation of several lymphocyte cytokines, mainly with reduced pro-inflammatory cytokines such as: LTA+ in B cells and TNFα and IFNγ+ in T cells, while increased anti-inflammatory cytokines such as IL10 and TGFβ+ in B cells and TGFβ+ in T cells.

Disclosure

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Changing disease modifying therapy switching dynamics for relapsing-remitting multiple sclerosis patients

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Background: The management of multiple sclerosis (MS) has changed substantially over the past 10 years. The availability of new, approved disease modifying therapies (DMTs) has provided physicians and patients with treatment options with different clinical profiles (levels of efficacy and type of risks associated), administration regimens (route and frequency), and associated risks.

Objective: To compare time between DMT initiation and first DMT switch by year of diagnosis, and to compare reasons for switching from previous DMT to current DMT by year of switch, amongst patients with relapsing-remitting MS (RRMS) currently treated with a DMT in real-world clinical practice.

Methods: RRMS patients diagnosed prior to 2016, currently receiving a DMT were identified from the Adelphi MS Disease Specific Programme, a global cross-sectional study of MS patients from clinical practice in various countries (France, Germany, Italy, Spain, UK and US). Time from DMT initiation to first DMT switch was compared across year of initial MS diagnosis (between ≤2006 and 2015) using a log-rank test, and a test for trend.

Results: Analysis of time from DMT initiation to first DMT switch was conducted on 5929 patients. Results differed significantly by year of initial MS diagnosis (log-rank P < 0.001; trend P < 0.001). The time taken for 25% of patients to replace their first DMT was 3.6 years for those diagnosed in ≤2006 and 1.3 years for those diagnosed in 2014, with corresponding trend of decreasing time taken between 2007 and 2013. Analysis on reasons for switching was conducted on 2939 patients. Reasons for switching from previous DMT to current DMT differed significantly by year of switch, for Efficacy (≤2011, 73.8%; 2012, 72.7%; 2013, 70.2%; 2014, 69.6%; 2015, 60.8%; P < 0.001) and for Any Other Reason (≤2011, 43.9%; 2012, 48.9%; 2013, 52.2%; 2014, 54.5%; 2015, 59.5%; P = 0.001).

Conclusion: The introduction of new DMTs for MS that vary in route of administration, frequency of dosing, and associated benefit/risk profile has been associated with a reduction in the time patients are treated with their first DMT before switching to a different DMT, and switching is increasingly driven by reasons other than efficacy.

Disclosure

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P685
Evaluation of the long-term treatment effect of teriflunomide on cognitive outcomes and association with brain volume change: data from TEMSO and its extension study
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Background: In TEMSO (NCT00134563) and TOWER (NCT00751881), teriflunomide 14 mg significantly reduced the risk of disability worsening vs placebo (PBO). In a post hoc, blinded SIENA (Structural Image Evaluation using Normalization of Atrophy) analysis of the TEMSO MRI dataset, teriflunomide significantly reduced brain volume loss (BVL) vs PBO. Further analysis indicated a strong correlation between BVL and disability worsening over 2 years in TEMSO; patients with lower rates of BVL had better disability outcomes. Studies in MS also show correlation between BVL and cognitive impairment, as measured using the Paced Auditory Serial Addition Test (PASAT).

Methods: The effect of teriflunomide on cognitive function was assessed by change from baseline (BL) in PASAT-3 scores, 1 of 3 components of the Multiple Sclerosis Functional Composite, a predefined outcome in the TEMSO core (N=1086) and extension (NCT00803049; N=740) studies. Additional analyses assessed change in PASAT-3 scores over 5 years by categorizing percentage brain volume changes from BL to Year 2 (assessed by SIENA) into groups of varying degree of BVL change.

Results: Adjusted mean changes from BL to Week 96 in PASAT-3 Z-score were 0.022 and 0.073 for PBO and teriflunomide 14-mg groups, respectively (positive score indicated an improvement); P=0.0435 for difference vs PBO. Improvements in PASAT-3 Z-score with teriflunomide 14 mg were observed over the long term: mean (SD) changes from BL at Weeks 156 and 276 were 0.194 (0.634) and 0.200 (0.677), respectively. In terms of raw PASAT-3 score for patients treated with teriflunomide 14 mg, the mean (SD) changes from BL at Weeks 96, 156, and 276 were 1.17 (5.90), 2.36 (7.73), and 2.43 (8.24) units of change, respectively.

In an association analysis, the group with the least BVL from BL to Year 2 demonstrated a significant improvement in PASAT-3 score with teriflunomide treatment over 5 years vs the group with the most BVL.

Conclusions: Teriflunomide significantly slowed the rate of cognitive decline, vs PBO, over 2 years in the TEMSO core study. This effect was maintained over the extension study, demonstrating the positive effect of long-term teriflunomide treatment on slowing cognitive decline, with the greatest effect observed in patients with the least BVL. This study highlights the long-term predictive value of BVL earlier in the disease course.

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P686
Incidence rates of malignancies in patients with multiple sclerosis in clinical trials and epidemiological studies
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Background: To provide an update on the IR of malignancies in the OCR clinical trial programme, in the context of data from other multiple sclerosis (MS) trials (PBO only), epidemiological data sources (MS registries) and the general population (National Cancer Institute [NCI] Surveillance, Epidemiology, and End Results [SEER]).

Objective: To provide an update on the IR of malignancies in the OCR clinical trial programme, in the context of data from other multiple sclerosis (MS) trials (PBO only), epidemiological data sources (MS registries) and the general population (National Cancer Institute [NCI] Surveillance, Epidemiology, and End Results [SEER]).
Methods: Crude IR of first malignancies were calculated across the OCR MS development programme (Phase II: NCT00676715; OPERA I: NCT01247324; OPERA II: NCT01412333; ORATORIO: NCT01194570) in a primary analysis (clinical cut-off dates 22 January–24 July 2015) and updated as of 20 January 2016 and 17 February 2017. Results are contextualised using a meta-analysis of published data of PBO-treated patients from up to 10 MS clinical studies (PBO-MSCS), and data derived from other published MS-specific epidemiological sources (Danish, Swedish or Canadian British Columbia MS registries [DMSR, SMSR, CBCMSR]). Age- and sex-standardised IR of malignancies from the OCR MS programme and the SEER database are provided.

Results: IRs per 100 patient-years (95% confidence interval) for all malignancies and breast cancer in the primary analysis for OCR were 0.43 (0.26-0.66) and 0.26 (0.11-0.54); for the January 2016 update, IRs were 0.44 (0.29-0.65) and 0.23 (0.10-0.46). As of 17 February 2017, the IR of all malignancies was 0.45 (0.32-0.63) for OCR, 0.50 (0.36-0.67) for PBO-MSCS and 0.67 (0.63-0.71) for the DMSR. The rate of female breast cancer was 0.19 (0.09-0.37) for OCR, 0.16 (0.06-0.32) for PBO-MSCS, 0.21 (0.18-0.23) for DMSR, 0.20 (0.18-0.22) for SMSR and 0.14 (0.11-0.16) for CBCMSR. The standardised IR for malignancies excluding non-melanoma skin cancer was 0.24 (0.15-0.41) for OCR and 0.27 (0.27-0.27) for SEER, and for female breast cancer was 0.19 (0.08-0.42) for OCR and 0.12 (0.12-0.13) for SEER.

Conclusions: With additional exposure, the rate of malignancies in OCR-treated patients fall within the range of PBO data from clinical trials in MS and epidemiological data. It is noted that indirect comparisons have limitations, and ongoing data collection through post-approval safety studies are required to characterize the potential risk of malignancies, including breast cancer.

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C. Li is an employee of F. Hoffmann-La Roche Ltd.
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P687
Subgroup analyses of annualised relapse rate in patients with relapsing multiple sclerosis who received ocrelizumab or interferon beta-1a in the Phase III OPERA I and OPERA II studies
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Background: Ocrelizumab (OCR) is an FDA-approved, humanised, CD20+ B cell-selective monoclonal antibody for the treatment of relapsing (RMS) or primary progressive forms of multiple sclerosis (PPMS). In the identical Phase III OPERA I (NCT01247324) and OPERA II studies (NCT01412333), OCR reduced annualised relapse rate (ARR; primary outcome) in patients with RMS relative to interferon β-1a (IFNβ1a) in both individual study analyses and a prespecified pooled analysis.

Objective: To assess the effect of OCR vs IFNβ1a on ARR in subgroups of the pooled OPERA studies.

Methods: In the OPERA trials, patients were randomised 1:1 to receive intravenous OCR 600 mg every 24 weeks or subcutaneous IFNβ1a 44 µg three times weekly for 96 weeks. In this post hoc analyses, ARR estimates were calculated within subgroups for the intent-to-treat population of the pooled OPERA studies (OCR, n=827; IFNβ1a, n=829) using the negative binomial or quasi-Poisson model, and the log-transformed exposure time as an offset variable (p values relate to the ARR of OCR vs IFNβ1a).

Results: Patient numbers and characteristics were comparable between treatments and within each subgroup stratum. The
reduction in ARR with OCR (ARR, 0.16) vs IFNβ1a (ARR, 0.29) in the overall pooled population (p< 0.001) was maintained across all subgroups and strata; however, variations in the magnitude of effect with OCR vs IFNβ1a were seen. Results by subgroup were as follows: age (< 40 years: OCR 0.15, IFNβ1a 0.36, p< 0.001; ≥40 years: OCR 0.17, IFNβ1a 0.23, p=0.073), gender (male: OCR 0.14, IFNβ1a 0.25, p=0.001; female: OCR 0.16, IFNβ1a 0.30, p< 0.001), prior disease-modifying therapy use in the last 2 years (yes: OCR 0.15, IFNβ1a 0.32, p< 0.001; no: OCR 0.16, IFNβ1a 0.28, p< 0.001), baseline Expanded Disability Status Scale (EDSS) score < 2.5≥2.5 (< 2.5: OCR 0.10, IFNβ1a 0.21, p< 0.001; ≥2.5: OCR 0.16, IFNβ1a 0.29, p< 0.001), baseline EDSS score < 4.0≥4.0 (< 4.0: OCR 0.11, IFNβ1a 0.21, p< 0.001; ≥4.0: OCR 0.11, IFNβ1a 0.22, p< 0.001), prior relapses in the last 12 months (≤1: OCR 0.14, IFNβ1a 0.24, p< 0.001; ≥2: OCR 0.20, IFNβ1a 0.38, p< 0.001) and T1 Gad' lesions at baseline (none: OCR 0.18, IFNβ1a 0.25, p=0.025; ≥1: OCR 0.13, IFNβ1a 0.35, p< 0.001).

Conclusions: The results of these subgroup analyses were consistent with those of the overall pooled population for OCR vs IFNβ1a in reducing ARR across all subgroups considered, including demographic, clinical and MRI characteristics, in patients with RMS.

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C. Papeix has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, and has participated in advisory boards in the past years with Biogen, MedDay, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva.
B. Cree has received personal compensation for consulting from AbbVie, Biogen, EMD Serono and Novartis.
B. Turner has received honoraria, travel grants and been a member of advisory boards for Biogen, Merck Serono, Novartis, Sanofi Genzyme and Roche.
L. Kappos’s institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos’s activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; license fees for Neurostatus products; and research grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, the Novartis Research Foundation and the Roche Research Foundation.
X. Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos.
J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaker honoraria from the following entities: AbbVie, Academic CME, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, Forward Pharma A/S, MedDay Pharmaceuticals, Novartis Pharmaceuticals, PRIME, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals and WebMD; royalties are received for outlicensed monoclonal antibodies through UTH ealth from Millipore Corporation.
R. Buffels is an employee of F. Hoffmann-La Roche Ltd.
H. Garren is an employee and shareholder of Genentech, Inc.
C.J. Guittari is an employee of Genentech, Inc.
J. Han is an employee of Genentech, Inc.
S.L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Symbiotix and Bionure; he has also received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

P688
Subgroup analyses of no evidence of disease activity in patients with relapsing multiple sclerosis who received ocrelizumab or interferon beta-1a in the Phase III OPERA I and OPERA II studies
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Background: Ocrelizumab (OCR), a humanised, CD20- B cell-selective monoclonal antibody, increased the proportion of patients with relapsing MS (RMS) with no evidence of disease activity (NEDA) vs interferon beta-1a (IFNβ1a) in the individual Phase III OPERA I (NCT01247324) and OPERA II studies (NCT014112333), and in a prespecified analysis of the pooled populations.

Objective: To assess the effect of OCR vs IFNβ1a on NEDA status in subgroups of the pooled OPERA studies.

Methods: In the OPERA trials, patients were randomised 1:1 to receive intravenous OCR 600 mg every 24 weeks or subcutaneous IFNβ1a 44 µg three times weekly for 96 weeks. In this post hoc analysis, proportions of patients with NEDA (absence of 12-week confirmed disability progression, protocol-defined relapse, new/enlarging T2 lesions or T1 Gad’ lesions) were compared using the Cochran-Mantel-Haenszel test based on the modified intent-to-treat population (exclusion of patients discontinuing treatment for reasons other than lack of efficacy or death and had NEDA prior to discontinuation) of the pooled OPERA studies (OCR, n=761; IFNβ1a, n=759); p values relate to OCR vs IFNβ1a.

Results: Patient numbers and characteristics were comparable between treatments and within each subgroup stratum. The increase in the proportion of patients with NEDA with OCR (47.7%) vs IFNβ1a (27.1%) in the overall pooled population (p<
0.001) was maintained across all subgroups and strata; however, variations in the magnitude with OCR vs IFNβ1a were seen. Results by subgroup were as follows: age (< 40 years: OCR 44.3%, IFNβ1a 22.6%, p< 0.001; ≥40 years: OCR 52.8%, IFNβ1a 33.7%, p< 0.001), gender (male: OCR 44.0%, IFNβ1a 22.2%, p< 0.001; female: OCR 49.7%, IFNβ1a 29.6%, p< 0.001), prior disease-modifying therapy use in the last 2 years (yes: OCR 42.8%, IFNβ1a 23.9%, p< 0.001; no: OCR 49.5%, IFNβ1a 28.3%, p< 0.001), baseline Expanded Disability Status Scale (EDSS) score < 2.5/≥2.5 (< 2.5: OCR 50.5%, IFNβ1a 27.5%, p< 0.001; ≥2.5: OCR 46.0%, IFNβ1a 26.9%, p< 0.001) baseline EDSS score < 4/≥4 (< 4: OCR 50.3%, IFNβ1a 26.4%, p< 0.001; ≥4: OCR 39.6%, IFNβ1a 29.4%, p=0.043), prior relapses in the last 12 months (≤1: OCR 49.2%, IFNβ1a 29.2%, p< 0.001; ≥2: OCR 44.2%, IFNβ1a 22.6%, p< 0.001) and T1 Gd+ lesions at baseline (none: OCR 59.6%, IFNβ1a 38.8%, p< 0.001; ≥1: OCR 30.1%, IFNβ1a 10.2%, p< 0.001).

**Conclusions:** The results of these subgroup analyses were consistent with those of the overall pooled population on maintaining NEDA status.

**Disclosure**

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B. Turner has received honoraria, travel grants and been a member of advisory boards for Biogen, Merck Serono, Novartis, Sanofi Genzyme and Roche.

C. Papeix has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, and has participated in advisory boards in the past years with Biogen, MedDay, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva.

B. Cree has received personal compensation for consulting from AbbVie, Biogen, EMD Serono and Novartis.

L. Kappos’s institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for Prof Kappos’s activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharma, Pfizer, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; license fees for Neurostatus products; and research grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, the Novartis Research Foundation and the Roche Research Foundation.

X. Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos. J.S. Wolinsky has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaker honoraria from the following entities: AbbVie, Academic CME, ACTRIMS, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, CMSC, ECTRIMS, Forward Pharma A/S, MedDay Pharmaceuticals, Novartis Pharmaceuticals, PRIME, Roche Genentech, Sanofi Genzyme, Strategic Consultants International, Takeda, Teva Pharmaceuticals and WebMD; royalties are received for outs Irelandized monoclonal antibodies through UTHealth from Millipore Corporation.

R. Buffels is an employee of F. Hoffmann-La Roche Ltd.

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S.L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Symbioxis and Bionure; he has also received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

**P689**

**Efficacy and safety of alemtuzumab versus fingolimod in RRMS patients after switch from natalizumab: a retrospective analysis**

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**Results by subgroup were as follows:** age (< 40 years: OCR 50.3%, IFNβ1a 26.4%, p< 0.001; ≥40 years: OCR 39.6%, IFNβ1a 29.4%, p=0.043), prior relapses in the last 12 months (≤1: OCR 49.2%, IFNβ1a 29.2%, p< 0.001; ≥2: OCR 44.2%, IFNβ1a 22.6%, p< 0.001) and T1 Gd+ lesions at baseline (none: OCR 59.6%, IFNβ1a 38.8%, p< 0.001; ≥1: OCR 30.1%, IFNβ1a 10.2%, p< 0.001).

Natalizumab is a highly efficacious treatment for relapsing-remitting multiple sclerosis (RRMS). However, it fails to sufficiently prevent disease activity in some patients and is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) that grows with treatment duration.

A significant proportion of patients therefore need to undergo a change in disease-modifying therapy (DMT). The currently available alternatives approved for (highly) active RRMS are alemtuzumab and fingolimod. However, so far there is no comparative data on the safety and efficacy of these substances after natalizumab cessation.

We therefore conducted a retrospective multicenter study of RRMS patients after cessation of natalizumab. 8 German centers provided data of about 130 patients who stopped natalizumab due to PML risk, or - in contrast to previous studies - required change in disease-modifying therapy (DMT). The currently available alternatives approved for (highly) active RRMS are alemtuzumab and fingolimod. However, so far there is no comparative data on the safety and efficacy of these substances after natalizumab cessation.

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lower likelihood of drug discontinuation. About 1 out of 10 patients discontinued treatment with alemtuzumab, whereas 1 out of 3 patients stopped fingolimod within the observation period, mostly because of breakthrough disease. Significant disability progression was detected in 1 out of 10 patients on alemtuzumab and in 1 out of 4 patients on fingolimod. Adverse events in the fingolimod group mainly comprised hepatopathy and lymphopenia. Alemtuzumab patients predominantly experienced infusion-associated reactions.

We conclude that alemtuzumab is a safe and efficacious alternative for patients that stopped natalizumab. It was superior to fingolimod in prevention of relapses and disability progression. Side effects were balanced between both groups; however, we did not yet discover secondary autoimmune disorders in the alemtuzumab group, which will expectedly peak in long-term follow-up. These data provide relevant advice for the development of treatment algorithms in patients with active RRMS. However, we are aware of the limitations of the retrospective study design. This project is supported financially by Sanofi Genzyme.

Disclosure

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P690

Cladribine tablets produce selective and discontinuous reduction of B and T lymphocytes and natural killer cells in patients with early and relapsing multiple sclerosis (ORACLE-MS, CLARITY and CLARITY Extension)

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Background: Efficacy of cladribine tablets 3.5mg/kg (cumulative dose given in short courses annually for 2 years) has been demonstrated in patients with early MS (ORACLE-MS) and in patients with relapsing-remitting multiple sclerosis (RRMS) in CLARITY/CLARITY Extension studies. Objective: To evaluate the effect on B and T lymphocyte and natural killer (NK) cell profiles after the first administration of cladribine tablets in the ORACLE-MS, CLARITY and CLARITY Extension studies. Methods: Longitudinal evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of cladribine tablets either as part of the initial 3.5mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo switched to active treatment groups (CLARITY Extension). Lymphocytes were immunophenotyped at baseline, and Weeks 5, 13, 24 and 48. Changes in absolute cell numbers and composition of lymphocyte subtypes were evaluated. Results: The baseline distributions of absolute lymphocyte counts (ALC) were similar across studies. Temporal profiles of CD19+ B lymphocytes and CD4+ and CD8+ T lymphocytes were generally consistent across studies. The most rapid reduction in cell numbers occurred in the CD19+ B cell compartment (approximately 75% at Week 5 in each study). Nadir for CD19+ B cells was reached at Week 13 with an 81%, 84% and 82% median reduction for patients treated with cladribine tablets in CLARITY (N=97), CLARITY Extension (N=136), and ORACLE-MS (N=41). Reconstitution of CD19+ B cells towards baseline occurred from Week 24 to 48. CD4+ and CD8+ T cells were also markedly reduced in numbers, but to a lesser degree than CD19+ B cells (at most 55% at Week 13 for CD4+ cells and 48% at Week 48 for CD8+ cells in patients treated with cladribine tablets in ORACLE-MS). Reductions in T cells were discontinuous but had not fully returned to baseline by week 48. CD16+/CD56+ NK cells were also transiently reduced with cladribine tablets; nadir occurred at Week 13 in ORACLE-MS (44% reduction), with recovery evident at Weeks 24 (29% reduction) and 48 (23% reduction). Conclusions: Cladribine tablets achieved an early and discontinuous reduction of peripheral blood B cells with a rapid
reconstitution to baseline, and a moderate and discontinuous reduction in T cell counts. Treatment with cladribine tablets is associated with early decreases in NK cells followed by rapid recovery.

Disclosure

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OS: serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, and Therapeutic Advances in Neurological Disorders. He has served on data monitoring committees for Pfizer and TG Therapeutics without monetary compensation. He has advised Genzyme and Novartis, and has participated in a Teva-sponsored meeting. He currently receives grant support from Teva Pharmaceuticals and Opeka Therapeutics. He is funded by a Merit Review grant (federal award document number (FAIN) I01BX001674) from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development.

PS-S: has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme.

GG: has received speaker honoraria and consulting fees from Abbvie, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec FivePrime, GlaxoSmithKline, GW Pharma, Merck, , Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genezyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood.

TL: has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, Teva Neuroscience.

YH, DD and UB are employees of EMD Serono, USA.

Results:

Although long-term depletion (70-95%) of memory CD4 T cells was evident during the 2 year observation period, memory B (CD19+, CD27+) were likewise substantially depleted during this time, and their loss was consistent with disease control. Flat-lining of memory B cells was masked by rapid hyper-repopulation of immature and mature B cells in the relative absence (>80% depletion) of CD4 T regulatory cells and CD8 T cells, an environment associated with the generation of B cell autoreactivity. This was also associated with the generation of binding (~85%) and notably neutralizing (~80%) alemtuzumab-reactive antibodies. At the population level these failed to significantly influence leukocyte depletion and disease activity, perhaps not surprising as only 0.6% of pwMS had neutralizing antibodies before cycle 2. However, at the individual level some pwMS people deplete poorly, and this may be more notable in people with anti-drug antibodies. Furthermore, such antibodies may be more prominent and problematic in pwMS requiring a third or forth treatment cycle as about 75% pwMS had binding and 31% pwMS had neutralizing antibodies at pre-cycle 3. These neutralizing antibodies appear to nullify treatment response in some individuals.

Conclusions: The European summary of product characteristic suggests alemtuzumab increases in memory T and B, and T regulatory cells. However, these figures are based on percentages to a reference population, thereby obstructing appreciation of their absolute numbers, which are all markedly depleted. This opens the new perspective on alemtuzumab exerting its effect mainly via memory B cell depletion, as shown with more specific B cell depleting drugs. Differential kinetics of B cell subset depletion and repopulation also provide an explanation for SAI. Neutralizing antibodies, not mentioned in the pivotal trial reports, are potentially of crucial importance for loss of depletion and, thus, drug efficacy in some individuals. These may need to be monitored.

Disclosure

None considered relevant.

DB is a shareholder and consultant to Canbex therapeutics and has received research support from Sanofi-Genzyme.

GG is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen-Idec, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck-Serono, Genzyme-Sanofi, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians’ summit and several medical education meetings. He is also the co-chief editor of Multiple Sclerosis and Related Disorders (Elsevier).

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P692
Monomethyl fumarate treatment impairs maturation of human myeloid dendritic cells and their ability to activate T cells
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Background: Dimethyl fumarate (DMF), and its active metabolite monomethyl fumarate (MMF), effectively lead to reduction in disease relapses and active MRI lesions. DMF and MMF are known to be effective in modulating T and B cell responses, although their effect on the phenotype and function of human myeloid dendritic cells (mDCs) is not fully understood.

Objective: To investigate the role of MMF on mDCs maturation and ability to prime T cells.

Methods: mDCs from healthy controls were purified and gene expression was assessed by PCR array after in vitro MMF treatment. The ability of mDCs to activate T cells was assessed by in vitro co-culture system. mDCs from DMF-treated MS patients were analyzed by flow cytometry and PCR.

Results: MMF treatment induces a less mature phenotype of mDCs with reduced expression of MHC-II, costimulatory molecules CD86, CD40 and CD83 and reduced expression of NF-xB subunits RELA and RELB. T cells co-cultured with MMF-treated mDCs show reduced proliferation with decreased production of IFN-g, IL-17, and RELB. T cells co-cultured with MMF-treated mDCs show reduced expression of MHC-II, costimulatory molecules CD86, and CD40 and CD83 and reduced expression of RELB.

Conclusion: We report a new mechanism of action of MMF on human mDCs that suggests its role in regulating mDCs function.

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P693
Effect of ocrelizumab on B and T cell immune repertoires in patients with relapsing multiple sclerosis
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Background: The B cell depleting anti-CD20 antibody ocrelizumab (OCR) effectively ameliorates multiple sclerosis (MS) disease activity. However, to date little is known about the effects of OCR on the adaptive immune system beyond B cell depletion.

Objective: To evaluate the effect of OCR on B and T cell repertoires in patients treated with OCR.

Methods: Longitudinal blood samples were collected from 8 patients enrolled in the OPERA I trial. We studied 4 RMS patients: 2 treated with OCR for the whole period and 2 treated with IFNβ1a followed by OCR in the open label extension. PBMCs were isolated and B- and T-cells analyzed by flow cytometry. Unsorted longitudinal PBMC samples (1x10⁷) were subjected to deep immune repertoire sequencing (RepSeq) of the immunoglobulin (IgM and IgG) heavy chain variable (VH) region. TCR-Vβ repertoires were generated from sorted CD4+ and CD8+ T cells.

Results: We observed the expected B-cell depletion under OCR treatment, while no significant depletion was found in the overall CD3+ T cell compartment. Very low numbers of B cells remained detectable even in OCR treated patients. B cell depletion was mirrored by reduced diversity of B cell receptors (BCR). Clonal relatedness between IgM and IgG suggest effective T cell receptor class-switch recombination was found throughout the study in residual B cells from OCR-treated patients. The diversity of the CD4+/CD8+ T-cell repertoires remained unaffected.

Conclusion: Presence of a diverse B cell repertoire with clonal relatedness between IgM and IgG-expressing B cells suggests persistence of a functional residual B cell compartment under active OCR treatment. Persistence of a highly diverse T cell repertoire suggests the adaptive character of the T cell compartment is maintained despite B cell depletion. Our pilot suggests that important functions of the adaptive immune system may remain intact under long-term OCR treatment.

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A. Herman is an employee of Genentech, Inc., and shareholder of F. Hoffmann-La Roche Ltd.
H.-C. von Buedingen is an employee of F. Hoffmann-La Roche Ltd.

P694
The immune receptor expression pattern in peripheral-blood associated with JCV seropositivity in patients with multiple sclerosis is not affected by natalizumab
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Background: The B cell depleting anti-CD20 antibody ocrelizumab (OCR) effectively ameliorates multiple sclerosis (MS) disease activity. However, to date little is known about the effects of OCR on the adaptive immune system beyond B cell depletion.

Objective: To evaluate the effect of OCR on B and T cell repertoires in patients treated with OCR.

Methods: Longitudinal blood samples were collected from 8 patients enrolled in the OPERA I trial. We studied 4 RMS patients: 2 treated with OCR for the whole period and 2 treated with IFNβ1a followed by OCR in the open label extension. PBMCs were isolated and B- and T-cells analyzed by flow cytometry. Unsorted longitudinal PBMC samples (1x10⁷) were subjected to deep immune repertoire sequencing (RepSeq) of the immunoglobulin (IgM and IgG) heavy chain variable (VH) region. TCR-Vβ repertoires were generated from sorted CD4+ and CD8+ T cells.

Results: We observed the expected B-cell depletion under OCR treatment, while no significant depletion was found in the overall CD3+ T cell compartment. Very low numbers of B cells remained detectable even in OCR treated patients. B cell depletion was mirrored by reduced diversity of B cell receptors (BCR). Clonal relatedness between IgM and IgG suggest effective T cell receptor class-switch recombination was found throughout the study in residual B cells from OCR-treated patients. The diversity of the CD4+/CD8+ T-cell repertoires remained unaffected.

Conclusion: Presence of a diverse B cell repertoire with clonal relatedness between IgM and IgG-expressing B cells suggests persistence of a functional residual B cell compartment under active OCR treatment. Persistence of a highly diverse T cell repertoire suggests the adaptive character of the T cell compartment is maintained despite B cell depletion. Our pilot suggests that important functions of the adaptive immune system may remain intact under long-term OCR treatment.

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J. Selner has nothing to disclose

Background: Natalizumab (NZB) is a monoclonal antibody which targets the cell adhesion molecule alpha-4 integrin (VLA4/CD49d). Treatment with NZB in patients with multiple sclerosis (MS) is associated with altered surface expression of additional molecules involved in cell migration and immune interactions. Here, we evaluated the impact of NZB treatment on immune receptor expression on peripheral-blood mononuclear cells (PBMC) with regard to the anti-JC virus antibody (JCV-Ab) serostatus.

Methods: We studied expression levels (median fluorescence intensities, MFI) of CD11a (LFA1), CD29 (integrin-beta1), CD49d, CD44, CD62L (L-selectin), CD162 (P-selectin), and CD197 (CCR7) on CD8 and CD4 T cells by flow cytometry. For the cross-sectional analysis, we used cryo-stored PBMC of 45 NZB-treated MS patients (n=20 JCV-Ab positive) with a minimum of 6 months NZB treatment. A longitudinal analysis was performed in 25 patients (n=10 JCV-Ab positive) following time points: T0 (pre-NZB), month 6 (T1), 12 (T2), and 24 (T3) of NZB treatment.

Results: The cross-sectional study revealed higher expression levels of CD162 on CD4 (p=0.02) with a similar trend on CD8 T cells (p=0.06), and of CD11a (p=0.04) and CD29 (p=0.01) on CD4 T cells of JCV-Ab positive patients. In the longitudinal study combining T1-T3 data, we confirmed higher CD162 expression levels on CD4 (p=0.04) and CD8 (p<0.001) T cells and observed higher CD49d levels on CD8 T cells (p=0.007) of JCV-Ab positive patients. The differential expression of CD162 (p=0.03) and CD49d (p=0.04) on CD8 T cells upon JCV serostatus was present in MS patients before initiation of NZB and persisted throughout the course of treatment. JCV-serostatus did not affect clinical or radiological surrogates of treatment response.

Discussion: The study of key immune receptors on the surface of T cells from MS patients revealed an expression pattern associated with JCV seropositivity. This presumably enhanced cellular activation state and persistence after NZB treatment warrants further attention in the context of increasing risk for progressive multifocal leukoencephalopathy with NZB treatment duration.

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P695
Achievement of no evidence of disease activity with daclizumab beta versus intramuscular interferon beta-1a treatment across patient subgroups in DECIDE
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Background: In DECIDE, significantly more patients treated with daclizumab beta (DAC BETA) 150mg achieved no evidence of disease activity (NEDA) vs intramuscular (IM) interferon (IFN) beta-1a 30mcg over 2 years (baseline [BL] to Week 96; P<0.0001). Evidence of DAC BETA benefits was more pronounced between Weeks 24-96.

Objective: Examine the influence of BL characteristics on achievement of NEDA in patients receiving DAC BETA vs IM IFN beta-1a in DECIDE.

Methods: NEDA (defined as no relapses, no 12-week confirmed disability progression, no new/enlarging T2 lesions, and no Gd+ lesions) was examined from BL to Week 96 and from Week 24 to 96. Analyses were based on logistic regression models adjusted for relevant BL characteristics. Also, a GUIDE machine learning algorithm for constructing classification trees was used for predicting NEDA from BL patient characteristics.

Results: Significantly more DAC BETA vs IFN beta-1a patients achieved NEDA across the majority of subgroups from BL to Week 96. Across all subgroups, percentages (odds ratio) of patients achieving NEDA were consistently higher for DAC BETA vs IM IFN beta-1a-treated patients: Age: ≤35y, 19.0 vs 6.5 (3.48), >35y, 30.2 vs 21.4 (1.60); male, 25.6 vs 13.6 (2.36), female, 24.1 vs 14.4 (1.93); Time since diagnosis: < 3y, 23.6 vs 13.4 (2.04), ≥3 to <10y, 23.4 vs 13.9 (2.17), ≥10y, 30.8 vs 18.0 (2.02); relapses in previous year: ≤ 1, 27.4 vs 14.5 (2.27), >1, 21.2 vs 13.8 (1.76); EDSS, < 3.5, 25.3 vs 13.3 (2.29), ≥3.5, 23.6 vs 16.1 (1.58); T2 lesion volume, < median, 30.0 vs 18.4 (1.90), ≥median, 19.0 vs 10.6 (2.15); Gd+ lesions: absent, 36.5 vs 21.2 (2.28), present, 10.2 vs 6.5 (1.61); prior IFN beta: yes, 20.7 vs 12.6 (2.09), no, 26.6 vs 14.9 (2.07); prior DMT: yes, 21.3 vs 12.7 (2.10), no, 26.9 vs 15.2 (2.06); disease activity: less active, 29.2 vs 17.1 (2.07), highly active (≥2 relapses in prior year and ≥1 Gd+ lesion at BL), 7.1 vs 4.7 (1.59). From BL to Week 96, treatment comparisons were significant (P<0.05) for all subgroups except: EDSS ≥3.5, Gd+ lesions present, highly active disease. For Weeks 24-96, more DAC BETA vs IM IFN beta-1a patients achieved NEDA, with higher ORs (2.17 to 4.23) and significant differences across all subgroups analysed.

Conclusion: DAC BETA demonstrated greater benefits on achievement of NEDA vs IM IFN beta-1a across clinically important subgroups. Higher odds of achieving NEDA were observed for lower EDSS and lower MRI burden at BL (also confirmed by GUIDE).

Disclosure
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**P696**

**Immunosuppressive potential of human Wharton jelly mesenchymal stem cells in multiple sclerosis patients**

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**Objective:** Mesenchymal stem cells derived from Wharton’s jelly (WJ-MSC) represent attractive MSC population, related to their high proliferation capacity and immunoregulatory and regenerative potential. Several clinical trials with MSC in patient with multiple sclerosis (MS) are in progress, but the mechanisms induced with human WJ-MSC are still unknown.

**Methods:** In this project we have examine *in vitro* immunosuppressive effect of WJ-MSC co-cultured with peripheral blood mononuclear cells (PBMC) isolated from patients with relapsing-remitting MS and healthy controls. PBMC were stimulated with concanavalin A, co-cultured in cell-to-cell and *transwell* systems. Next immunosuppressive potential of WJ-MSC was assessed using proliferation assay. Prostaglandin E2 (PGE2) and interferon gamma (INFγ) levels were checked in culture supernatant with ELISA.

**Results:** We observed significant immunosuppressive effect of WJ-MSC co-cultured cell-to-cell with PBMC. This effect was attenuated in co-cultures using *transwell* system but remained statistically significant. The importance of the secretory mediators in the WJ-MSC immunosuppressive function was confirmed with assay of PGE2, a previously defined mediator of stem cell induced immunoregulation. The results of co-culture experiments showed that the level of PGE2 was 8 fold increased in direct cell-to-cell condition and 2 fold in *transwell* system. There was no differences in PGE2 secretion between MS patients and healthy controls. Interestingly, the production of INFγ was decreased in WJ-MSC and PBMC co-cultures and this effect was more pronounced in healthy controls.

**Conclusions:** WJ-MSC showed strong immunosuppressive effect which was related to both direct contact with immune cells and secretory mediators. WJ-MSC might represent a promising therapeutic approach in patient with multiple sclerosis.

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**P697**

**“Real-life” outcomes in a monocentric cohort of highly active multiple sclerosis patients treated with alemtuzumab**

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**Background:** Alemtuzumab (ALEM) is a monoclonal antibody anti-CD52 approved for the treatment of active MS patients. Randomized clinical trials (RCT) and their extension studies had shown ALEM, in comparison to first line disease modifying therapies (DMT) and in naïve patients, to maintain a higher percentage of patients with no evidence of disease activity (NEDA). Although well tolerated, it is related with several adverse events, frequently infusion-associated reactions (IAR), but also infections and autoimmune diseases (AID). Observational data are scarce for new DMT and more studies are needed to attain personalized therapy.

**Methods:** Data were retrospectively collected from patients’ clinical records in MS Center of San Raffaele Hospital. The objectives of this study were to characterize clinical, radiological and safety data of MS patients during the first 2 years of ALEM treatment and to compare it with RCT data.

**Results:** From December 2014 to May 2017, 32 patients were treated with ALEM: 21 females, with mean age of 31 years (18-48), disease duration of 6,5 years (0,1-24,6), relapses in previous year of 3 (1-5) and 5 Gd-enhancing lesions (0-30) in MRI before ALEM. Naïve patients for DMT accounted for 34,4%; 18 patients received 2 cycles of ALEM; mean follow-up (F-U) of 13 months (2-30). During F-U: 69,2% patients achieved NEDA after the first cycle, 77,8% after the second (14/18); 6 patients had relapses (19%) and 11 relapses were reported - 10 in the first year and 1 in the second; 37% patients showed MRI activity. Baseline median EDSS was 2,5 (1,5-6,5); after one year of F-U, median EDSS decreased by 20%. Nearly 3/4 of patients (78%) reported adverse events (AE), a total of 57 AE: 45 IAR, 6 cases of AID, 4 infections and 2 minor hematologic abnormalities. Serious AE (SAE) were reported in 3 patients - allergic reaction, listeriosis and hemophilia.

**Conclusions:** In this study, more than 2/3 of patients after first and 3/4 after second cycle of ALEM reached NEDA. Such
results are slightly higher than those reported in RCT, both in phase 3 (59-68% at 2 years) and in their extension studies (54-62% at 6 years). Concerning total AE (78%) and SAE (9%), we observed a smaller number compared to RCT (96-99% and 18-25%, respectively). Small cohort and short F-U could explain both higher efficacy and safety. Our cohort included highly active patients, compared to RCT, and ALEM showed to be very effective and well tolerated in such naïve and non-naïve patients.

**Disclosure**

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**P698**

**Efficacy and safety of generic glatiramer acetate Timexon®: results of the 12-month extension of BCD-063-1 international double-blind randomized placebo-controlled clinical study of efficacy and safety of Timexon® in comparison with Copaxone®**

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**Background:** Efficacy and safety of generic glatiramer acetate (gGA) Timexon® in comparison with originator GA Copaxone® was shown during 48 weeks - the 1st period of BCD-063-1 study.

**Objectives:** To assess the efficacy, safety, and tolerability of the long-term treatment with Timexon® and those after switching patients from Copaxone® to gGA.

**Materials and Methods:** During the first year of the study, 158 patients (2:2:1) received Timexon®, Copaxone® or placebo in the double-blind settings. After that, all the patients were switched to Timexon® for open-label observation for the next 12 months (Group 1: Timexon®, Group 2: Copaxone®/Timexon®, Group 3: placebo/Timexon®).

**Results:** According to results of the first study period, Timexon® and Copaxone® did not differ by the number of CUA (combined unique active lesions) and other key MRI outcomes, relapse-related outcomes or safety parameters. Both drugs of GA showed their superiority to placebo.

At Week 96, mean number of CUA was 1.06±1.69, 1.06±2.04 and 0.31±0.602 in Groups 1, 2 and 3 respectively (p=0.407). In Group 3, CUA values decreased after switching to Timexon® (2.7±3.3, 1±2.033, 0.312±0.602 at Weeks 48, 72 and 96 respectively). At Week 96, the mean number of Gd+ lesions were 0.78±1.36, 0.43±1.17 and 0.06±0.25 in Groups 1, 2 and 3, respectively. Similar data were obtained for other MRI outcomes. No significant negative dynamics vs the 1st year of treatment in Groups 1 and 2 and decreased mean values of MRI outcomes in Group 3.

During the whole study period (96 weeks), MRI-confirmed relapses were recorded in 7 (11.48%), 8 (13.11%) and 5 (17.86%) patients in Groups 1, 2 and 3 respectively (p=0.712). Of those, relapses during the second year were recorded in 3 (4.92%), 3 (4.92%) and 2 (7.14%) patients in Groups 1, 2 and 3 respectively (p=0.800). During the whole study period (96 weeks), groups did not differ by EDSS, MSFC, SF-36 or Beck’s depression scores.

Groups did not differ by the frequency, nature, and severity of adverse events. Most common adverse events were local reactions, which were recorded in 25.8-30.2% of cases. Patients of Group 2 after switching from Copaxon® to Timexon®, did not show increased frequency of adverse events or local reactions or aggravation of the main disease.

**Conclusions:** Timexon® demonstrated stable efficacy and good safety and tolerability profile during the long-term period (96 weeks) and in switching from Copaxone® in patients with RRS.

**Disclosure**

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Zinkina-Orikhan A., Tursunova C. are employees for Biocad company.

**P699**

**Secukinumab in relapsing multiple sclerosis: experience in two cases with concomitant ankylosing spondylitis**

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**Objective:** Secukinumab is a fully human monoclonal antibody against interleukin-17A which is approved for the treatment of patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis (AS). Based on several studies supporting a central role for IL-17 in multiple sclerosis (MS) pathophysiology, a phase 2 trial showed that secukinumab reduced significantly the number of cumulative new gadolinium-enhancing T1 lesions (Gd+) compared to placebo. We present 2 patients with AS and concomitant MS treated with secukinumab.

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Material and Methods: We describe the clinical features, neurologi- cal examination, neuroimaging and clinical-radiological follow-up.

Results: A 46-year-old woman diagnosed with AS at age 22 years treated with etanercept from 2009 to 2012 and etanercept from 2012 to 2016. In May 2016, he presented symptoms consistent with a spinal relapse. Neurological examination revealed a residual Kurtzke scale (EDSS) of 2.0. A craniospinal MRI showed abundant demyelinating lesions with Gd+ being diagnosed of MS according to the McDonald 2010 criteria. The CSF showed BOCG+. Secukinumab was started in November 2016. He is remaining clinically stable so far without any new neurological symptoms. A control cranial MRI showed improvement in inflammatory activity.

A 41-year-old man diagnosed with AS at age 25 years treated with infliximab from 2009 to 2012 and etanercept from 2012 to 2016. In May 2016, he presented symptoms consistent with a spinal relapse. Neurological examination revealed a residual EDSS of 2.0. A craniospinal MRI showed abundant demyelinating lesions with Gd+ being diagnosed of MS according to the McDonald 2010 criteria. The CSF showed BOCG+. Secukinumab was started in November 2016. He is remaining clinically stable so far without any new neurological symptoms.

Conclusions: The role of Tumour Necrosis Factor-α blockers inducing demyelination (either with a progressive or a monophasic course) or triggering pre-existing demyelinating predisposition (as it might be for these patients), still remains controversial. Secukinumab may be an optimizing, feasible and cost-benefit therapeutic approach for patients with concurrence of MS and other rheumatologic diseases reducing, thereby, overexposure to other biological treatments as well as the incidence of adverse effects.

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P700
A cost-effectiveness analysis using real-world data from the MSBase Registry: comparing natalizumab to fingolimod in patients with inadequate response to disease modifying therapies in relapsing-remitting multiple sclerosis in Scotland

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Objectives: To estimate the cost-effectiveness (CE) of switching to natulizumab (NAT) compared with switching to fingolimod (FTY) for highly active relapsing-remitting multiple sclerosis (RRMS) patients with inadequate response to first line therapies (BRACETD) from the perspective of NHS Scotland using real-world data (RWD) from the MSBase Registry.

Methods: A Markov model with health states based on the Expanded Disability Status Scale (EDSS) was developed to capture RRMS progression, conversion to secondary progressive MS, and associated relapses. Treatment-specific EDSS transition matrices, annualized relapse rates by EDSS state and comparative effectiveness results were obtained from 3-way propensity score matched cohorts from MSBase (companion paper submitted at this meeting). Costs and utilities for disease management and relapses were taken from the United Kingdom (UK) MS Survey 2016. Treatment costs were based on UK list prices with discounts considered in scenario analyses. Additional clinical data were obtained from the published literature and other publicly available sources. Scottish general mortality data were utilized. The CE analysis estimated lifetime clinical and economic outcomes and the incremental cost per quality-adjusted life-year (QALY) gained. Extensive scenario and sensitivity analyses were conducted to estimate the impact of alternative data sources, assumptions, and parameter uncertainty on CE outcomes.

Results: The MSBase analysis suggests that patients experiencing disease activity on BRACETD clearly benefit from therapy escalation to NAT as compared to switching among BRACETD. The benefit was less marked for the therapy escalation to FTY. In the base-case CE analysis, NAT dominated FTY, leading to higher QALY’s (0.393 higher per patient) and lower costs (£19,148 lower per patient). NAT remained dominant across scenarios considering a societal perspective, alternative discount rates, a 10-year time horizon, and equal treatment discontinuation rates. For FTY price discounts up to 23.2%, NAT remained dominant; for FTY discounts of up to 32.8% and 37.6%, NAT remained cost-effective at thresholds of £20,000/QALY and £30,000/QALY, respectively.

Conclusions: In this analysis, switching to NAT dominated switching to FTY in highly active RRMS with inadequate response to BRACETD. NAT remained dominant across a range of alternative scenarios and was likely to be cost-effective with up to a 32.8-37.6% discount on the price of FTY.

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TM, FU, AC, HR: Full-time employees of and stockholders in Biogen.
ST, BH: Received honoraria for consultancy, funding for travel, and compensation for serving on scientific advisory boards from Biogen.

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P701
Teriflunomide: immunomodulatory effect on adaptive and innate immune cell subsets

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Teriflunomide, a drug approved for treatment of relapsing-remitting multiple sclerosis (MS) acts on highly proliferating cells, such as activated lymphocytes, inhibiting enzyme dihydroorotate dehydrogenase, involved in de novo pyrimidine biosynthesis, without impacting on protective immunity. Clinical trials in MS showed that teriflunomide can cause a mean decrease in leukocyte counts of approximately 15 % during the first months of treatment, but its effect on immune cell subpopulations is not clearly understood. We have therefore studied the immunomodulatory effect of this drug on innate and adaptive immune cell populations. Blood lymphocytes were isolated from 10 MS patients before and after 3 or 12 months of treatment. Adaptive and innate immune cell subsets were analyzed by flow cytometry, as follows: B cells (memory, regulatory and mature subsets), T cells (effector and regulatory subsets) and natural killer (NK) cells (CD56dim and CD56bright subsets). Our results show that teriflunomide impacts B-cell subsets, significantly reducing absolute counts of total CD19+ B cells, and mature and regulatory B-cell subsets. T cells were affected to a lesser extent, with a trend in reduction of absolute counts for both T effector CD4+ cells (Th1, Th17 and Th1/17) and T regulatory CD8+ and CD4+ cells. Teriflunomide had no detectable impact on NK-cell numbers. In conclusion our data showed that, in a small studied cohort of patients, teriflunomide treatment impacts mainly and significantly on B-cell numbers, while having a milder effect on T-cell numbers. Larger cohorts are necessary to confirm these findings and understand the impact of teriflunomide on the functionality of these cells.

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P702
Fingolimod induces BAFF and expands circulating transitional B cells without activating memory B cells and plasma cells in multiple sclerosis

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Background: Fingolimod is a sphingosine-1-phosphate receptor agonist used as a disease-modifying drug for multiple sclerosis (MS). We have previously shown that MS patients treated with fingolimod have an increased proportion of circulating transitional B cells, a naïve B cell subset with immune regulatory properties, but the underlying mechanism remains unknown. B cell activating factor of the tumor necrosis factor family (BAFF) is a cytokine involved in the maturation, survival, and selection of B cells. Mice overexpressing BAFF have been shown to have increased numbers of naïve B cells after the late transitional stage; therefore, we hypothesized that BAFF is involved in the increase in transitional B cells in MS patients treated with fingolimod.

Subjects and Methods: Serum samples were collected from 25 healthy subjects, 32 untreated MS patients, and 30 MS patients treated with fingolimod. Serum concentrations of BAFF, soluble transmembrane activator and calcium-modulating cyclophilin ligand interactor (sTACI: a marker for activated memory B cells), and soluble B cell maturation antigen (sBCMA: a marker for plasma cell activation) were quantified by ELISA. In addition, alterations in serum BAFF levels after starting fingolimod were analyzed in three treatment-naive MS patients. The proportions of B cell subsets in 22 MS patients treated with fingolimod were determined by flow cytometry, and the relationships between serum BAFF concentrations and each B cell subset were analyzed.

Results: Serum concentrations of BAFF were significantly higher in fingolimod-treated MS patients than in healthy subjects or untreated MS patients (p< 0.001). Serum levels of BAFF rose significantly after starting fingolimod treatment in the longitudinal study (p=0.014). A significant positive correlation was found between the serum concentration of BAFF and the proportion of transitional B cells in blood (p=0.0057). Despite the elevated concentrations of BAFF in fingolimod-treated MS patients, serum levels of sTACI and sBCMA were not elevated in these patients.

Conclusion: Fingolimod induces BAFF in the circulation and expands transitional B cells, but does not activate memory B cells and plasma cells, which is favorable for the treatment of MS.

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P703
Induction of disease remission with one cycle of alemtuzumab in relapsing remitting multiple sclerosis

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Background and goals: Alemtuzumab (Alem) is a monoclonal anti-CD52 antibody which rapidly depletes circulating lymphocytes followed by their reconstitution. It is approved for the
treatment of Relapsing Remitting Multiple Sclerosis (RRMS). The currently practiced treatment regimen with two courses one year apart, is a highly effective therapy in achieving disease control. However, treatment with Alemtuzumab is associated with significant adverse events and requires prolonged monitoring. Optimizing its balance of therapeutic index, cost, and adverse event profile is imperative. We investigated the efficacy of a single course treatment with Alemtuzumab in RRMS.

Methods: We performed a retrospective review of 26 patients (15:9 F:M) with a median disease duration (DD) of 53.5 months and median age of 36, treated with Alemtuzumab who had at least 12 months post infusion follow up. Average follow up was 24.2 months post infusion.

Results: At 12 months’ post infusion, one patient (1/26) had a clinical relapse and two patients had one new lesion on MRI without clinical relapse. The mean Annual Relapse Rate (ARR) was 0.04 compared to 0.68 pretreatment. 11/23 patients who were clinically and radiologically progression-free at 12 months’ post treatment opted not to have the second course of Alemtuzumab at year two. We followed these patients over a mean of 9.3 additional months, and they had no subsequent clinical or radiologic progression. 5/26 patients developed autoimmune thyroid disease, but no other autoimmune disorder. Further clinical data, including disability, will be provided at the time of presentation.

Conclusion: Given Alemtuzumab’s mechanism of action, the ability for immunologic reconstitution, there could potentially be patients for whom induction of disease remission could be achieved with just one cycle of Alemtuzumab. Additionally, the shorter treatment period could potentially decrease the risk of autoimmunity and decrease the duration of post infusion monitoring. We believe our findings warrant further study and long-term analysis.

References

Disclosure
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P704
Real-life experience with rituximab for the treatment of multiple sclerosis: report from two MS referral centres
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Background: Rituximab (RTX) has been administrated as an off-label therapy in relapsing-remitting (RRMS) and progressive multiple sclerosis (PMS). We ought to describe the effectiveness and safety in these 2 indications.

Methods: Eighty-one patients with MS (26 RRMS, 55 PMS of whom 43 secondary progressive MS, 12 primary progressive MS) received treatment with RTX, within off-label Spanish Ministry of Health regulations, and had a minimal follow-up of 6 months in 2 tertiary hospitals of Valencia (Spain). Effectiveness was measured as the percentage of patients without evidence of disease activity (NEDA), defined as the absence of new clinical (relapses, EDSS worsening) and radiological activity (gadolinium-enhancing lesions -GEL-). The presence of adverse events (AE) was registered.

Results: The mean age at the time of RTX infusion was 41.7 (10.9) years old, 61.7% were females, mean MS evolution time was 12.6 (9.9) years; median number of previous therapies was 2 (interquartile range [IQR] 1-3), with 60 patients being treated before with 2nd line (natalizumab/fingolimod) or immunosuppressants (74.1%); the mean follow-up time was 33.8 (18.0) months.

In RRMS patients, significant changes were observed in the relapse rate (from 1.42 [1.07] to 0.27 [0.45]), EDSS worsening (from 30.8% to 0%), and presence of GEL (from 73.1% to 3.8%); pre-RTX NEDA was observed in 1 patient (3.8%), and post-RTX NEDA in 20 patients (76.9%). In PMS patients, significant changes were observed in the relapse rate (from 0.6 [1.0] to 0.02 [0.14]), EDSS worsening (from 67.3% to 30.9%), and presence of GEL (from 46.3% to 5.5%); pre-RTX NEDA was observed in 4 patient (7.3%), and post-RTX NEDA in 36 patients (65.5%). RTX infusions were generally well tolerated; 15 patients experienced infusion-related AEs (71.4% mild; 2 cases with moderate-to-severe anaphylaxis). Significant AEs included one case of toxic neutropenia, 2 deep venous thromboses and one death due to pulmonary embolism. RTX was withdrawn in 20 patients (24.7%); main reasons were EDSS worsening (10 cases) and AEs (10 cases).

Conclusion: RTX helped to achieve NEDA status in both RRMS and PMS patients. Although generally well tolerated, concern for thrombotic complications was observed in our series.

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P705
Ozanimod does not impact cytotoxic T lymphocyte function in vitro demonstrating differentiation from fingolimod's activity on SET-PP2A
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Background: CD8+ cytotoxic T lymphocytes (CTL) are critical for immune surveillance and protection from infection. Fingolimod (FTY720) is approved for the treatment of relapsing MS and shows activity on SET-PP2A. Ozanimod (Rozomax) is a sphingosine 1-phosphate receptor modulator designed for oral use and has shown activity on a unique subset of kinases including SET-PP2A. The aim of this study was to examine the effects of ozanimod on cytotoxic T lymphocyte function.

Methods: Three human T cell lines were treated with ozanimod at concentrations of 0.1, 1, 10, or 100 μM. The in vitro effect of ozanimod on CD8+ T lymphocyte proliferation, cytotoxic function, and cytokine production was assessed. Results: Ozanimod did not affect T cell proliferation, cytotoxic function, or cytokine production.

Conclusion: Ozanimod does not impact cytotoxic T lymphocyte function in vitro demonstrating differentiation from fingolimod's activity on SET-PP2A.
multiple sclerosis (RMS); it’s converted to its phosphorylated form (FTY720p) by intracellular sphingosine kinases and modulates S1P₃ to retain lymphocytes in lymphoid tissue. FTY720 does not stimulate S1P receptors but has similar plasma steady-state concentration as FTY720p. Unlike FTY720p, FTY720 inhibits the SET protein (I2P2A, IGAAD, TAF1b), leading to enhanced protein phosphatase 2 (PP2A) activation, reduced granzyme B and impaired CTL function. We hypothesized that ozanimod, a selective S1P₁₉/R₉ modulator structurally distinct from fingolimod, is not active on SET-PP2A and compared it to FTY720 on CTL viability and function in vitro.

Methods: Splenocytes were purified from C57BL/6 mouse spleens and directly cultured for 24 hours or further purified into CD₈⁺ T cells. After a 24 hour rest period, cells were stimulated with IL-12 and IL-33 for 48 hours in the presence of FTY720, FTY720p or ozanimod. IFNg and granzyme B was determined by flow cytometry and ELISA. CTL target cell killing was assessed by a ⁵¹Cr-release assay. CD₈⁺ T cell viability was determined by flow cytometry.

Results: CTL treated with FTY720 in vitro demonstrated decreased survival, while CTL treated with ozanimod or FTY720p did not. In addition to affecting cell viability, the surviving FTY720-treated live cells had reduced function, as demonstrated by a reduced capacity to kill target cells by ≥50% and reduced production of IFNg and granzyme B. Conversely, ozanimod did not impair the ability of CTL to kill target cells, and showed only minimal or no effect on IFNg or granzyme B production. Similar to ozanimod, FTY720p did not impact CTL viability or function, supporting an off-target S1P₁₉/R₉-independent mechanism of FTY720 on CTLs.

Conclusion: These findings suggest that in vitro, ozanimod does not alter CTL viability and function, highlighting a potential difference between ozanimod and fingolimod on SET-PP2A. This effect appears independent of S1P₁₉/R₉ activation. These data support the hypothesis that infections observed in patients under fingolimod treatment may, in part, be attributable to off-target effects of FTY720. Our findings suggest that ozanimod may have no clinically relevant effect on CD₈⁺ cytotoxic T lymphocytes through SET-PP2A, which may reduce infection risks relative to fingolimod.

Disclosure

D. Guimond, Shareholder: Celgene.
B. Clemons, Shareholder: Celgene.
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G. J. Opiteck, Shareholder: Celgene.
F. L. Scott, Shareholder: Celgene.

P706

In vitro data reveals potential novel mechanism of action of teriflunomide on CNS microglia and astrocytes

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Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS (RRMS) in 70 countries, with more than 71,000 patients currently being treated worldwide. In the periphery, teriflunomide selectively and reversibly blocks the mitochondrial enzyme dihydroorotate dehydrogenase, limiting the expansion of peripherally activated lymphocytes and thereby reducing the number of these cells available to enter the CNS and mediate inflammatory processes. Teriflunomide is also able to cross the blood-brain barrier and, via a novel mechanism, may directly impact microglia and astrocyte effector functions that contribute to neuroinflammation and neurodegeneration in MS.

Objective: To measure the direct impact of teriflunomide on activated microglia and astrocytes in vitro.

Methods: Primary astrocytes and microglia were isolated from rodent neonatal brains. Cells were pretreated with teriflunomide prior to stimulation with lipopolysaccharide (LPS), or LPS and interferon (IFN) γ, and cell viability was measured. Cytokine production, nitrite production, and phagocytosis were also measured.

Results: Teriflunomide had no impact on the viability of activated primary rodent microglia or astrocytes in vitro. In activated microglia, teriflunomide pretreatment decreased production of the pro-inflammatory mediators, interleukin (IL)-6, IFN γ-induced protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), IL-12p40, and nitrite, and increased production of the anti-inflammatory cytokine IL-10. However, no change was observed in the production of tumour necrosis factor (TNF) or IL-1B. Additionally, there was no effect of teriflunomide on the phagocytic activity of microglia. Pretreatment with teriflunomide also decreased production of the inflammatory mediators, TNF, IL-6, and nitrite, by activated astrocytes.

Conclusions: Teriflunomide treatment can directly impact activated microglia and astrocyte functions in vitro. These data suggest a novel mechanism of action of teriflunomide that may provide neuroprotective effects within the CNS and could contribute to the benefits on clinical outcomes, and the reduction in brain volume loss, observed in patients with RRMS treated with teriflunomide.

Disclosure

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P707

Teriflunomide use in European clinical practice in patients with relapsing forms of multiple sclerosis: an overview of regional real-world studies

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Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS (RRMS). Teri-PRO (NCT01895335), a global phase 4 study, previously

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demonstrated high levels of treatment satisfaction with teriflunomide together with improvements on other patient-reported outcomes (PROs). TAURUS-MS I and II (Germany), TACO (Switzerland), Teri-LIFE (Nordics), AURELIO (Greece), and Teri-CARE (Spain) are regional studies evaluating quality of life (QoL) and treatment satisfaction in patients with RRMS treated with teriflunomide in a real-world clinical setting.

Objective(s): To evaluate patient-reported QoL and treatment satisfaction from several separate regional studies throughout Europe in patients with RRMS treated with teriflunomide.

Methods: TAURUS-MS I and II, TACO, Teri-LIFE, AURELIO, and Teri-CARE are multicentre, prospective, non-interventional, ≤2-year studies in patients with RRMS receiving teriflunomide 14 mg, as per local labelling. These studies will evaluate a range of PROs to assess the impact of teriflunomide on QoL, fatigue, disease and disability progression, safety and overall treatment satisfaction. Target enrolment: n=1115 for TAURUS-MS I, n=1080 for TAURUS-MS II, n=120 for TACO, n=200 for Teri-LIFE, n=350 for AURELIO, and n=323 for Teri-CARE. Visits are scheduled at baseline and at Month (M)1 (AURELIO only), M3 (TAURUS-MS I and II), M6, M12, and M18 until M24 (end of study) after start of teriflunomide treatment.

Results: The majority of these regional studies are currently ongoing, and a full update will be presented. The most advanced of these studies, TAURUS-MS I, has completed enrolment. Out of the 1115 patients enrolled in TAURUS-MS I, data from 733 patients who received teriflunomide treatment for 1 year (≥9 months) are available. Mean (SD) TSQM-9 scores at baseline/M12 were: Global Satisfaction 64.7 (24.1)/74.6 (22.3); Conveniences 74.8 (24.2)/91.0 (11.2); and Effectiveness 62.1 (23.6)/69.0 (23.8).

Conclusions: PROs provide valuable additional insights into the effect of MS therapies on QoL and disease progression, and may help inform decisions regarding patient treatment and care. These non-interventional studies will evaluate the impact of teriflunomide on PROs in different countries. As many of the PROs included are identical across the studies, data will ultimately be integrated to further characterise the real-world effectiveness of teriflunomide.

Disclosure

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P708

EVOLVE-MS-2: A randomized, double-blind, phase 3 study of the gastrointestinal tolerability of ALKS 8700 versus dimethyl fumarate in relapsing-remitting multiple sclerosis

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Background: Phase 3 and real-world studies have shown that gastrointestinal (GI) events are an important concern for patients taking oral dimethyl fumarate (DMF), approved for the treatment of relapsing forms of multiple sclerosis (MS). ALKS 8700 is a prodrug of monomethyl fumarate, the active metabolite of DMF. ALKS 8700 has physicochemical properties that are distinct from DMF, and thus is designed to effectively treat relapsing forms of MS in a manner similar to DMF but with the potential for improved GI tolerability.

Objectives: EVOLVE-MS-2 (NCT03093324) evaluates the safety and GI tolerability of ALKS 8700 and DMF in patients with relapsing-remitting MS (RRMS).

Methods: In this double-blind, Phase 3 study, ~420 patients with RRMS will be randomized 1:1 to oral treatment with ALKS 8700 462 mg (twice daily) or DMF 240 mg (twice daily) for 5 weeks. Key GI symptoms will be assessed using 2 patient-reported symptom-rating scales: the Individual GI Symptom and Impact Scale (IGISIS) and the Global GI Symptom and Impact Scale (GGISIS). The IGISIS assesses the incidence, intensity, onset, duration, and functional impact of individual GI symptoms: nausea, vomiting, upper and lower abdominal pain, and diarrhea. The GGISIS assesses the overall intensity, bothersomeness, and functional impact of GI symptoms experienced over the past 24 hrs. Key inclusion criteria: age 18-65 yrs, confirmed diagnosis of RRMS (2010 revised McDonald criteria), Expanded Disability Status Scale score ≤ 6.0, and no evidence of relapse within 30 days prior to randomization. Key exclusion criteria: progressive forms of MS or prior treatment with DMF. Primary and secondary endpoints will be based on the IGISIS and GGISIS. Safety will be assessed via adverse events and standard clinical, laboratory, and imaging measures. Patients completing this study will be eligible to participate in an ongoing open-label, long-term safety study (EVOLVE-MS-1; NCT02634307).

Results: Patient enrollment began in March 2017. The study is currently recruiting patients from 17 sites in the United States. Patient demographics and baseline characteristics as of September 2017 will be presented.

Conclusions: GI tolerability issues with DMF can negatively affect patient experience and adherence. EVOLVE-MS-2 will provide important insight into the GI tolerability of ALKS 8700 compared with DMF in patients with RRMS.

Disclosure

RTN has consulted for Acorda, Alkermes, Bayer, Biogen, EMD Serono, Genentech, Genzyme, Mallinckrodt, Novartis, and Pfizer and was on the speaker bureau for Acorda, Biogen, and Genzyme. RAL-P, DR, TG, LvM are employees and stockholders in Alkermes, Inc. AJL has consulted for Alkermes, Ardelyx, Salix, Prometheus, Allergen, Valeant, and Ironwood.

JSW has served on advisory boards, data monitoring or steering committees, has consulting agreements, or received speaker

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P709

Spanish registry of patients with multiple sclerosis treated with fingolimod (GILENYA Registry): safety and effectiveness after four years of registry


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Background: The aim of the Spanish Gilenya Registry is to study the evolution of patients being treated with fingolimod in Spain.

Objectives: The aim of this preliminary analysis is to assess the safety and effectiveness of fingolimod after 4 years of registry.

Methods: Observational, retrospective/prospective and multicenter registry of cases, including all patients with relapsing remitting MS starting treatment with fingolimod in Spain.

Results: Data of 695 evaluable patients included in the registry until March 2017 was analyzed. Safety data were available for 548 patients after 1 year of treatment, 373 after 2 years, 229 after 3 years and 102 after 4 years. Mean age at baseline was 39.1 years (± 8.8), 70.7% women. Mean time since onset of symptoms of MS was 11.1 years (± 6.9) and mean time since diagnosis of MS was 8.9 years (± 6.1). The test for JC virus antibodies was performed in 446 patients (67.1%), being seropositive in x patients (85.9%). Patients switched from natalizumab (29.6%), glatiramer acetate (21.73%), interferon beta-1a sc (Rebif®) (14.82%), interferon beta-1b sc marcas (9.50%), interferon beta-1a im (Avonex®) (9.78%), mitoxantrone marca (0.43%), and other (0.43%), respectively, to fingolimod. Main reason for switching to fingolimod was efficacy (54.8%), followed by safety (36.8%) and other (15.5%). Mean time under treatment with fingolimod was 36.3 months (± 15.6). Mean monitoring time was 7.1 hours (± 6.5) and 9.1% of patients were monitored more than 6 hours after the first dose of fingolimod and 53 patients (7.2%) withdrew from the study.

17.3% of patients had adverse reactions, a total of 153 events were observed, being 9 of them serious (2 bilateral pneumonias, 2 atrioventricular block of 2nd degree, 1 lymphopenia, 1 bilateral neoplasia, 1 basal cell carcinoma, 1 acute toxic hepatitis and 1 influenza A). After 4 years in treatment with fingolimod and compared to the previous year, 89.4% of patients reported no relapses, 86.3% were free of disability progression [improvement or non-change of Expanded Disability Status Scale (EDSS) scores] and 75.6% were free of clinical activity (no relapses and free from disability progression).

Conclusions: The results obtained in this preliminary analysis support the safety and effectiveness of fingolimod after 4 years of registry.

Disclosure

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J.E. Meca-Lallana has received consulting or speaking fees from Biogen, Genzyme, Merck Serono, Novartis, Roche and Teva. C. Oreja-Guevara has received honoraria as moderator and speaker at meetings and participated in clinical trials sponsored by Biogen-Idec, Novartis, Merck-Serono, Almirall, Teva and Genzyme.

D. Muñoz has worked in consulting work, clinical trials and speaker at congresses held by Merck, Biogen, Teva, Novartis and Genzyme.

Javier Olascoaga serves on scientific advisory boards for Biogen Idec, Genzyme and Novartis has received speaker honoraria from Biogen Idec, Bayer-Schering, Genzyme, Merck-Serono, Novartis and Teva and receives research grants from Biogen Idec, Merck Serono, Novartis and Teva.

A. Pato has participated as a speaker and consultant for Novartis, Biogen and Genzyme Almirall.

L.I. Ramíó serves on scientific advisory boards for Biogen Idec and Merck-Serono and has received speaker honoraria from Biogen Idec, Novartis, Bayer, Merck-Serono, Genzyme, Teva Pharmaceutical Industries Ltd.

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P710
An update on pregnancy outcomes following ocrelizumab treatment in patients with multiple sclerosis and other autoimmune diseases
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Background: Ocrelizumab, a humanised monoclonal antibody that selectively targets CD20+ B cells, is approved by the Food and Drug Administration for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS), and has also been studied in clinical trials for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Objective: To provide an update of pregnancy outcomes in women treated with ocrelizumab during clinical trials.

Methods: This analysis includes pregnancies in women with MS, RA and SLE in ocrelizumab clinical trials (dose range 20 to 2000 mg) up to 31 January 2017. Across trials, women of childbearing potential were required to use two methods of contraception and continue contraception for 48 weeks after the last ocrelizumab infusion or until B cells repleted, whichever was longer. Urine pregnancy tests were performed at all infusion visits; if positive, dosing was stopped and the result confirmed with a serum pregnancy test. An embryo/foetus was considered exposed to ocrelizumab in utero if the last infusion occurred within 3 months of conception or during pregnancy if the date was unknown. All pregnancies occurring during clinical trials were followed to determine outcome.

Results: As previously reported, between 2008 and September 14, 2015, 46 women randomised to ocrelizumab in clinical trials (15 MS, 10 SLE, 21 RA) reported 48 pregnancies (15 MS, 11 SLE, 22 RA). This cumulative update provides approximately 16 months’ additional data on pregnancies in clinical trials up to 31 January 2017, and will review 58 pregnancies reported in 56 women (25 MS and 31 non-MS). Among the 25 pregnancies in patients with MS, 13 were considered to have foetal ocrelizumab exposure. Eleven pregnancies had no foetal ocrelizumab exposure and one pregnancy is not assessable for foetal ocrelizumab exposure.

Conclusions: As a large proportion of patients with MS are women of reproductive age, pregnancy outcomes in patients exposed to ocrelizumab are important to understand. B-cell levels in neonates following maternal exposure to ocrelizumab have not been studied in clinical trials and the effect of ocrelizumab on the immune system of the newborn is unknown. Transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20+ antibodies during pregnancy.

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J. Napieralski is an employee of F. Hoffmann-La Roche Ltd.
S.L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Symbiotix and Bionure; he has also received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

P711 Sustained modifications of subsets and capacities of cytokine production of B cells under interferon-β in multiple sclerosis
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Introduction and objectives: Efficiency of multiple sclerosis (MS) treatment has been reported associated with a reconditioning of the immune system, with emergence of immature populations associated with a more anti-inflammatory cytokine profile. We aimed to analyze B cell homeostasis and cytokine production of B cells in a non depleting immunotherapy, as interferon-β.

Patients, materials and Methods: Eighteen relapsing remitting (RR) MS patients naïve of any disease modifying drugs were prospectively enrolled. All of them initiated an interferon-β treatment immediately after inclusion and were clinically and biologically followed up during 12 months. Proportions and counts of main peripheral blood lymphocyte subsets and of B cell subsets were defined according to cell surface expression of specific markers analyzed by cytometry. Studied B cell subsets were: transitional, mature naïve, marginal zone, switched memory, IgM only, IgD only, double negative (IgD-/CD27-) “exhausted” B cells and plasmablasts.
Proportions of IL-6 producing B cells and of IL-10 producing B cells, evaluated using a cytometric approach after polyclonal stimulation, were used to assess pro-inflammatory and anti-inflammatory functional properties of peripheral blood B cells, respectively.

**Results:** Interferon-β induced a mild total lymphopenia which predominate on CD8+ T and NK cells. Whereas total B cell count remained stable under treatment, transitional B cell count sustainably increased significantly at 3, 6 and 12 months after initiation of treatment. By contrast, mature naïve, marginal zone, switched memory and double negative B cells durably decreased. Under treatment, B cells showed significant increased capacities of IL-6 and IL-10 production. However, the IL-6/IL-10 producing B cell ratio was durably reduced under treatment, suggesting a higher increase of IL-10 production than IL-6 by B cells. Most of patients (83%) were clinically stable at last follow up (no relapses and no modification of EDSS).

**Discussion and Conclusion:** Interferon-β treatment induces a durable modification of B cell homeostasis, with both a reduction of memory and increase immature B cells associated with an anti-inflammatory profile.

**Disclosure**
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**Background and aims:** Rituximab is a chimeric monoclonal anti-CD20 B-lymphocyte depleting antibody used off-label in multiple sclerosis (MS). The clinical relevance of anti-drug antibodies (ADA) against rituximab in MS is currently unknown. We here sought to determine the frequency of ADA using an in-house validated electrochemiluminescent (ECL) immunoassay and a commercial enzyme-linked immunosorbent assay (ELISA) to compare methods.

**Method:** Cross-sectional study in 339 MS patients with variable treatment duration (mean treatment duration 1.54 ± 0.84 (0.4 - 5.3) years) immediately before a scheduled rituximab infusion. Occurrence of rituximab ADA was related to B-lymphocyte counts, allergic reactions and clinical efficacy (relapses and contrast-enhancing lesions on magnetic resonance imaging) derived from review of clinical charts.

**Results:** The ECL method was significantly more sensitive than the ELISA method, with 5.6% of the cohort detected as positive with ELISA compared to 32.7% with ECL. Using data from the latter platform rituximab ADA were detected in 37% of relapsing-remitting MS and 26.5% in progressive MS. The presence of ADA decreased with increasing number of rituximab infusions. There was a significant association between both presence and titres of ADA, and incomplete B-lymphocyte depletion, but not with infusion/adverse reactions at the group level. There was no significant difference in clinical outcomes between ADA positive and negative patients, but the power to detect a difference was low due to few events of insufficient treatment effect (ten events in nine patients). Only five patients terminated rituximab during follow up, four of which were ADA positive.

**Conclusions:** Collectively, these findings suggest that rituximab ADA is common in treated MS patients, but that the frequency decreases with increasing number of rituximab infusions. Furthermore, while ADA correlates with duration of B-lymphocyte depletion, there was no significant difference between ADA positive and negative patients regarding clinical outcomes. Further studies are needed to adress long term implications of rituximab ADA.

**Disclosure**
The research leading to these results were conducted as part of the ABIRISK consortium (Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk). For further information, please refer to www.abirisk.eu.

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**Neuroprotection and Repair**

**P713**

Once daily oral CHS-131, a novel PPARγ agonist, reduces both neuroinflammation and gray matter volume depletion in patients with relapsing-remitting multiple sclerosis: a randomized, placebo controlled double-blind, Phase 2b, multicenter study

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**Background:** We recently completed a successful Phase 2B study of oral CHS-131, a novel, first-in-class, highly-selective partial PPARγ agonist, for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). In preclinical studies CHS-131 crossed the intact blood-brain barrier and attained pharmacologically relevant levels in the neural parenchyma. In PLP-induced REEA CHS-131 reversed neuroinflammation and blocked relapse. Phase 1 and 2 human studies to date have included > 600 subjects in RRMS, Type 2 Diabetes and healthy volunteers. The current study is a 2-part design: Part 1 was double-blind, placebo-controlled, three arm design (1 mg/day CHS-131; 3mg/day CHS-131; or placebo) to evaluate safety and efficacy of CHS-131 in treatment-naive subjects with RRMS. In Part 2 the subjects were given the choice to continue treatment with 1mg daily of CHS-131. The results of Part 1 are reported here.

**Methods:** 227 treatment-naive adult subjects (mean age 31 [range 18-50]; 65% female) were randomized into one of three arms: oral CHS-131 at 3 mg (n=76); oral CHS-131 at 1 mg (n=76); placebo (n=75), at 21 sites in Russia. 97% completed Part 1. Inclusion criteria: RRMS for ≤3 years, ≥1 gadolinium-positive lesion within 1-year of enrollment, and an EDSS ≤ 6 at screening. The patients underwent monthly MRI examinations with contrast to identify new inflammatory lesions. All MRIs were read blinded at the Buffalo Neuroimaging Center (Buffalo, NY). In addition to CE lesions the images were scored for cumulative new/enlarged T2 lesions, and serial cortical and whole brain volumetric analysis.

**Results:** CHS-131 treatment resulted in a dose-dependent reduction in cumulative CE lesions over 6 months (complete case analysis). 3 mg daily reduced CE lesion burden by 52% (4.2 lesions [LSMean 3.10]) vs. placebo (7.8 [LSMean 6.49]) (p=0.003). 1mg treatment was less robust- 21% reduction vs. placebo (7.6 [LSMean 5.15]) (p=ns). New/enlarged T2 lesions were reduced by 30% (3mg)(p=0.0767) and 14% (1mg)(p=ns) compared to placebo. In addition to the dose-dependent anti-neuroinflammatory effects, CHS-131 treatment appeared to attenuate gray matter volume loss at 6-months. Compared to placebo, there was 34.2% less cortical volume loss and 50% less whole brain volume loss in the 3mg cohort. Volume losses in the 1mg treatment group were similar to placebo at 6 months.

CHS-131 was safe and well-tolerated, and was without treatment-emergent serious adverse events.

**Disclosure**

D. Weinstein is a consultant, and stock holder in Coherus Biosciences, and a stock holder and former employee of InteKrin Therapeutics, Inc which is a wholly owned subsidiary of Coherus Biosciences

L. Pugliese is an employee and stock holder for Coherus Biosciences

H. Tang is an employee and stock holder for Coherus Biosciences

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A. Boyko is a consultant for ZAO InteKrin

R Zivadinov is an employee of the Buffalo Neuroimaging Analysis Center which provided services to ZAO InteKrin

**P714**

Investigating neuroprotective effects of phenytoin on optic nerve magnetization transfer ratio (MTR) in acute optic neuritis

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**Aims:** A phase II randomized, placebo-controlled trial of acute demyelinating optic neuritis (ON) demonstrated a neuroprotective effect of phenytoin at six months on peripapillary retinal nerve fibre layer (RNFL) thickness. We present the results of a larger trial that investigated the effects of phenytoin on optic nerve MTR, as a biomarker of possible neuroprotective effects of phenytoin on the tissue microstructure of the optic nerve.
Methods: 62 patients (29 active [21F, mean age (SD) 34.3(8.1) yrs] vs 33 placebo [21F, 35.2(9.2) yrs]) underwent MT and structural (fat-suppressed T1 and T2) optic nerve imaging at baseline and six months on a 3T Philips Achieva MRI scanner (London). Each optic nerve was imaged individually (0.5x0.5x3mm, 26 slices, axial-oblique plane perpendicular to nerve). Optic nerve MTR values were extracted slice by slice after co-registering with T1 maps. Optic nerve lesions were identified on the baseline T2 images and the lesion locations were registered to the MTR images to determine lesional MTR values for each nerve. To compare mean MTRs by region, lesion position and treatment group, mixed models were used with slice as the unit of analysis and subject random effects.

Results: Raw mean affected MTR at follow-up (FU) over all slices was 33.2 (SD 6.1) in the active group and 32.7 (6.4) in the placebo group. Mean affected MTR anterior to the lesion showed a significant beneficial treatment effect (i.e. more positive MTR change from baseline to follow-up in active relative to placebo groups) (p=0.022). Treatment was also associated with non-significant positive treatment effects in the lesion (p=0.342) and optic nerve posterior to the lesion (p=0.178). Further analyses were performed for slice position relative to lesion (anterior, lesion, posterior) interacting with position relative to nerve anatomy (orbital, canalicular, intracranial). Results for affected nerve MTR anterior to lesion remained significant for orbital (p=0.032) and canal (p=0.039) locations. In addition, intracranial lesions MTR also showed a significant treatment effect (p=0.03).

Conclusions: Treatment with phenytoin appears to have a beneficial effect on tissue microstructure in the optic nerve after optic neuritis. The effect is more apparent in MTR measures anterior to the lesion where the changes are likely to be secondary to lesional disruption and may reflect selective susceptibility to neuroprotection.

Disclosure
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References:

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Dimethyl fumarate (DMF) improves behavioral outcomes in a mouse model of progressive multiple sclerosis
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Background: Multiple sclerosis (MS) is an inflammatory demyelinating disease in which immune cells attack and destroy myelin. Despite treatment with immunomodulatory drugs, MS patients slowly transition into a progressive disease state of accumulating and irreversible neurological decline. Dimethyl fumarate (DMF) is approved for relapsing forms of MS and may protect axons through upregulation of endogenous stress resistance genes. We have developed a progressive MS mouse model consisting of three cycles of cuprizone-treatment and spontaneous recovery, engendering a significant loss of axons in the corpus callosum and progressive neurological decline between 62-77 weeks.

Objective: To determine whether early use of DMF improves behavioral outcomes and preserves corpus callosum axons in a progressive MS mouse model.

Methods: Eight-week-old C57BL/6J mice were subjected to three cycles of cuprizone/rapamycin treatment followed by remyelination. DMF treatment was started either after the first, second or third insult, and continued daily for 72 weeks. Neurological function was evaluated in the NeuroCube\textsuperscript{®} (NC) platform and white matter myelin was evaluated using a myelin-loss sensitive magnetization transfer ratio (MTR) following MRI scanning.

Results: Mice receiving DMF treatment following the first insult showed significant behavioral improvements compared with mice receiving vehicle when analyzed in NC at 36-weeks (P=0.002) and continued to show significant behavior improvements at 48-weeks (P=0.009). Mice starting DMF-treatment following the second insult also showed significantly improved behavior readouts compared with mice receiving vehicle at 36-weeks (P=0.02) and 48-weeks (P=0.018). Mice receiving DMF after the third insult showed smaller improvements compared with the vehicle group when analyzed at 36-weeks (P=0.05) and 48-weeks (P=0.04).

Conclusions: DMF treatment immediately following the first insult, rather than the second or third insult, demonstrated the...
most significant functional improvement compared with vehicle, suggesting DMF may have neuroprotective effects in this progressive MS mouse model. Longitudinal evaluation of behavioral outcomes and white matter integrity at the 60- and 72-week time points will further characterize the long-term neuroprotective effect of DMF.

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Disclosure


Bruce D. Trapp: employee of and holds stock/stock options in Renovo.

Background: Fingolimod (FTY) and natalizumab (NAT) reduce disease activity and atrophy progression in relapsing-remitting multiple sclerosis (RRMS), but comparative studies are limited. Aims: To compare the effects of FTY and NAT on preventing regional gray matter (GM) and white matter (WM) volume loss in RRMS after two years of treatment.

Methods: Fifty-five RRMS patients starting FTY (n=25) or NAT (n=30) underwent 3T brain scans at baseline (T0), month-6 (M6), year-1 (Y1) and year-2 (Y2). Tensor-based morphometry and SPM12 were used to assess the longitudinal patterns of regional GM/WM volume changes during study period (p< 0.05, FWE corrected).

Results: At T0, no GM/WM volume difference was found between groups. At M6 vs T0, FTY-patients experienced a decreased GM volume of bilateral cerebellar cortex and hippocampi, right thalamus and right cingulate cortex. At Y1 vs M6 and Y2 vs Y1, a further atrophy of bilateral cerebellar cortex, left thalamus, several fronto-temporo-occipito-parietal regions, and cingulate cortex occurred in FTY-patients. NAT-patients showed a significant atrophy of left cingulate cortex and thalamus and bilateral fronto-temporo-parietal regions only at Y2 vs Y1. At M6 vs T0, both groups showed a significant WM atrophy of some supratentorial clusters, while bilateral cerebellar WM volume loss was observed in FTY-patients only. At Y1 vs M6 and Y2 vs Y1, a further supratentorial WM volume loss occurred in both groups, and cerebellar WM atrophy progressed in FTY-patients. Compared to NAT-patients, FTY-patients showed only a significant cerebellar cortical and WM atrophy at M6 vs T0. No regional GM/WM volume increase was detected at any timepoint.

Conclusions: The anti-inflammatory effects of NAT and the pleiotropic effects of FTY on the peripheral immune system and in the central nervous system differently modified GM/WM atrophy progression in RRMS patients, with NAT having a more significant effect on preventing regional tissue loss.

Disclosure

P. Preziosa received speakers honoraria from Biogen Idec, Novartis, and Excemed. G. Riccitelli, M. Rodegher, L. Moiola, A. Falini have nothing to disclose. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Teva Neurosciences and Genzyme and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla.

G. Comi has received compensation for consulting services for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Exemed, Roche, Almirall, Chugai, Receptos, and Forward Pharma, and compensation for speaking activities for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Exemed, and Roche.

M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARISLA (Fondazione Italiana di Ricerca per la SLA).

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Patterns of regional gray matter and white matter atrophy in patients starting fingolimod or natalizumab: a 2-year tensor-based morphometry study

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Background: Fingolimod (FTY) and natalizumab (NAT) reduce disease activity and atrophy progression in relapsing-remitting multiple sclerosis (RRMS), but comparative studies are limited. Aims: To compare the effects of FTY and NAT on preventing regional gray matter (GM) and white matter (WM) volume loss in RRMS after two years of treatment.

Methods: Fifty-five RRMS patients starting FTY (n=25) or NAT (n=30) underwent 3T brain scans at baseline (T0), month-6 (M6), year-1 (Y1) and year-2 (Y2). Tensor-based morphometry and SPM12 were used to assess the longitudinal patterns of regional GM/WM volume changes during study period (p< 0.05, FWE corrected).

Results: At T0, no GM/WM volume difference was found between groups. At M6 vs T0, FTY-patients experienced a decreased GM volume of bilateral cerebellar cortex and hippocampi, right thalamus and right cingulate cortex. At Y1 vs M6 and Y2 vs Y1, a further atrophy of bilateral cerebellar cortex, left thalamus, several fronto-temporo-occipito-parietal regions, and cingulate cortex occurred in FTY-patients. NAT-patients showed a significant atrophy of left cingulate cortex and thalamus and bilateral fronto-temporo-parietal regions only at Y2 vs Y1. At M6 vs T0, both groups showed a significant WM atrophy of some supratentorial clusters, while bilateral cerebellar WM volume loss was observed in FTY-patients only. At Y1 vs M6 and Y2 vs Y1, a further supratentorial WM volume loss occurred in both groups, and cerebellar WM atrophy progressed in FTY-patients. Compared to NAT-patients, FTY-patients showed only a significant cerebellar cortical and WM atrophy at M6 vs T0. No regional GM/WM volume increase was detected at any timepoint.

Conclusions: The anti-inflammatory effects of NAT and the pleiotropic effects of FTY on the peripheral immune system and in the central nervous system differently modified GM/WM atrophy progression in RRMS patients, with NAT having a more significant effect on preventing regional tissue loss.

Disclosure

P. Preziosa received speakers honoraria from Biogen Idec, Novartis, and Excemed. G. Riccitelli, M. Rodegher, L. Moiola, A. Falini have nothing to disclose. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Teva Neurosciences and Genzyme and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla.

G. Comi has received compensation for consulting services for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Exemed, Roche, Almirall, Chugai, Receptos, and Forward Pharma, and compensation for speaking activities for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Exemed, and Roche.

M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARISLA (Fondazione Italiana di Ricerca per la SLA).

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Blocking LINGO family promotes axon regeneration in the optic nerve crush model

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Background: Leucine-rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein-1 (LINGO-1) is a negative regulator of oligodendrocyte differentiation, myelination and remyelination. The LINGO family has 4 members: LINGO-1, -2, -3 and -4. LINGO-1, -2 and -3 are specific to the central nervous system. Knock out of LINGO-1, -2, or -3 individually promotes axon regeneration and retinal ganglion cell (RGC) survival in the optic nerve crush model. Previously we demonstrated that anti-LINGO-1 antibody promotes optic nerve regeneration versus antibody-treated controls in an optic nerve crush animal model.

Objectives: To determine if blocking LINGO-1, -2, -3 simultaneously in the optic nerve crush model could result in greater axon regeneration and neuronal protection than targeting LINGO family members individually.

Methods: LINGO-2/3 double knockout and wild type (WT; C57BL6/J) mice were treated with intraperitoneal injections of
6 mg/kg control or anti-LINGO-1 antibodies 1 day before optic nerve crush and weekly thereafter. Optic nerves were crushed ~1 mm behind the optic disk with number 5 forceps for 2 seconds. 2 µg/µl Alexa 647 conjugated cholera toxin β subunit (CTB) was injected intravitreally on day 26 and the mice sacrificed 2 days after, which optic nerves were dissected and processed. Regenerated axons were quantified by counting the numbers of CTB-label axons located 0.5 mm from the crush site. The unpaired t test was used for data analyses.

**Results:** We observed a 1.3-fold increase in regenerating axons in anti-LINGO-1 antibody-treated LINGO-2/3 double knockout mice compared with anti-LINGO-1 antibody-treated WT mice. At 0.5 mm from the crush site, the estimated mean number of regenerating axons per nerve was 19 (standard error of the mean ±2; n=32) in control antibody-treated WT mice, 28 in anti-LINGO-1 antibody-treated WT mice (±5; n=10), 24 in control antibody-treated LINGO-2/3 double knockout mice (±5; n=4), and 37 in anti-LINGO-1 antibody-treated LINGO-2/3 double knockout mice (±6; n=4).

**Conclusions:** Optic nerve crush data suggests that blocking LINGO-1/2/3 simultaneously is more efficacious in promoting axon regeneration than blocking LINGO-1 alone. These results support the development of pan-specific anti-LINGO family antibodies to potentially improve axonal regeneration.

**Supported by:** Biogen.

**Disclosure**

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**P718**

**Predictors of an opicinumab treatment effect and identification of an efficacy subpopulation: a post hoc analysis of the SYNERGY study**

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**Background:** SYNERGY (NCT01864148) assessed the efficacy and safety of opicapumab in participants with relapsing forms of MS when used concurrently with IM IFN beta-1a. The primary endpoint was 12-week confirmed improvement in ≥1 test of a multicompontent endpoint (EDSS, T25FW, 9HPT-D, 9HPT-ND, PASAT-3) over 72 weeks. A non-monotonic, inverted U-shaped dose response to opicapumab was observed, with favourable outcomes in the 10 and 30 mg/kg groups. Identification of participants who experienced larger and more durable effects would enable a more targeted treatment approach.

**Objectives:** To identify demographic and baseline predictors of opicapumab treatment response, and identify a subpopulation with a greater treatment response.

**Methods:** A multivariate modelling approach anchored on the overall response score (ORS), a pre-specified endpoint based on EDSS, T25FW, 9HPT-D and 9HPT-ND, was used. At each visit, each component was scored relative to baseline (worsening threshold met: -1; no change met threshold: 0; improvement threshold met: +1). Multivariate repeated measure mixed models with stepwise model selection were used to identify treatment response predictors. Baseline candidate covariates included nine demographic/clinical and 13 MRI characteristics. The likelihood ratio test was used to select significant predictors; a numerical search identified optimal cutoff values. Cross validation and tree-based classification algorithms evaluated the robustness of identified subpopulations.

**Results:** Three predictive characteristics of greater and more durable efficacy were identified by the ORS: shorter disease duration (≤20 y), lower baseline magnetisation transfer ratio (MTR) values in T2 lesions (may be consistent with lower myelin content), and lower baseline diffusion tensor imaging-radiodiffusivity (DTI-RI-D) values in T2 lesions (may be consistent with higher structural integrity). For the subpopulation with these characteristics, the proportions of participants with 12-week confirmed improvement over 72 weeks were 36% for placebo (IM IFN beta-1a only) and 81% for the 10 mg/kg opicapumab group, vs 49% and 63%, respectively, in the ITT population.

**Conclusions:** This post hoc analysis identified three predictive characteristics (disease duration, MTR and DTI-RI-D in T2 lesions) associated with a greater and more durable treatment effect. The subpopulation identified may allow a more targeted (personalised) approach for future opicapumab studies.

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**Disclosure**

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P719
Keeping mitochondria on the road: teriflunomide maintains mitochondrial motility levels in axons challenged with oxidative stress
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In Multiple Sclerosis (MS), oxidative stress, mitochondrial dysfunction in axons, and subsequent bioenergetic failure are well recognized pathogenic factors that contribute to the progression of disease disability. We previously showed that oxidative stress reduces the motility and alters the morphology of axonal mitochondria, limiting their transport and inducing conformation changes that lead to axonal damage. Teriflunomide, an oral immunomodulator approved for the treatment of relapsing-remitting MS, reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH). This enzyme is crucial for the de novo pyrimidine biosynthesis and is the only enzyme in this pathway located in the mitochondria and not in the cytosol, thus conferring an attractive link between immune modulation, mitochondria activity and axonal protection. To investigate how DHODH-inhibition may affect mitochondrial behavior in the context of oxidative stress, we employed a model of transected murine spinal roots, previously developed and characterized in our lab. First, we verified that DHODH is indeed expressed in peripheral roots extracted from C57BL/6 mice. Using confocal live-imaging of axonal mitochondria, we then showed that in unmanipulated axons, teriflunomide increased significantly the mitochondria length without altering their transport characteristics. Even on a high teriflunomide concentration, we did not observe any evidence of mitochondrial or axonal toxicity. In mitochondria challenged with 100 µM H₂O₂ to induce oxidative stress, we observed that the presence of teriflunomide was able to restore, in a dose-dependent manner, mitochondrial motility to the control levels, while mitochondrial shape was not affected. Both the fraction of moving mitochondria and the distance covered by the mitochondria were comparable to those observed in control unmanipulated mitochondria. Thus, our results demonstrate a previously undescribed link between DHODH and mitochondrial dynamics, and point to a potential neuroprotective effect of DHODH-inhibition in the context of oxidative-stress induced damage of mitochondria and axons.

Discussion
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P720
Selective estrogen receptor modulators significantly enhance remyelination in an estrogen receptor-independent manner
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Introduction: Multiple Sclerosis (MS) is characterized by widespread demyelination and subsequent degeneration of axons. Remyelination of the affected axons represents a key therapeutic target to prevent progression of clinical disability associated with disease pathogenesis and resulting neurodegeneration. Utilizing a novel screening technique (binary indicant for myelination using micropillar arrays (BIMA)), we previously identified selective estrogen receptor modulators (SERMs) as a cluster that enhance oligodendrocyte precursor cell (OPC) differentiation and subsequently promote remyelination. To date, SERMs have been reported to mediate OPC differentiation by acting on estrogen receptors (ERα and ERβ), expressed at low levels on OPCs.

Methods: To validate the effects and target receptor of SERMs, we selected 3 SERMs with high clinical translational potential. We employed in vitro assays, in vivo models, and human embryonic cell-derived OPCs. To validate the SERM targets, we used genetic mouse models of estrogen receptor (ERα and ERβ) knockouts, as well as double ER-knockouts, to culture OPCs in isolation.

Results: When administered to OPCs cultured in isolation as well as co-cultured with dorsal root ganglion neurons, each SERM significantly enhanced OPC differentiation and myelination. We measured significantly enhanced OPC differentiation with SERM treatment across all knockout (ERα, ERβ), and double ER) models. Further, we assessed for remyelination in an in vivo focal demyelination model in the corpus callosum in wild-type and ER-double knockout mice. All mice treated with SERMs following demyelination displayed significant improvements in remyelination when compared with vehicle-treated mice. Finally, human ES cell-derived OPCs treated with each SERM showed enhanced differentiation.

Discussion: Our findings indicate that the selected SERMs are potent regulators of remyelination, and in contrast to the existing literature, that ERs are not necessary for these SERMs to elicit their remyelination effects. Using bioinformatics profiling, we are working to identify the receptor target. Due to their tolerability in clinical trials, SERMs hold significant translational potential to move from bench to bedside.

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Ari J. Green: founder of Inception 5 Biosciences and is on the scientific advisory board of Bionure.
Jonah R. Chan: Co-founder of Inception; Consultant for Inception Sciences/Roche Pharmaceuticals.

P721
Phase I/II clinical trials testing multiple dosing of intrathecal mesenchymal stem cell-derived neural progenitors in patients with progressive multiple sclerosis
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Introduction: Multiple Sclerosis (MS) is characterized by widespread demyelination and subsequent degeneration of axons. Remyelination of the affected axons represents a key therapeutic
Background: Mesenchymal stem cell-neural progenitors (MSC-NPs) are an autologous bone marrow-derived population of cells with neuroectodermal lineage characteristics currently under investigation as a novel MS treatment targeting CNS repair and regeneration. In mouse EAE, we established that multiple dosing of intrathecal (IT) MSC-NPs was associated with cell migration to lesion areas, suppression of local inflammatory response, trophic support for damaged cells at the lesion site, and improvement in clinical scores of EAE. In a pilot clinical study, IT-MSC-NP treatment also supported the dosing, safety, feasibility, and potential efficacy of this approach in MS.

Objectives: To evaluate safety (phase I) and efficacy (phase II) of repeated dosing of IT-MSC-NP treatment in patients with progressive MS.

Methods: MSCs obtained from bone marrow aspirates were isolated, expanded, and cryopreserved. Prior to dosing, a portion of MSCs were thawed, expanded, and cultured with neural progenitor media to generate MSC-NPs. MSC-NPs were harvested and administered to the patient within 30 minutes. Quality testing of MSC-NPs included sterility, identity, and chromosomal stability. Clinical assessments were performed at baseline, at each treatment, and 3 and 6 months post-treatment.

Results: In the 20 patient open-label phase I trial, IT-MSC-NPs were injected at a dose of 10 million cells every 3 months. The only notable adverse event included transient headache and fever found in 72% and 15% of the treatments, respectively. Of the 20 study subjects, 15 (or 75%) demonstrated functional neurological improvement associated with IT-MSC-NP treatment. Improvements were noted in EDSS, 25 foot walk, and muscle strength, and occurred more frequently in ambulatory patients (EDSS ≤ 6.5). In addition, 50% of subjects demonstrated symptomatic and/or urodynamic improvement in bladder function. A phase II trial is underway to investigate efficacy of IT-MSC-NP treatment compared to a placebo sham-IT control. Fifty patients with EDSS between 3.5 and 6.5 will be randomized as matched treatment compared to a placebo sham-IT control. Fifty patients were injected at a dose of 10 million cells every 3 months.

Conclusions: IT-MSC-NP therapy is a promising regenerative therapy for progressive MS.

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P722
Fingolimod-mediated axonal protection during demyelination facilitates myelin increase during recovery
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Background: In the demyelinating disease multiple sclerosis (MS), loss of myelin exposes axons to metabolic and environmental stresses, leading to axonal degeneration or transection and the development of irreversible neurological disabilities. Protecting demyelinated axons from transection may reduce accumulation of axonal damage, enhance remyelination and improve the outcome for MS patients. Fingolimod is an MS drug that has been shown to reduce the rate of relapses by modulating S1P receptor function and lymphocytes entry into the brain.

Objective: To evaluate whether fingolimod protects demyelinated axons and to determine whether fingolimod-mediated axonal protection promotes myelin production during recovery.

Methods: We tested the effect of fingolimod in an immunemediated demyelination mouse model, where C57BL/6J male mice were fed cuprizone chow and subjected to daily rapamycin injections for 6 weeks to induce demyelination. Fingolimod was delivered daily at 0.3 mg/kg, for 6 weeks concurrent with demyelination, or for 9 weeks (6 weeks during demyelination and an additional 3 weeks during recovery). Axonal ovoids were visualized in the corpus callosum by SMI32 antibody staining and quantitated; myelinated axons were counted in 1 micron thick Epon sections. Myelin in the cerebral cortex and hippocampus was visualized by PLP antibody staining and quantitated.

Results: When mice were given fingolimod for 6 weeks during cuprizone-induced demyelination, there was a 36% reduction in the number of SMI32+ axonal ovoids in corpus callosum compared with vehicle-treated control (P< 0.01). Fingolimod treatment did not alter the extent of demyelination. When mice were given 3 more weeks of fingolimod during remyelination (in addition to 6 weeks during demyelination), the number of axonal ovoids was 43% lower than that of the vehicle (P< 0.01), and the number of myelinated axons in corpus callosum increased by 20%. Moreover, there were significant increases (P< 0.01) in myelin in the cerebral cortex and hippocampus, and a significant reduction in Iba1+ microglia (12% less, P< 0.01).

Conclusion: Fingolimod treatment during cuprizone-mediated demyelination significantly reduces collateral axonal degeneration in the corpus callosum. Continuous treatment with fingolimod during 6 weeks of demyelination and 3-weeks of remyelination provide additional axonal protection and this increase in axonal survival correlated with a significant increase in remyelination.

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P723
Protection of mitochondrial function by dimethyl fumarate in an animal model of multiple sclerosis
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Background: In the demyelinating disease multiple sclerosis (MS) is increasingly recognized, and mitochondrial membrane
potential (∆Ψm) is decreased in animals with experimental autoim-
nune encephalomyelitis (EAE), a model of MS. Dimethyl fumarate
(DMF), an MS therapy, is thought to act via anti-inflammatory and
antioxidant mechanisms, specifically through activation of the tran-
scriptional factor Nrf2. Considering that Nrf2 affects mitochondrial
metabolism, and that fumarate participates in the Krebs cycle, we
have explored whether DMF might protect mitochondria in EAE.

Methods: Female mice expressing a cyan fluorescent protein tar-
geted to neuronal mitochondria were immunized with MOG 35-55
and treated prophylactically with DMF (30mg/kg; twice daily), or
vehicle. At eight days post-immunisation, and on the first day of
neurological deficit, animals were terminally anaesthetised and
the spinal cord exposed for in vivo confocal measurement of ∆Ψm
in axons using the fluorescent dye TMRM. Inflammation and oxida-
tive damage were examined immunohistochemically. Finally,
the acute effect of DMF on mitochondria was examined by topical
application of the drug on the exposed spinal cords of mice on the
first day of neurological deficit (200uM and 400uM) shortly
before in vivo examination of their axonal mitochondria.

Results: Prophylactic DMF treatment significantly reduced EAE
incidence, but not disease severity in affected animals. DMF sig-
nificantly protected axonal mitochondria from depolarisation
before the onset of neurological deficit, but this protection was
lost with disease onset. Microglial activation, iNOS production
and oxidative damage were all reduced by DMF treatment.
Topical application of DMF had no significant effect on ∆Ψm com-
pared with vehicle-treated mice.

Conclusions: Prophylactic, but not acute, DMF therapy protects
mitochondria from the depolarisation normally experienced in
animals immunised for EAE, providing an explanation for the
reduced incidence of disease expression. DMF also reduces oxida-
tive stress and inflammation in the spinal cord.

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Long-term treatment monitoring

P724
Alemtuzumab reduced MRI lesions and slowed brain volume
loss in CARE-MS II patients switching from SC IFNB-1a:
5-year follow-up after alemtuzumab (TOPAZ study)
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A. Rovira6, S. Schippling7, B.V. Singer8, A. Traboulsee9, D.H.
Margolin10, S. Santra11, K. Nakamura12, D.L. Arnold13,14, on
behalf of the CARE-MS II, CAMMS03409, and TOPAZ
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Background: In CARE-MS II (NCT00548405), alemtuzumab sig-
nificantly improved MRI outcomes, including brain volume loss
(BVL), vs SC IFNB-1a over 2 years (y) in patients (pts) with active
RRMS and inadequate response to prior therapy. In a completed
extension (NCT00930553), SC IFNB-1a-treated pts discontinued
that therapy and initiated alemtuzumab 12 mg (2 courses: baseline,
5 days; 12 months later, 3 days), which demonstrated durable efficacy
in the absence of continuous treatment. Pts could receive as-needed
alemtuzumab retreatment (12 mg/day on 3 consecutive days, ≥12
months after previous course for relapse/MRI activity) or other dis-
ease-modifying therapy (DMT; per investigator discretion). Pts
completing ≥48 months of extension could enrol in TOPAZ, a 5-y,
phase 3b/4 study (NCT02255656) for further evaluation.

Goal: Evaluate alemtuzumab MRI efficacy 5 y after switching
from SC IFNB-1a.

Methods: In TOPAZ, pts can receive alemtuzumab retreatment
(≥12 months apart) or other DMT at any point in time (both per
investigator discretion, no criteria). Assessments: annual MRI
scored for disease activity (gadolinium [Gd]-enhancing T1 lesions
or new/enlarging T2 hyperintense lesions) and brain parenchymal
fraction (BPF) change.

Results: Of 175 SC IFNB-1a-treated pts completing CARE-MS
II, 143 (82%) received alemtuzumab in the extension; 123 (86%)
of these completed Y4 of post-alemtuzumab follow-up and
entered TOPAZ; 119 (97%) completed Y5 post-alemtuzumab.
Percentages free of Gd-enhancing T1 lesions were 78% in SC
IFNB-1a Y2, increasing to 91% in post-alemtuzumab Y2, and
86%-89% in Y3-5. Percentages free of new/enlarging T2 hyperin-
tense lesions were 48% in SC IFNB-1a Y2, 81% in post-alemtuz-
umab Y2, and 72%-67% in Y3-5. Percentages free of MRI
disease activity increased from 47% in SC IFNB-1a Y2 to 91% in post-alemtuzumab-Y2, and were 72%-67% in Y3-5. Median
yearly BPF percent change decreased post-alemtuzumab (SC
IFNB-1a Y2: -0.33%; alemtuzumab Y1-5: 0.02%, -0.04%,
-0.15%, -0.14%, -0.08%). 61% received no further treatment after
the initial 2 courses.

Conclusion: In pts with inadequate response to prior therapy plus
2 y of SC IFNB-1a treatment, switching to alemtuzumab improved
MRI lesion and BVL outcomes over 5 y. These findings are con-
sistent with core study conclusions, and suggest that alemtuzumab
may provide a unique treatment approach for RRMS pts treated
previously with SC IFNB-1a, offering durable efficacy in the
absence of continuous treatment.

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P725
Predictors of relapses and disability progression after stopping disease-modifying therapies for multiple sclerosis
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Background: MS patients often stop disease-modifying therapy (DMT). MSBase, a 50,000-patient, global observational MS registry, provides a unique opportunity to identify predictors of relapses and disease progression after DMTs are stopped.

Objectives: To identify predictors of relapse and confirmed disability progression after stopping DMTs.

Methods: We included MS patients who, at the time of stopping DMT, were ≥18 years and were on a DMT continuously for ≥1 year.

We also required that, after stopping DMT, each patient be followed for ≥2 years; did not restart DMT for > 6 months (to exclude therapy ‘switchers’); and did not become pregnant for ≥1 year. Predictors of time to first relapse and 3-month confirmed progression (1.5 EDSS steps for baseline EDSS 0; 0.5 - for baseline EDSS 6-6.5; 1 - for all others) were analyzed using Cox proportional hazards regression. Hazard proportionality was assessed with scaled Schoenfeld residuals; p< 0.05 was considered significant.

Results: We identified 4,842 patients in the MSBase who met our inclusion criteria (74% female; mean (SD) age 40.7 years (10.4); mean (SD) disease duration 11.6 years (7.7)). Median (IQR) EDSS at baseline was 3 (1.5, 5.5). The discontinued DMTs were: IFNb-1a sc in 28%; IFNb-1b - 26%; IFNb-1a im - 19%; glatiramer acetate 18%; natalizumab - 6%; fingolimod 3%. Most common reasons for discontinuation, recorded for 48% patients, were adverse events (9%), inconvenience (7%) and intolerance (7%). Post-DMT follow up was 31,691 patient-years. Post-DMT annualized relapse rate (ARR) was 0.22 and was lowest post-IFNb-1b (ARR=0.19) and highest post-Natalizumab (ARR=0.32). Disability data was available for 2,678 patients. The incidence of post-DMT confirmed disability progression was 8.23 per 100 person-years (95% CI: 7.72, 8.76); it was lowest post-IFNb-1a (6.40 (5.45, 7.51)) and highest post-Natalizumab (12.55 (10.04, 15.69)). DMT was restarted by 2,984 (61.6%) patients after a median reason for discontinuation, recorded for 48% patients, were adverse events (9%), inconvenience (7%) and intolerance (7%). Post-DMT follow up was 31,691 patient-years. Post-DMT annualized relapse rate (ARR) was 0.22 and was lowest post-IFNb-1b (ARR=0.19) and highest post-Natalizumab (ARR=0.32). Disability data was available for 2,678 patients. The incidence of post-DMT confirmed disability progression was 8.23 per 100 person-years (95% CI: 7.72, 8.76); it was lowest post-IFNb-1a (6.40 (5.45, 7.51)) and highest post-Natalizumab (12.55 (10.04, 15.69)). DMT was restarted by 2,984 (61.6%) patients after a median (IQR) of 18.22 months (IQR 10.97, 36.60). For each DMT, we will present predictors of time to relapse and confirmed disability progression, and DMT restart based on Cox regression model.

Conclusions: Understanding risk factors for post-DMT relapses and disability accumulation after cessation of DMTs may allow clinicians to identify patients at low risk of disease worsening, who may choose to safely discontinue a particular DMT, and those at high risk, who would be well advised to continue on therapy.

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P726
Alemtuzumab after Natalizumab SWitch in Evolving Rapidly Severe Multiple Sclerosis (ANSWERS MS)
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Background: Sequential use of high-efficacy monoclonal antibodies is commonly encountered in real world practice, but data on its safety and efficacy are rarely available from randomised trials and little guidance is available on how to manage the switch. The pre-licensing use of alemtuzumab in the UK & Ireland (from 1999) provides an opportunity to examine the long term safety and effectiveness of this compound in real world scenarios, including its use after the failure of natalizumab.

journals.sagepub.com/home/msj
Methods: Retrospective clinical and radiographic data are being collected from 18 MS Centres in the UK and Ireland. The aim is to collect all UK and Irish patients switching to alemtuzumab due to natalizumab failure, with centres encouraged to enter data on the switchers with the longest follow-up periods first. 77 patients have been identified to date and preliminary results are presented here on long term safety.

Results: 37 patients had more than 2 years of follow-up data since their first alemtuzumab infusion (mean 4.96 years (SD 1.88, range 2.2-8.0)). Of these, 29 (78.4%) were female, with median age 29.4 years (range 15-61) at diagnosis. Median EDSS at diagnosis was 1.5 (range 0-7). Median duration of disease prior to natalizumab use was 3.9 years (range 0.2-18.5). Mean duration on natalizumab treatment was 1.4 years (median 0.8, range 0.1-5.5). Natalizumab was usually stopped due to lack of efficacy (n=21, 56.8%), hypersensitivity (n=6, 16.2%) and PML risk (n=5, 13.5%). No DMTs were used during the switch period for the majority (n=34, 91.9%). The switch period (from final natalizumab to initial alemtuzumab infusion) lasted a mean of 136 days (median 101, range 28-524).

Most subjects received 2 alemtuzumab courses (n=23, 62.2%). Infusion reactions occurred in 13 subjects; 12 had one infusion reaction and 1 had 2 infusion reactions. The switch period (from final natalizumab to initial alemtuzumab infusion) lasted a mean of 136 days (median 101, range 28-524).

The serious adverse events included infections (n=3, 8.1%), malignancies (n=3, 8.1%), thyroid disease developed in 6 patients (16.2%). Significant infections occurred in 5 patients (13.5%): VZV (n=3), bacterial (n=1) and CMV (n=1). Thrombocytopaenia occurred in 2 patients (5.4%) and 1 patient (2.7%) developed proteinuria.

Conclusions: No new safety signals were identified in this long term cohort of 37 patients switching to alemtuzumab from natalizumab.

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Efficacy of a third course of alemtuzumab in patients with active relapsing-remitting multiple sclerosis who experienced disease activity after the initial two courses: pooled analysis of CARE-MS I and II

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Background: Alemtuzumab improved clinical and MRI outcomes in two, 2-year (y), phase 3 trials vs SC IFNB-1a in patients (pts) with active RRMS who were treatment-naive (CARE-MS I; NCT00530348) or had inadequate response to prior therapy (CARE-MS II; NCT00548405). Pts continuing in an extension study (NCT00905533) demonstrated durable efficacy through Y6; 24% of pts from CARE-MS I and 30% of pts from CARE-MS II received 1 alemtuzumab retreatment through Y6.

Goal: Evaluate efficacy of alemtuzumab retreatment in pooled CARE-MS I and II pts who received a third course (C3) due to relapse and/or MRI activity.

Methods: Pts received 2 courses of alemtuzumab 12 mg/d (baseline: 5 d; 12 months (mo) later: 3 d) in CARE-MS I and II. Pts who completed the core studies could enter the extension and receive as-needed alemtuzumab retreatment (for relapse and/or MRI activity) or another DMT (per investigator discretion). Assessments in pts who received C3 during the extension: annualised relapse rate (ARR) 12 mo prior/up to 3 y after C3, change in mean EDSS, improved/stable EDSS (vs core study baseline) 12 mo prior/12 mo after C3, and 6-month confirmed disability

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improvement (CDI) 12 mo prior/12 mo after C3. Pts who received
>3 courses (>1 retreatment) or another DMT during the extension
were not included in this analysis.

Results: Through Y6, 669/742 (90%) pooled CARE-MS I and II
pts entering the extension remained on study. 198/742 (27%)
pooled CARE-MS I and II pts received 1 additional course of
alemtuzumab (Y2: 2%, Y3: 31%, Y4: 27%, Y5: 23%, Y6: 17%)
without further retreatment or other DMT. Mean time from C2
to C3 was 2.6 y. ARR decreased from 0.74 12 mo prior to C3 to 0.06
12 mo after C3 (rate ratio [95% CI], 0.09 [0.046-0.161]; P<
0.0001), and remained low (0.08) 3 y after C3. Change in mean
EDSS 12 mo after C3 was −0.12. The percentage of pts with sta-
bility/improved EDSS was higher 12 mo after C3 vs at the time of
C3 administration (71% vs 62%). The percentage of pts with CDI
was significantly higher 12 mo after C3 vs 12 mo prior to C3
(17.5% vs 5.0%; P=0.0117).

Conclusion: In CARE-MS pts who received a third course due to
relapse and/or MRI activity, alemtuzumab effectively reduced relapses
and improved disability without further treatment. These data
support administering a third course of alemtuzumab in pts
with disease activity to achieve durable disease control.

Study support: Sanofi and Bayer HealthCare Pharmaceuticals.

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Alemtuzumab decreased MRI disease activity and slowed
brain volume loss over 5 years after switching from SC
IFNB-1a: follow-up of CARE-MS I (TOPAZ study)

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Background: In CARE-MS I (NCT00530348), alemtuzumab
significantly improved MRI outcomes, including brain volume
loss (BVL), versus SC IFNB-1a over 2 years (y) in treatment-
naive patients (pts) with active RRMS. In a completed extension
study (NCT00930553), SC IFNB-1a-treated pts discontinued
that therapy and initiated alemtuzumab 12 mg (2 courses: baseline,
5 days; 12 months later, 3 days), which demonstrated durable effi-
cacy in the absence of continuous treatment. In the extension, pts
could receive as-needed alemtuzumab retreatment (12 mg/day on
3 consecutive days, ≥12 months after previous course for relapse/
MRI activity) or other disease-modifying therapy (DMT; per
investigator discretion). Pts completing ≥48 months of the exten-
sion could enrol in TOPAZ, a 5-y, phase 3b/4 study (NCT02255656)
for further evaluation.

Goal: Evaluate alemtuzumab MRI efficacy 5 y after switching from SC IFNB-1a.

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Methods: In TOPAZ, pts can receive alemtuzumab retreatment (≥12 months apart) or other DMT at any time point (both per investigator discretion, no criteria). Assessments: annual MRI scored for disease activity (gadolinium [Gd]-enhancing T1 lesions or new/enlarging T2 hyperintense lesions) and brain parenchymal fraction (BPF) change.

Results: Of 173 SC IFNB-1a-treated pts completing CARE-MS I, 139 (80%) were treated with alemtuzumab in the extension; 122 (88%) of these completed Y4 of post-alemtuzumab follow-up and entered TOPAZ, and 118 (97%) completed Y5 post-alemtuzumab. Percentages free of Gd-enhancing T1 lesions were 81% in SC IFNB-1a Y2, increasing to 96% in post-alemtuzumab Y2, and 92%-89% in Y3-5. Percentages free of new/enlarging T2 hyperintense lesions were 60% in SC IFNB-1a Y2, 82% in post-alemtuzumab Y2, and 72%-67% in Y3-5. Percentages free of MRI disease activity increased from 59% in SC IFNB-1a Y2 to 82% in post-alemtuzumab Y2, and were 72%-67% in Y3-5. Median yearly BPF percent change decreased post-alemtuzumab (SC IFNB-1a Y2: -0.50%; alemtuzumab Y1-Y5: -0.07%, -0.15%, -0.05%, 0.01%, -0.13%). 71% of pts received no further treatment after the initial 2 alemtuzumab courses.

Conclusion: In pts with prior SC IFNB-1a treatment, switching to alemtuzumab improved MRI lesion and BVL outcomes over 5 years. These findings are consistent with core study conclusions, and suggest that alemtuzumab may provide a unique treatment approach for RRMS pts treated previously with SC IFNB-1a, with durable efficacy in the absence of continuous treatment.

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Objectives:

(1) Estimate effects of exposure to first generation disease-modifying drugs (DMDs) - interferon β-1a IM, interferon β-1a SC, interferon β-1b, glatiramer acetate - on disability progression speed in relapsing-onset multiple sclerosis (R-onset MS);
(2) test hypothesis that marginal effects are larger when disability is milder, and diminish with years since exposure;
(3) estimate natural history (NH) paths, new natural history (NNH) paths and health outcomes;
(4) estimate cost-effectiveness;
(5) estimate costs avoided by stopping treatment when marginal effects approach zero.

Study design: An observational, population-based, retrospective, treatment intervention study from an intention-to-treat perspective, for study period 1979-2010.


Methods: MS disability is measured by Expanded Disability Status Scale (EDSS) and by Health Utility Index Mark III (HUI3). EDSS observations are adjusted for interval censoring. A fixed effect regression model estimates disability NH paths, NNH paths and marginal DMD exposure effects. Our reference treatment group and historical self-controls group includes 1,114 persons in ambulatory range EDSS 0-6.5; each person has a year of onset and pre- and post-DMD exposure observations. Health outcomes - as measured by edss-DALYs avoided and hui3-QALYs gained - are computed by area-under-the-curve methods. Nova Scotia costs per DMD treatment year are expressed as 2017 US dollars.

Results: Marginal effects are larger when disability at exposure is milder, and diminish with years since exposure. Marginal effects are significant in range EDSS 0-4.5 for patients who did not progress to SPMS. Health outcomes per person - as measured by edss-DALYs avoided (0.6) or hui3-QALYs gained (1.1) -- are modest. Cost/hui3-QALY gained diminishes to “C/E acceptability threshold” US $100,000 only after 25 years since onset, when cost per treatment year is US $12,191. Costs avoidable -- by stopping DMD treatment when marginal effects approach zero -- range from 30% (stop after conversion to SPMS) to 38% (and stop after EDSS 4.5) without loss of benefits.

Conclusions: Exposure to DMDs slows disability progression in range EDSS 0-4.5. Health outcomes are modest. DMDs may be cost-effective, given low DMD costs. Stopping treatment when marginal effects approach zero avoids costs without loss of benefits.

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P731
Sustained efficacy of daclizumab beta over up to 6 years of treatment and improvements in efficacy outcomes in relapsing MS patients who switched from intramuscular interferon beta-1a to daclizumab beta: interim results from EXTEND

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Background: EXTEND is an ongoing, multicentre, open-label safety/efficacy extension study of daclizumab beta (DAC BETA) in patients with relapsing multiple sclerosis who completed DECIDE or transitioned from SELECTED or OBSERVE.

Objectives: To evaluate the effects of DAC BETA on clinical and radiologic disease outcomes after up to 3 years of treatment in patients who completed DECIDE.

Methods: Patients who received DAC BETA during the DECIDE ITT population in the combined DECIDE/EXTEND ITT population. 24-week confirmed disability progression (CDP) was analysed in the DECIDE ITT population in the combined DECIDE/EXTEND treatment period.

Results: 1516 patients received ≥1 dose of DAC BETA in DECIDE or EXTEND (exposure, 4637 patient-years; median [range], 34.0 [1-83] doses). 1203/1841 patients enrolled in DECIDE or EXTEND (exposure, 4637 patient-years; median [range], 34.0 [1-83] doses). 1203/1841 patients enrolled in DECIDE or EXTEND (exposure, 4637 patient-years; median [range], 34.0 [1-83] doses). 1203/1841 patients enrolled in DECIDE or EXTEND (exposure, 4637 patient-years; median [range], 34.0 [1-83] doses).

In EXTEND, effects on clinical outcomes and brain volume change were maintained during prolonged DAC BETA treatment (up to 6 years) and patients who switched from IFN in DECIDE to DAC BETA in EXTEND showed improved outcomes over up to 3 years of DAC BETA treatment.

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P732
Disease modifying therapy improves disability outcomes in relapsing-remitting multiple sclerosis over 22 years

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Background: The question whether multiple sclerosis (MS) therapies improve long-term disability outcomes in relapsing-remitting MS has not been satisfactorily answered.

Objective: To evaluate disability outcomes during treated vs. untreated epochs in patients from MSBase followed from disease onset up to 22 years.

Methods: Marginal structural models allow evaluation of MS outcomes adjusted for confounders of treatment effect as well as treatment choice in hypothetical populations that remained untreated vs. untreated for the whole duration of follow-up. Using the international MSBase cohort study, we identified all patients followed from ≤3 months after their first clinical presentation of MS, with ≥1-year follow-up, ≥1 EDSS visit per year and ≥3 EDSS scores, and exposed to an MS therapy. Marginal structural proportional hazards models were built to evaluate cumulative hazards of 12-month confirmed disability progression and disability regression events, relapses and conversion to secondary progressive MS. The outcomes were evaluated in 3-monthly epochs. Stabilised weights were constructed using treatment status (treatment vs. untreated) conditional on patient sex, age, pregnancy status, date, disease course, time from first symptom, relapses during prior 3 and 12 months, relapses of high severity, with incomplete recovery or occurring on MS therapies, EDSS, change in disability over the last 3 and 12 months, and MRI activity over the last 12 months. In addition, models were adjusted for visit frequency and nested by MS centre. Sensitivity analyses using only patients with high-density follow-up or patients enrolled at any stage of their disease were carried out.

Results: 2194 patients (69% female) with the cumulative follow-up of 15,083 patient-years were included. Mean age at inclusion was 31±9 years, and median EDSS was 2. 81% patients were diagnosed with relapsing-remitting MS and 10% have converted to secondary progressive MS at the end of follow-up. Patients were exposed to MS therapies for the median of 81% of the follow-up time. During the treated epochs, patients had lower cumulative hazard of disability progression (HR 0.59, p=0.01) and relapses (HR 0.51, p=10^{-5}), and greater probability of disability regression (1.4, p=0.04). No difference in conversion to secondary progressive MS was observed (HR 1.1, p=0.9).

Conclusion: Continued MS therapy markedly reduces disability accrual and increases the probability of recovery over up to 22 years.

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Javier Olascoaga serves on scientific advisory boards for Biogen, Genzyme and Novartis; has received speaker honoraria from Biogen, Bayer-Schering, Genzyme, Merck, Novartis and Teva and research grants from Biogen, Merck, Novartis and Teva.

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P733

Clinical outcomes were better for patients who remained on natalizumab compared to those who switched to oral or injectable therapies after 2 years in the TYSABRI Observational Program

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Background: Natalizumab (NAT) is a high-efficacy therapy for relapsing-remitting multiple sclerosis (RRMS). After 2 years on NAT, many patients discontinue, mainly due to progressive multifocal leukoencephalopathy risk concerns. Data on predictors of post-NAT disease activity may be important for physician consideration. We assessed this in the TYSABRI Observational Program (TOP), an ongoing, 10-year observational study of NAT-treated RRMS patients.

Objectives: To compare outcomes in patients who switched to an oral or injectable (INJ) therapy with those who stayed on NAT and to analyze predictors of post-NAT relapse.

Methods: TOP data as of 1 November 2016 were analyzed for patients who stayed on NAT (≥3 years NAT and only NAT during follow-up; n=2466; mean time on NAT: 5.5 years) vs patients who switched to oral (n=660) or INJ (n=95) therapies for ≥1 year after ≥2 years on NAT (mean post-NAT follow-up: 2.5 years and 2.4 years, respectively). Annualized relapse rates (ARRs) were compared. Disability worsening was defined as an Expanded Disability Status Scale (EDSS) score increase of ≥1.5 from 0.0, ≥1.0 from 1.0-5.5, or ≥0.5 from ≥6.0, confirmed at ≥24 weeks. Risks and predictors of disease activity were compared using adjusted Cox models (covariates: age, sex, symptom onset, EDSS, prior relapses, washout (WO) time, and time on NAT).

Results: Relapse risk was higher for patients who switched to oral (hazard ratio [HR]=2.18; P< .001) or INJ (HR=3.02; P< .001) therapies than for patients who stayed on NAT after 2 years. EDSS worsening risk was similar for oral (HR=1.19; P= .266) and higher for INJ (HR=2.52; P< .001) switchers compared to stayed-on-NAT patients. ARRs decreased after the first 2 years by 20.2% for stayed-on-NAT patients but increased from rates on NAT by 17.8% and 108.1% for oral and INJ switchers, respectively (P< .001 for each). In oral switchers, lower relapse risk was predicted by shorter WO time (>12 weeks vs ≤4 weeks; HR=1.97; P= .001), fewer pre-NAT relapses (HR=1.24/relation in the prior year; P< .001), lower EDSS at NAT start (>3.5 vs ≤3.5; HR=1.44; P= .007), and longer time on NAT (HR=0.87/additional year on NAT; P< .019).

Conclusions: Staying on NAT for >2 years yields better clinical outcomes than switching to oral or INJ therapies. For those discontinuing NAT, switching to an oral yields better outcomes than switching to an INJ. Disease activity risk in oral switchers is predicted by WO time, pre-NAT disease activity and EDSS, and time on NAT. Supported by Biogen.
B cells above therapeutic target became longer. The proportion of CD27+ memory B cells among repopulating CD19+ B cells decreased continuously over repeated cycles of therapy (initial 2 year: mean 25% vs. 2-5 years: mean 8% vs. 5 years after: mean 5% of CD19+ B cells at retreatment).

Conclusion: After repeated cycles of rituximab, a shift toward naïve B cells in peripheral blood may contribute to maintenance of remission despite more prolonged retreatment interval than that on initial treatment phase.

References:

Disclosure
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P735
A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of natalizumab (IMSE 1)
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Background: Natalizumab (NTZ) is a highly effective disease modulatory treatment for relapsing-remitting multiple sclerosis (RRMS). Post-marketing surveillance is important for determination of long-term safety and effectiveness in a real-world setting. To this end the “Immunomodulation and Multiple Sclerosis Epidemiology Study” (IMSE 1) was initiated upon NTZ launch in Sweden (Aug 2006).

Objective: To follow-up the long-term safety and effectiveness of NTZ in a real-world setting.

Methods: In Sweden MS patients are registered in the nationwide Swedish Neuroregistry (Neuroreg). IMSE 1 includes patients starting NTZ treatment and data is collected from Neuroreg. Adverse events (AEs), JC-virus status (JCV) and clinical effectiveness measures are registered prospectively.

Results: 2968 patients (72% female; 90% RRMS) have been included in IMSE 1 from August 2006 until May 2017. Mean age at treatment start was 36 years. Mean treatment duration was 43.6 months. 1244 were currently treated with NTZ at cutoff date, 186 (15%) of which were JCV+ with a mean JCV index at 1.09±0.89. A total of 1907 patients (64%) discontinued NTZ treatment at some time point, where the main reason for discontinuation were anti-JCV antibodies (JCV+) (41%) and pregnancy/planning pregnancy (15%). 1264 (42.6%) patients starting NTZ were JCV+ and 760/1126 (68%) later discontinued their NTZ treatment due to JCV+. In contrast, JCV negative (JCV-) patients mainly discontinued due to pregnancy/planning pregnancy (39.2%). The one and two-year drug survival rate was 88% and 68% for JCV+ and 91% and 83% for JCV-. The overall drug survival rate was 11% for JCV+ and 69% for JCV-. 95 Serious AEs had been reported to the Swedish MPA and included 8 cases (1 fatal) of progressive multifocal leukoencephalopathy (PML), reported between 2008 and 2012. A total of 15 patients have died during or within 6 months after NTZ discontinuation, as reported in Neuroreg. None were reported to be associated to NTZ.

In patients with continuous NTZ treatment for ≥5 years (n=728), long lasting stabilization of disease activity was observed.

Conclusions: Neuroreg functions well as a post-marketing drug surveillance platform, providing long-term data on drug effects and AEs. NTZ is generally well tolerated with sustained effectiveness. The introduction of JCV testing has led to fewer treated JCV+ patients, which likely explains a reduced incidence of PML.

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**P736**

**Durable improvements in clinical outcomes with alemtuzumab in patients with active RRMS in the absence of continuous treatment: 7-year follow-up of CARE-MS II patients (TOPAZ study)**

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**Background:** In CARE-MS II (NCT00548405), alemtuzumab significantly improved clinical outcomes vs SC IFNB-1a over 2 years (y) in patients (pts) with active RRMS and inadequate response to prior therapy. Durable efficacy of alemtuzumab was demonstrated over 6 y in a completed extension study (NCT00930553; 2-y core study plus 4-y extension) in the absence of continuous treatment. CARE-MS II pts received 2 courses of alemtuzumab 12 mg/day (baseline: 5 days; 12 months later: 3 days); in the extension, pts could receive as-needed alemtuzumab retreatment (12 mg/day on 3 consecutive days; ≥12 months after previous course for relapse or MRI activity) or other disease-modifying therapy (DMT; per investigator discretion). Pts completing at least 48 months of the extension could enrol in the 5-y TOPAZ study (NCT02255656) for further long-term evaluation.

**Goal:** Evaluate 7-y efficacy/safety of alemtuzumab in CARE-MS II pts who received alemtuzumab.

**Methods:** In TOPAZ, pts can receive alemtuzumab retreatment ≥12 months after previous course or other DMT at any time point (both per investigator discretion; no criteria); MRI scans were done annually. Assessments: annualised relapse rate (ARR); 6-month confirmed disability worsening (CDW); 6-month confirmed disability improvement (CDI); no evidence of disease activity (NEDA); adverse events (AEs).

**Results:** 338/393 (86%) CARE-MS II pts who entered the extension remained on study until end of Y6 and then entered TOPAZ; 317 (94%) remained on study through Y7. ARR remained low (0.14 at Y7); proportion of pts with stable or improved EDSS remained high (Y7: 73%). Through Y 7, 69% of pts were free from 6-month CDW, 44% achieved 6-month CDI, and the majority achieved NEDA each year. These effects were achieved with 47% of pts receiving no additional treatment (alemtuzumab or other DMT) after their initial 2 courses of alemtuzumab. Incidences of overall AEs, infusion-associated reactions, and infections decreased over time and were reduced vs the 2-y core study. Thyroid AE incidence peaked at Y3 and then declined.

**Conclusion:** Clinical efficacy of alemtuzumab was maintained for 7 y in pts who had inadequate response to prior therapy, despite 47% receiving no additional treatment since the initial 2 courses of alemtuzumab. 44% of pts also showed improvement in disability. These findings suggest that alemtuzumab may provide a unique treatment approach for RRMS pts, offering durable efficacy in the absence of continuous treatment.

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P737
Lateral ventricular volume as a proxy for brain volume loss in the assessment of no evidence of disease activity: results from a longitudinal, multicentre, real-world study
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Aim: Assess no evidence of disease activity (NEDA) using two alternative criteria for brain atrophy: percent brain volume change (PBVC) or percent lateral ventricular volume change (PLVVC); and evaluate the impact of baseline disease activity on NEDA, in patients with relapsing-remitting multiple sclerosis (RRMS) receiving fingolimod in US clinical practice.

Background: Challenges of assessing PBVC in clinical practice limit the use of these data for research purposes. PLVVC may be a strong proxy for PBVC and is more feasible in routine practice than PBVC.

Methods: Clinical and magnetic resonance imaging (MRI) data were retrospectively collected from 590 patients with RRMS who initiated fingolimod 0.5mg at 33 MS centres in the USA (index date: date of fingolimod initiation). Patients were required to have an index (6 months before or 1 month after fingolimod initiation) and post-index (9-24 months after fingolimod initiation) MRI scan. NEDA-4 [PBVC] was defined as the proportion of patients with no new/enlarged T2 lesions or gadolinium-enhancing (Gd+) lesions, no confirmed relapses, no disability progression (according to Expanded Disability Status Scale scores) and no pathological PBVC (<0.4% annualized PBVC). An alternative definition, NEDA-4 [PLVVC], substituted PBVC for PLVVC (<3.5% annualized PLVVC). Patients with active disease had ≥1 relapse in the year before index date or ≥1 Gd+ lesion in the index period.

Results: In total, 325 (55.1%) and 570 (96.6%) patients had data to assess NEDA-4 [PBVC] and NEDA-4 [PLVVC], respectively. During follow-up (median: 16 months), 37.2% and 38.4% of patients achieved NEDA-4 [PBVC] and NEDA-4 [PLVVC] status, respectively. When stratified by presence of Gd+ lesions in the index period, a greater proportion without Gd+ lesions versus those with ≥1 Gd+ lesion achieved NEDA-4 [PBVC] (40.1% vs 25.8%; p=0.038) and NEDA-4 [PLVVC] (42.3% vs 22.9%; p=0.0001) at follow-up. Similar observations were made when patients were stratified into those without active disease versus those with active disease at baseline for NEDA-4 [PBVC] (41.2% vs 31.0%; p=0.063) and NEDA-4 [PLVVC] (43.0% vs 32.1%; p=0.008).

Conclusion: Similar proportions achieved NEDA-4 status whether brain atrophy was measured using PLVVC or PBVC, but the number of patients eligible for assessment was nearly doubled when PLVVC was used. This supports the potential of NEDA-4 [PLVVC] in clinical practice; further studies should be performed to confirm this.

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**P738**

**Big Multiple Sclerosis Data network: data sharing among five large MS registries**

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**Background:** There is a large unmet need in areas of MS research requiring big data which single country or even international registries lack the sample size and power to address. MSBase, OFSEP and the Danish, Italian and Swedish MS registries merged data for specific projects in the Big Multiple Sclerosis Data (BMSD) Network.

**Objectives:** To describe the data structure, procedures for data sharing and feasibility of an initial demonstrator project in the BMSD network.

**Methods:** A feasibility phase of the study has been performed to evaluate differences and commonalities among the five registries. Data counts of the minimum dataset variables needed to describe the disease course of an typical MS patient have been performed and compared among sources. A standardization of definitions and procedures have been performed to ensure the possibility to merge data from different sources. Data counts to evaluate capacity to perform a demonstrator project, namely longitudinal treatment efficacy evaluation in Relapsing-Remitting MS (RRMS) patients followed for more than 10 years have been performed.

**Results:** The BMSD merged dataset has collected longitudinal data on 138,148 MS patients. A total of 143,345 disease modifying drug (DMD) treatment episodes were available. At least 1 DMD treatment episode was available in 73,820 MS patients. An EDSS evaluation at both the treatment start and stop dates was available in 67,009 MS patients. A total of 23,336 RRMS patients with ≥ 10 years follow-up and at least 3 EDSS evaluations were retrieved. Of these, 19,283 received ≥ 1 DMD prescription during the follow-up, whereas 4,053 were completely untreated. For this cohort of RRMS patients a total 480,565 EDSS evaluations were available.

**Conclusions:** The BMSD network will allow pooling of MS data at a scale that raises MS research to a new level, with the ultimate aim to lessen in the future the burden of the disease for MS patients. BMSD will overcome major unmet scientiﬁc needs in MS requiring long-term longitudinal data.

**Disclosure**

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Jan Hillert has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker’s fees from Biogen, Novartis, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, BiogenIdec, Merck-Serena, TEVA, Sanofi-Genzyme and Bayer-Schering. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation.

Robert Hyde is employed by Biogen and holds stock in Biogen. Melinda Magyari has served on scientiﬁc advisory board for Biogen Idec and Novartis, Merck, Sanofi, has received honoraria for lecturing from Biogen Idec, Merck, Novartis, Genzyme, has received support for congress participation from Biogen Idec, Novartis, Genzyme, Teva, Maria Trojano has received honoraria for consultancy or speaking from Biogen, Sanofi-Aventis, Merck Serono and Bayer-Schering and research grants from Merck Serono, Biogen and Novartis.

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**P739**

**Serum neurofilament light chain levels are increased at the onset of PML in natalizumab treated MS patients**

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**Background:** The monoclonal antibody natalizumab is a highly effective treatment for patients with multiple sclerosis (MS).
However, the drug is associated with increased risk of progressive multifocal leukoencephalopathy (PML), a severe infection of the CNS caused by the reactivation of JC virus. Huge efforts have been made to improve risk stratification algorithms and to facilitate early disease recognition, but no serum biomarker is currently available for the condition.

**Objective:** To assess whether serum neurofilaments light chains (NFL) are a reliable biomarker for the early recognition of PML during natalizumab treatment.

**Methods:** Patients were recruited from 2 European MS cohorts. Of 213 patients with MS, 102 had been treated with natalizumab (9-84 months), 37 received other immune-modulatory treatments, and 74 were untreated. 12 healthy controls (HC) were also enrolled. We had access to samples from 25 natalizumab PML patients. Serum NFL concentration was assessed using an ECL immunoassay.

**Results:** NFL levels were higher in treated (18.0 ± 11.8 pg/ml) or untreated (22.7 ± 17.5 pg/ml) MS patients than in HC (10.8 ± 6.9 pg/ml) (p < 0.004 and p < 0.004 respectively), and were associated with the presence of recent clinical relapses or enhancing lesions at MRI (p < 0.01). Natalizumab treated patients had similar NFL levels (17.0 ± 10.4 pg/ml) to that of other MS patients. At the onset of PML, serum NFL levels were highly increased (346.1 ± 95.9 pg/ml, p < 0.001), and they continued to grow till the onset of immune reconstitution inflammatory syndrome (710.5 ± 468.5).

**Conclusions:** If replicated in future studies, serum NFL may represent a reliable and easily accessible biomarker of early PML detection in natalizumab treated MS patients.

**Disclosure**

G.D.C., A.F., F.S., B.C., P.C., E.K., report no disclosures. AH received speaker’s fees from Bayer Healthcare and Biogen Idec, and limited research grants from Genzyme. RG received speaker’s fees and board honoraria from Baxter, Bayer Schering, Biogen Idec, Chugai, CLB Behring, Genzyme, Merck Serono, Novartis, Talecris, TEVA, and Wyeth. RG’s department received grant support from Bayer Schering, BiogenIdec, Genzyme, Merck Serono, Novartis, and TEVA. V.M. has received honoraria for activities with Biogen, Merck Serono, Bayer Schering, TEVA, and Sanofi Aventis as a speaker. L.M. has received honoraria for speaking in scientific meetings and for advisory board from Biogen TEVA, Sanofi-Genzyme, and Merck. R.F. has received honoraria for speaker activities from Biogen, Merck, Novartis, Roche, and Teva. G.C. has received personal compensation for consulting services and/or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Serono Symposia International Foundation, Roche, Almirall, Receptos, Celgene, Forward Pharma.

**Disclosure**

MW is part-time employed at SyntheticMr AB Sweden.

**P741**

Patients with active RRMS experience durable reductions in MRI disease activity and slowing of brain volume loss with alemtuzumab: 7-year follow-up of CARE-MS II patients (TOPAZ study)

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**Background and purpose:** The presence of edema will result in an increased brain volume which may obscure progressing brain atrophy. Similarly, treatment-induced edema reduction may appear as accelerated brain tissue loss (pseudo-atrophy). Recently, there has been a substantial progress in Magnetic Resonance quantification of brain tissue properties such as R1 relaxation rate, R2 relaxation rate and proton density (PD). Especially PD is expected to reflect the water content of the brain and hence should be correlated to the extent of edema. The purpose of this study was to correlate mean PD of the brain to brain volume, in order to investigate the possibilities for edema correction and the resulting improvement of the precision of automated brain volume measurements.

**Materials and Methods:** A group of 38 patients with clinically isolated syndrome (CIS) or newly diagnosed multiple sclerosis (MS) were imaged at inclusion, and after 1, 2 and 4 years using an MR quantification sequence. Brain parenchymal fraction (BPF = intracranial volume / brain parenchymal volume) and mean proton density (PD) of the brain was measured by fully automated software (SyMRI 8.0, SyntheticMR AB, Sweden).

**Results:** The reduction of BPF as a function of age was 0.167%/y, whereas the reduction as a function of time after inclusion was 0.273%/y. The mean standard deviations were 0.508%, 0.526%, 0.454% and 0.687% at baseline, 1, 2 and 4 years. Linear regression showed a slope of 0.488 (p < 0.001) between the relative change of BPF and the relative change of mean PD. Applying the measured PD as a correction factor, the mean standard deviations became 0.385%, 0.500%, 0.303% and 0.567%, an improvement of 24.2%, 4.8%, 33.3% and 17.4%, respectively. The observed atrophy rate reduced from 0.273%/y to 0.238%/y (13%).

**Conclusions:** Edema correction for brain volume using the mean proton density of brain tissue improved the precision of brain volume measurements with up to 33% and may have reduced the effect of pseudo-atrophy.

**Disclosure**

MW is part-time employed at SyntheticMr AB Sweden.

**P740**

Improved precision of automatic brain volume measurements in patients with clinically isolated syndrome and multiple sclerosis using edema correction

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**Background and purpose:** To assess whether serum neurofilaments light chains (NFL) are a reliable biomarker for the early recognition of PML during natalizumab treatment.

**Methods:** Patients were recruited from 2 European MS cohorts. Of 213 patients with MS, 102 had been treated with natalizumab (9-84 months), 37 received other immune-modulatory treatments, and 74 were untreated. 12 healthy controls (HC) were also enrolled. We had access to samples from 25 natalizumab PML patients. Serum NFL concentration was assessed using an ECL immunoassay.

**Results:** NFL levels were higher in treated (18.0 ± 11.8 pg/ml) or untreated (22.7 ± 17.5 pg/ml) MS patients than in HC (10.8 ± 6.9 pg/ml) (p < 0.005 and p < 0.004 respectively), and were associated with the presence of recent clinical relapses or enhancing lesions at MRI (p < 0.01). Natalizumab treated patients had similar NFL levels (17.0 ± 10.4 pg/ml) to that of other MS patients. At the onset of PML, serum NFL levels were highly increased (346.1 ± 95.9 pg/ml, p < 0.001), and they continued to grow till the onset of immune reconstitution inflammatory syndrome (710.5 ± 468.5).

**Conclusions:** If replicated in future studies, serum NFL may represent a reliable and easily accessible biomarker of early PML detection in natalizumab treated MS patients.

**Disclosure**

G.D.C., A.F., F.S., B.C., P.C., E.K., report no disclosures. AH received speaker’s fees from Bayer Healthcare and Biogen Idec, and limited research grants from Genzyme. RG received speaker’s fees and board honoraria from Baxter, Bayer Schering, Biogen Idec, Chugai, CLB Behring, Genzyme, Merck Serono, Novartis, Talecris, TEVA, and Wyeth. RG’s department received grant support from Bayer Schering, BiogenIdec, Genzyme, Merck Serono, Novartis, and TEVA. V.M. has received honoraria for activities with Biogen, Merck Serono, Bayer Schering, TEVA, and Sanofi Aventis as a speaker. L.M. has received honoraria for speaking in scientific meetings and for advisory board from Biogen TEVA, Sanofi-Genzyme, and Merck. R.F. has received honoraria for speaker activities from Biogen, Merck, Novartis, Roche, and Teva. G.C. has received personal compensation for consulting services and/or speaking activities from Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Serono Symposia International Foundation, Roche, Almirall, Receptos, Celgene, Forward Pharma.

**Disclosure**

MW is part-time employed at SyntheticMr AB Sweden.

**P741**

Patients with active RRMS experience durable reductions in MRI disease activity and slowing of brain volume loss with alemtuzumab: 7-year follow-up of CARE-MS II patients (TOPAZ study)

D. Pelletier1, A. Traboulsee2, M. Barnett3, G. Comi4, J. De Sèze5, A. Rovira6, S. Schippling7, D.H. Margolin8, S. Santana9, K. Nakamura10, D.L. Arnold11,12, on behalf of the CARE-MS II, CAMMS03409, and TOPAZ Investigators

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Background: In CARE-MS II (NCT00548405), alemtuzumab significantly improved clinical and MRI outcomes, including brain volume loss (BVL), vs SC IFNβ-1a over 2 years (y) in active RRMS patients (pts) with inadequate response to prior therapy. Durable efficacy of alemtuzumab was shown over 6 y in a completed extension study (NCT00930553; 2-y core plus 4-y extension) in the absence of continuous treatment. CARE-MS II pts received 2 courses of alemtuzumab 12 mg/day (baseline: 5 days; 12 months later: 3 days). In the extension, pts could receive as-needed alemtuzumab retreatment (12 mg/day on 3 consecutive days; ≥12 months after previous course for relapse or MRI activity) or other disease-modifying therapy (DMT; per investigator discretion). Pts completing at least 48 months of the extension could enroll in the 5-y TOPAZ study (NCT02255656) for further long-term evaluation.

Goal: Evaluate the effect of alemtuzumab on MRI lesion outcomes and BVL over 7 y in pts who received alemtuzumab in CARE-MS II.

Methods: In TOPAZ, pts can receive alemtuzumab retreatment ≥12 months after previous course or other DMT at any time point (both per investigator discretion; no criteria). Assessments: Annual MRI scored for proportions of pts with no evidence of MRI disease activity (no new Gd-enhancing lesions; no new/enlarging T2 lesions); new T1 hypointense lesions; and BVL, derived by relative change in brain parenchymal fraction (BPF).

Results: 383 of 393 (86%) CARE-MS II pts who entered the extension remained on study until the end of Y6 and then entered TOPAZ: 317 (94%) remained on study through Y7. At Y7, 67% of pts each remained free of MRI disease activity and new/enlarging T2 lesions. 90% were free of new Gd-enhancing lesions and 88% were free of new T1 hypointense lesions. Alemtuzumab consistently slowed median yearly BPF change over 2 y, remaining low in Y3-7 (Y1: -0.48%, Y2: -0.22%, Y3: -0.10%, Y4: -0.19%, Y5: -0.07%, Y6: -0.10%, Y7: -0.14%). These results were achieved with 47% of pts receiving no alemtuzumab retreatment or another DMT.

Conclusion: Alemtuzumab durably reduced MRI disease activity and slowed BVL over 7 y in pts with inadequate response to prior therapy, despite 47% receiving no additional treatment after the initial 2 courses of alemtuzumab. These findings suggest alemtuzumab may provide a unique treatment approach for RRMS pts, offering durable efficacy in the absence of continuous treatment.

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DHM: Employee of Sanofi.

SSa: Provides statistical support as a paid consultant for Sanofi.

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P742 Effect of teriflunomide on lymphocyte counts and infections over the long-term in the pooled TEMSO and TOWER extension studies

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Background: In TEMSO (NCT00134563) and TOWER (NCT00751881) core studies, teriflunomide was associated with reduced lymphocyte counts early in treatment, although mean counts remained within the normal range. Lower grade lymphopenia was reported infrequently during the long-term extension studies and was not associated with increased risk of infection. Objective(s): To describe the effect of long-term teriflunomide treatment on lymphocyte counts and infection rates in the pooled TEMSO and TOWER core and extension studies.

Methods: Data from the pooled core studies are reported for patients treated with placebo or teriflunomide 14 mg. Placebo-treated patients were re-randomized to active treatment in the extensions; results from the pooled core and extension studies are reported for the teriflunomide 14-mg group. Lymphocyte counts were obtained every 6 weeks until Week 24, and every 24 weeks thereafter. Lymphopenia was identified from 2 consecutive assessments of lymphocyte counts that remained below the lower limit of normal and was graded by the Common Terminology Criteria for Adverse Events.

Results: The cumulative duration of exposure to teriflunomide 14 mg in the pooled core and extension studies was 4449 patient-years. In the core studies, placebo- (n=745) and teriflunomide-treated patients (n=729) experienced Grade 1 (0.7%; 2.1%) and 2 (0.5%; 1.4%) lymphopenias infrequently. Infections occurred in placebo/teriflunomide-treated patients with Grade 1 (0.3%/1.5%) and 2 (0.4%/0.3%) lymphopenia. No patients with Grade 1 lymphopenia and only 1 (0.1%) placebo-treated patient with Grade 2 lymphopenia experienced serious infection. Teriflunomide-treated patients in the combined core and extension studies (n=1354) experienced few Grade 1 (3.0%) or 2 (2.5%) lymphopenias;
Lymphocyte decline and reconstitution after discontinuation in patients with severe, prolonged lymphopenia treated with delayed-release dimethyl fumarate

P743

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Background: Delayed-release dimethyl fumarate (DMF) has demonstrated a favourable benefit-risk profile in patients (pts) with relapsing-remitting multiple sclerosis (RRMS). There has been no increased incidence of infection observed with DMF, aside from rare cases of PML. The DMF label recommends considering treatment interruption for pts with absolute lymphocyte count (ALC) < 0.5×10^9/L for ≥6 months to minimize risk of developing sustained severe, prolonged lymphopenia.

Objectives: Examine the dynamics and clinical implications of on-DMF ALC decline and post-DMF ALC reconstitution in pts with RRMS treated with DMF.

Methods: We conducted an integrated analysis of the Phase 2b, Phase 3 (DEFINE/CONFIRM) and extension (ENDORSE) DMF studies. Data starting from the first exposure to DMF were analyzed. ALCs were assessed at wks 4, 8, 12, and at least every 4 wks thereafter, or every 4 wks in pts that discontinued DMF. Pts were categorized by on-treatment ALCs.

Results: The total analysed population comprised 2513 pts and 9702 pt-years (yrs) of DMF exposure as of 1 October 2016. Among the 2470 pts with any on-treatment ALC, mean ALC decreased by ~30% during the first yr of treatment and then stabilized above the lower limit of normal (LLN; 0.91×10^9/L). The incidence of serious infection (4%) and serious herpes zoster (<1%) was low; no increased incidence was observed regardless of ALC or T-cell subset count. One opportunistic infection occurred (fatal case of PML). Of 53 (2.1%) pts who developed severe, prolonged lymphopenia (< 0.5×10^9/L for ≥6 mos), the majority (44/53, 83%) did so within 3 yrs of initiating DMF. Of these, 34 pts continued treatment for median (range) 72 (16, 97) mos before discontinuing DMF, and ALCs were followed for ≥6 mos after discontinuation. The proportion of pts with ALC ≥0.8×10^9/L and ≥0.91×10^9/L after 6 mos of discontinuation was 41% (14/34) and 24% (8/34). In the 6 mos after DMF discontinuation, unadjusted ARR was 0.384 vs 0.496 at 6 mos on placebo in DEFINE/CONFIRM.

Conclusions: Lymphocyte decline is well characterized in RRMS pts treated with DMF for up to 10 yrs. No increased incidence of serious or opportunistic infection was observed. ALCs generally increased after DMF discontinuation following severe lymphopenia. Other analyses are ongoing to characterize lymphocyte reconstitution in pts with a shorter duration of lymphopenia. Monitoring ALC is an effective way to identify pts at risk for prolonged lymphopenia.

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P744
Outcomes of discontinuing disease modifying therapy in patients with multiple sclerosis over age 60
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Background: Disease modifying therapies (DMTs) in multiple sclerosis (MS) have robust inflammatory effects. As the immune system becomes less functional in older patients, it is unclear whether continued immunomodulation remains beneficial. There is insufficient data regarding the necessary duration of DMT or impact of discontinuation to guide clinicians. This study evaluates outcomes of DMT discontinuation in patients with MS over age 60 in real world settings.

Methods: Patients were identified from our MS specialty clinics who were over age 60, on DMT for >2 years, with corresponding clinician and patient-reported outcomes. Cox proportion hazards regression modeled the association between time to restart DMT and covariates of disease course, gender, disease duration, time on DMT, number of DMTs, DMT at discontinuation, provider vs patient initiated, and walking ability at discontinuation. Pre and post discontinuation comparisons of MS Performance Scales (MSPS), Timed 25 Foot Walk and Patient Health Questionnaire-9 (PHQ9) were analyzed using linear mixed models.

Results: 644 patient with confirmed MS diagnosis and initial DMT use before age 60 were included, with 194 (30.1%) patients discontinuing. There were 2 relapses and little MRI activity in discontinuers, with 10.3% of patients restarting DMT. The only significant predictor of restarting was provider vs patient initiated with provider-initiated discontinuors less likely to restart DMT (HR 0.37, 95% CI 0.136 to 0.987; p=0.047). Estimated survival curves show that 87.6% of patients who stopped DMT after age 60 remain off DMT at 4 years. For outcomes in the discontinuation group, on average, relapse-remitting patients had a lower MSPS by 2.3 compared to primary progressive (95% CI -4.095 to -0.473; p=0.014). Provider-initiated discontinuation was associated with lower MSPS score, with a difference of 2.3 (95% CI -3.6 to -1.0; p=0.001). There were no significant differences in Timed 25 Foot Walk or PHQ9 pre and post discontinuation.

Discussion: Most patients over age 60 who discontinued DMT after at least 2 years treatment, remained off DMT. Patients are more likely to remain off therapy when the provider initiated discontinuation. MSPS improved in discontinuers with RR disease and when providers initiated discontinuation. No other significant differences in outcomes were seen. This study provides real world data that may help guide clinicians and patients considering discontinuing DMT.

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P745
5 years effectiveness of fingolimod in daily clinical practice: results of the non-interventional study PANGAEA
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Background: Once-daily fingolimod (Gilenya®; Novartis Pharma AG) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing MS. As of February 2017 more than 204,000 patients have been treated with fingolimod; total patient exposure exceeds 424,000 patient-years.

Objective: Here we present first interim results on the effectiveness of fingolimod in RRMS patients treated for up to 5 years in daily clinical practice.

Methods: PANGAEA is a non-interventional study, conducted in Germany, to investigate long-term safety, effectiveness and patient reported outcomes in daily clinical practice. Recruitment into the study finished in December 2013. 4229 patients were enrolled. By January 2017, 474 patients finished the 5 year documentation period.

Results: The mean annual relapse rate of all PANGAEA patients improved from 1.5±0.04 (95%CI; baseline) to 0.42±0.02 in the first year and further improved to 0.27±0.05 in the fifth year of treatment.

The mean baseline EDSS in PANGAEA was 3.0 (±0.03; 95%CI) and remained stable over 5 years. In each year of treatment more than 85% of the patients had a stable EDSS or experienced a 6 months confirmed improvement. The proportion of patients free of relapses and 6 months confirmed disability progression increased from 60% in year 1 to 67% in year 4 of treatment. 42.3% of the patients neither had a relapse nor a 6 months confirmed disability progression over 4 years of treatment. The overall state of health compared to 12 months ago as stated by patients in the EQ-5D questionnaire changed from 75.9% stating “same” or “better” to 89.0% in the first and 88.7% in the second year of fingolimod treatment. The EQ-5D index (mean ± 95%CI) improved from 0.87 ± 0.01 to 0.90 ± 0.01 in year one of treatment and remained stable. The nature of reported adverse events is consistent with previous findings from clinical trials.

Conclusions: The results of the 5 year interim analysis of PANGAEA support the positive efficacy profile of fingolimod demonstrated in phase III clinical trials with real world evidence data.

Disclosure
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C. Cornelissen is an employee of the Novartis Pharma GmbH, Nuremberg, Germany.

P746
Characteristics of real-world disability improvement in relapsing-remitting multiple sclerosis patients treated with natalizumab in the TYSABRI® Observational Program
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Background: In clinical trials and real-world studies, natalizumab (NAT) treatment has been associated with disability improvement as indicated by a decrease in Expanded Disability Status Scale (EDSS) score. Better understanding of the timing, magnitude, and duration of disability improvement during long-term NAT treatment may help inform clinical decision making.

Objective: To characterize confirmed disability improvement (CDI) in patients participating in the TYSABRI Observational Program (TOP), an ongoing 10-year observational study of relapsing-remitting multiple sclerosis patients initiating NAT in clinical practice.

Methods: Analyses included patients with CDI, defined as a decrease of ≥1.0 from a baseline EDSS score of ≥2.0 confirmed at ≥24 weeks, as of 1 November 2016. Kaplan-Meier (KM) time-to-event analyses evaluated the proportion of patients reaching EDSS improvement-from-baseline milestones of ≥1.5 and ≥2.0 and the duration of improvement (time from EDSS improvement to return to baseline).

Results: Of the 5119 patients in TOP with baseline EDSS ≥2.0, 1204 (23.5%) had CDI. The cumulative probability of CDI was 14% at year 1, 22% at year 2, 27% at year 3, 29% at year 4, and 36% at 8.5 years. CDI patients had a mean (standard deviation [SD]) EDSS score of 3.8 (1.3) at baseline and 4.2 (1.9) years of on-NAT follow-up in TOP. Among CDI patients, 683 (57%) and 414 (34%) had EDSS improvement of ≥1.5 and ≥2.0, respectively. Over 408 weeks, the KM-estimated probabilities of improvements of ≥1.5 and ≥2.0 were 69% and 44%, respectively. The estimated probability of maintaining improvement was >50% up to 408 weeks after the CDI event. In the 301 CDI patients (25%) who returned to baseline (mean [SD] time to return to baseline: 129.3 [72.4] weeks), mean (SD) EDSS change from baseline through on-NAT follow-up was −0.01 (1.15). Additional analyses will explore predictors of earlier, higher magnitude, and longer duration CDI events.

Conclusions: In TOP, >20% of patients experienced CDI. More CDI events occurred in the first year of NAT treatment. Most CDI patients had an EDSS improvement of ≥1.5 points and many had improvement of ≥2.0 points. The majority of CDI patients maintained improvement over 8 years, and in those who returned to baseline, mean EDSS score change from baseline through the last visit remained below baseline. These results highlight CDI as a functional outcome that may be an important consideration for treatment decisions.

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Disclosure
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P747
Comparative effectiveness of first line treatment strategies for multiple sclerosis
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Background and aims: Comparative real world effectiveness studies of first line disease modulatory treatments (DMT) in relapsing-remitting multiple sclerosis (RRMS) that include rituximab are lacking. We assessed the relative effectiveness of rituximab among newly diagnosed RRMS patients compared to (i) injectable DMT, (ii) dimethyl fumarate, (iii) highly effective DMT (natalizumab and fingolimod).

We also compared outcomes in Stockholm versus Västerbotten Counties, utilizing differences in choice of drug as a natural experiment.

Method: Retrospective observational study in two Swedish County-based samples of RRMS patients diagnosed Jan 1st 2012 to Oct 31st 2015 in Stockholm (n=440) and Västerbotten (n=52) Counties starting their first DMT and prospectively followed in the Swedish MS registry.

Results: Among 494 patients starting first line DMT, 215 (43.5%) started with injectable DMT, 86 (17.4%) dimethyl fumarate, 67 (13.6%) highly effective DMT, 120 (24.3%) rituximab and 6 (1.2%) other DMT. Regional differences were pronounced, with 81% rituximab and 6% injectable DMT in Västerbotten County and 18% rituximab and 48% injectable DMT in Stockholm County. The hazard ratios (HR) for drug discontinuation, for injectable DMT, dimethyl fumarate and highly effective DMT compared to rituximab were 20.3 (95% CI 5.8-70.2), 12.4 (3.1-49.4) and 25.0 (6.5-95.8), respectively, after correcting for differences in baseline factors. The rate of clinical relapses was significantly lower for patients treated with rituximab compared to injectable (p < 0.001) and highly effective DMT (p < 0.001). Significantly fewer patients treated with rituximab had gadolinium enhancing MRI scans compared to injectable DMT (p < 0.05) and dimethyl fumarate (p < 0.05).

Finally, the HR for discontinuing DMT, not considering choice of DMT, was 0.19 (0.09-0.39) in Västerbotten compared to Stockholm.

Conclusion: Rituximab was superior to all other DMT both in terms of overall drug survival and clinical efficacy measures. The natural experimental situation created by differences in DMT channeling between the two counties to some degree mitigates concerns of concealed residual confounding factors. Collectively, our findings suggest that rituximab has better clinical performance than traditional first line DMT over the studied observation period.

Disclosure

Mathias Granqvist; Malin Boremalm; Amyar Poorghobad and Thomas Frisell report no conflicts of interest.

Anders Svenningssson reports no conflicts of interest.

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Pregnancy outcomes in patients with RRMS treated with alemtuzumab from the clinical development program

Asa Leandersson has nothing to disclose.
Stina Kågström has nothing to disclose.
Linda Forsberg has nothing to disclose.

Jan Hillert has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker’s fees from Biogen, Novartis, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, BiogenIdec, Merck-Seron, TEVA, Sanofi-Genzyme and Bayer-Schering. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation.
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Anders Svemningsson has nothing to disclose.

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Risk management for disease modifying treatments

**Background:** Alemtuzumab is approved in >60 countries for the treatment of RRMS. Although alemtuzumab is low/undetectable in serum within 30 days of IV administration, women of childbearing potential are advised to use effective contraception for 4 months (mo) after treatment. Murine studies show no alemtuzumab-related teratogenicity, but no controlled human clinical studies of alemtuzumab in pregnancy exist.

**Goal:** Provide updated pregnancy outcomes in alemtuzumab-treated female patients (pts) from the clinical development program.

**Methods:** In phase 2 (CAMMS223 [NCT00507778]) and phase 3 (CARE-MS I [NCT00530348], CARE-MS II [NCT00548405]) studies, pts received 2 annual courses of alemtuzumab. Pts could enter an extension (NCT00930553) for ≥48 mo, and then a second extension for further long-term evaluation (TOPAZ; NCT02255656), both with as-needed alemtuzumab retreatment. Pregnant/lactating pts were ineligible for treatment but remained on study for safety follow-up.

**Results:** As of 1 April 2017, 248 pregnancies occurred in 156 of 972 alemtuzumab-treated female pts (mean [SD] age at conception, 32.5 [4.4] years (y); mean [SD] time from last alemtuzumab dose to conception, 34.4 [22.7] mo; 9 within 4 mo of dosing), with 218 completed, 14 ongoing, and 16 with unknown outcomes. Of completed pregnancies with known outcomes, 147 (67%) were live births with no congenital abnormalities or birth defects. There were 48 (22% overall; < 35 y: 13%, ≥35 y: 33%) spontaneous abortions, 22 (10%) elective abortions, and 1 (0.5%) stillbirth (nuchal cord and amniotic band syndrome; reported previously). Elective abortions were due to personal choice (n=6), extrauterine pregnancy (n=3), anembryonic gestation (n=2), chromosomal abnormality (n=2), or foetal defect (n=1; cystic hygroma and hypoplastic heart, reported previously); 8 had no information available.

**Conclusions:** In the alemtuzumab MS clinical trials, the most common outcome was delivery of full-term healthy infants. To date, there has been no signal for teratogenicity. The spontaneous abortion rate was comparable with rates seen in treatment-naive MS pts (5%-21%) and the general population (17%-22%). For MS pts outside the clinical development program, real-world data are currently collected by the International Lemitra Pregnancy Exposure Registry, a prospective, noninterventional, observational safety study enrolling pts in ≥19 countries who become pregnant within 4 mo of alemtuzumab exposure.

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**Disclosure**

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P750
Breakthrough disease under high-dose biotin treatment in progressive multiple sclerosis
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Background: Progressive multiple sclerosis (PMS) can be considered an orphan disease, because of lack of effective therapy currently available. Recently, oral high-dose biotin has been investigated as PMS treatment in a randomized clinical trial with promising results and without serious adverse events. Then, even though without indication by drug regulatory agencies, biotin has been prescribed by many clinicians in MS centres.

Aim: To report an unexpected increase of inflammatory activity in PMS patients treated with oral high-dose biotin.

Methods: We included all consecutive PMS patients who started biotin (300mg/die) in our centre, collecting clinical (relapses, EDSS score), brain and spinal MRI, tolerability and safety data.

Results: We included a total of 41 PMS patients (F 53.7%, mean age 54.3±9.82 years, mean EDSS 5.3±1.62, mean disease duration 15.8±9.28 years), with a primary progressive (PP) phenotype in 39.0% and secondary in 61.0% of cases. Mean treatment duration 15.8±9.28 years), with a primary progressive (PP) phenotype from 0.10 in the previous year to 0.27 on treatment. Nine patients (22%), including 2 PP patients with no history of MS attacks, showed 12 relapses, 9 of them requiring steroid administration and 4 leaving residual disability. Seven patients (17%) showed MRI activity (new and/or enlarged T2 and/or Gd+ lesions), 3 of them with relapses. In 28 patients with treatment duration ≥ 12 months, EDSS score improved in 1, remained stable in 17 (60.7%), and worsened in 10 (35.7%) patients.

Conclusions: In our cohort of PMS patients treated with high-dose biotin we recorded an unexpected high rate, both clinical and radiological, of inflammatory activity. Clinicians should be very cautious when prescribing this drug until its efficacy and safety are definitely proven.

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E. Curti has served on scientific advisory boards for Merck Serono; has received funding for travel from Biogen, Merck Serono, Novartis and Sanofi Genzyme.

E. Tsantes: nothing to disclose
E. Siena: nothing to disclose

P751
The ultrasensitive JCV DNA Tri-Plex qPCR® detects JCV specific genomic sequences in T protein, distinguishes pathogenic from non-pathogenic variants using the NCCR (Non-Coding Control Region) and identifies the virion capsid protein gene (VP1)
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Detection of JCV DNA in a patient’s CSF is used as one diagnostic marker for progressive multifocal leukoencephalopathy (PML). The Multiplex qPCR developed by the NINDS/CLIA Laboratory detects as few as 10c/ml of JCV DNA targeting the highly conserved T protein gene for specificity and sensitivity and distinguishing variants at the NCCR associated with PML from the non-pathogenic variant associated with urinary excretion. The Multiplex assay uses unique sets of primer pairs and probes for each region. This information can be useful in analyzing samples from patients with a high degree of risk for PML, notably MS patients whose treatment includes natalizumab and other immune modulatory therapies like rituximab, fingolimod, and dimethyl fumarates. The LMNN/CLIA laboratory has added another set of primers and probe to the viral genome in the VP1 coding gene that detects the prototype capsid protein, the principle cell attachment protein and major immunogen used in the antibody ELISA assays. In rare PML cases, viral DNA may not be detected in the patient’s CSF. Although highly unlikely, if a mutation occurred in the T protein of JCV DNA that resulted in a false negative qPCR, the Tri-PLEX result could identify the presence of JCV DNA by the identification of VP1. The Tri-PLEX and Multiplex assays were compared using 50 CSF clinical samples from PML/MS patients from the CLIA inventory data base, including positive and negative samples. There was no decrease in sensitivity from 10c/ml using the Tri-PLEX assay with the additional VP1 primers. VP1 was not detected in the Tri-PLEX assays in CSFs of 5 PML cases that were also not detected in T protein. The lack of JCV DNA detection in CSF of clinical and imaging confirmed cases of PML is rare, perhaps due to very low viral copy numbers or other CSF sample issues. The Tri-PLEX assay provides additional information to the treating physicians whose decisions on MS treatment options have become more complex due to PML risk.

Disclosure
Nothing to disclose for either author

P752
Pregnancy planning and outcome in MS patients after Mitoxantrone therapy
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Background: Multiple sclerosis (MS) does not affect the possibility to be pregnant, but persons with MS often have many pregnancy-related doubts and fears, and a careful counselling with a neurologist expert in MS is important. Mitoxantrone (MITO) is a treatment used in patients with very aggressive course of the disease and may affect reproductive capacity in women, in particular if administered at older age.

Aim: Our study aimed to investigate the pregnancy planning and outcome in a group of MS patients who underwent to MITO therapy, both before and after this treatment.

Materials: Patients with MS diagnosis and MITO therapy in clinical history were recruited. Clinical, demographic data and treatments history were recorded. A telephonic questionnaire about the planning and outcome of pregnancies before and after MITO, including abortions and long-term follow-up of the offspring, was administered. Parametric and non-parametric tests were performed by SPSS 22 software.

Results: We included 238 subjects (F/M=158/80; mean age at onset 27 years-old, mean age at the enrolment 45 years-old). One-hundred-five subjects planned a pregnancy before MITO and 40 after. Out of them, respectively 102 (97%) and 35 (85%) had at least one natural conception, 19 (19%) and 7 (18%) at least one abortion, 6 (6%) and 1 (3%) at least one voluntary interruption, and 98 (96%) and 32 (91%) at least one at term pregnancy. One female patient started the pregnancy during MITO, after 6 infusions, and delivered a healthy baby. The patients who planned a pregnancy only before MITO were 96 (40%), while only after 30 (13%), p< 0.01. Among the patients who did not plan a pregnancy (103 before and 133 after MITO), the reason was disease-related (13%), p< 0.01. Among the patients who did not plan a pregnancy especially at the initiation of the treatment, we suggest monitoring both the JCV index value and IgG levels, especially for patients who are negative for JCV exposure, to avoid any false-negative results.

Conclusions: In our study MITO does affect neither the possibility to conceive, nor the pregnancy outcome. No differences in a term pregnancies, abortions and voluntary interruptions were showed among the period before and after MITO. Nevertheless, the attitude of patients in pregnancy planning is different before and after the treatment. In fact, a large quote of patients stop to plan a pregnancy after MITO, and in more than 25% of them the reason was disease-related.

Disclosure
The authors have nothing to disclose about this work

P753
Does IgG level impact JC virus index value?
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Objectives: Following the discovery of one patient with multiple sclerosis (MS) on natalizumab who developed a confirmed progressive multifocal leucoencephalopathy (PML) on natalizumab despite negative JCV serology due to hypogammaglobulinemia, we wanted to evaluate the impact of total IgG level on JCV index value.

Methods: Biological data were collected from patients on natalizumab in our MS center between 2007 and 2015. The data issued from the quantitative JCV serology was obtained by GEN-2. The evolution of the IgG and M levels and the JCV index over time during treatment was studied by multivariate linear regression models.

Results: Analysis involved 1419 coupled JCV index and Ig quantitative assays from 348 patients. There was a significant decrease of IgG level during the first 6 months of treatment (p < 0.001). Beyond this period, the effect was not significant. During follow-up on natalizumab, 74 patients had an IgG level below the normal lower limit, but there was no significant correlation found between JCV index and IgG level.

Conclusion: The lack of correlation between the IgG level and the JCV index value may be related to the low number of patients with abnormally low levels of IgG in our sample population. However, because of the significant decrease of IgG level on natalizumab especially at the initiation of the treatment, we suggest monitoring both the JCV index value and IgG levels, especially for patients who are negative for JCV exposure, to avoid any false-negative results.

Disclosure
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Nawal Hadhoum received invitations for international congresses from LFB.
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Nawal Hadhoun received invitations for national and international congresses from BIOGEN IDEC, TEVA and ROCHE.

P754
Cardiac safety of ozanimod in a QT/QTc trial and a phase 2 trial in RMS
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Objectives: Evaluation of the cardiac safety of ozanimod (ARZ)-CI-295 (ARZ) in healthy volunteers and patients with relapsing-remitting MS (RRMS) and progressive RRMS (PRMS) in a phase 2 trial. ARZ, a potent, selective and orally active sphingosine 1-phosphate (S1P) receptor-1 (S1P1) selective receptor agonist, is under development as a novel treatment for RRMS.

Methods: The phase 2 trials included 400 subjects (300 RRMS and 100 PRMS) randomized to once-daily ARZ at 0.5, 1, 2, 4, or 8 mg or placebo (PBO) for 24 weeks. The primary objective was the safety and tolerability of ARZ in subjects with RRMS or PRMS, and the primary endpoint was the percentage of subjects with nonserious QT interval prolongation (ΔQTc > 20 ms).

Results: Compared with baseline, ARZ 1 mg and above significantly increased ΔQTc compared with placebo (1 mg, 1.5% vs 0%; 2 mg, 2.6% vs 0%; 4 mg, 4.1% vs 0%; 8 mg, 7.5% vs 0%), which was dose dependent (p = 0.0003). There were significant increases in ΔQTc and other ECG parameters, and the percentage of subjects with severe QTc prolongation was increased for ARZ compared with placebo (1 mg, 9.4% vs 0%; 2 mg, 24.2% vs 0%; 4 mg, 28.0% vs 0%; 8 mg, 34.7% vs 0%). ARZ was associated with a higher incidence of cardiovascular events compared with placebo, including atrial fibrillation and ventricular tachycardia.

Conclusion: ARZ is associated with a substantial increase in QT prolongation and an increased risk of cardiovascular events, particularly in the high dose groups. ARZ should be used with caution in patients with cardiac risks.

Disclosure
The authors have nothing to disclose about this work.
Background: Ozanimod is an oral, once daily immunomodulator selectively targeting sphingosine 1-phosphate (S1P) 1 and 5 receptors and is in development for relapsing multiple sclerosis (RMS) and inflammatory bowel disease. Ozanimod does not engage S1P3R, which may play a role in cardiac conduction (Sanna et al. Mol Pharmacol. 2016), and has optimized pharmacokinetic (PK) properties, including a short half-life (t1/2), which allows for dose escalation. The low in vivo maximum plasma concentration at steady state (Cmax,ss) minimizes off-target effects, which in conjunction with lower systemic drug concentrations may contribute to reduced first-dose heart rate effects.

Methods: Clinical data on cardiac safety of ozanimod from a thorough QT (TQT) study (Hartung et al. Mult Scler J. 2013) and a Phase 2 study in RMS (Cohen et al. Lancet Neurol. 2016) are reviewed. In the TQT study, subjects received ozanimod an initial dose of 0.25, escalated to 2 mg over 14 days. Patients with RMS in the Phase 2 study were randomized to once-daily ozanimod 1 mg or 0.5 mg or placebo for 24 weeks. Treatment with ozanimod was initiated with a 7-day dose escalation at an initial dose of ozanimod of 0.25 mg.

Results: In the TQT study, multiple doses of ozanimod 1 mg (therapeutic) and 2 mg (supratherapeutic) at steady state showed no evidence of QTc prolongation, and therefore no effect on cardiac repolarization. The dose escalation regimen employed in this study starting at 0.25 mg attenuated first dose effects on heart rate (HR) on Day 1, with no reduction in HR when compared to predose baseline. In a Phase 2 study in RMS, the mean HR in ozanimod-treated patients did not decrease below predose baseline at any time point during the first 6 hours post-dose, with no patient experiencing a minimum HR < 45 bpm within 6 hours. No Type II or 3:1 atrioventricular block, prolongation of QTc, or significant blood pressure changes were observed with ozanimod. The incidence of cardiac events with ozanimod was similar to placebo.

Conclusion: Ozanimod at doses of 0.5 mg and 1 mg in patients with RMS appears to provide an acceptable cardiac safety profile. There was no evidence of QTc prolongation, and therefore no effect on cardiac repolarization including at a supratherapeutic dose of 2 mg in healthy subjects. Ozanimod’s receptor selectivity, PK properties, and the use of dose escalation potentially differentiates its cardiac profile from other S1P receptor modulators.

Disclosure

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P755

Patient initiation of fingolimod treatment: comparison of cardiac monitoring in-clinic and in the Gilenya®@Home program

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State of the Heart Cardiology, Grapevine, TX, ©Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States
Background: Fingolimod (Gilenya®) 0.5 mg/day is approved for relapsing forms of multiple sclerosis. Asymptomatic, transient heart rate (HR) decrease at treatment initiation is a pharmacodynamic effect of fingolimod. US prescribing information requires first-dose observation (FDO) of HR and blood pressure for ≥6 hours. FDO can be conducted in clinics, and now the Gilenya@Home program allows most US patients to initiate fingolimod at home.

Objectives: Compare Gilenya@Home FDO findings in patients starting fingolimod with in-clinic FDO findings.

Methods: Retrospective FDO safety data were collated from anonymized Gilenya@Home patient records for October 2014 to April 2015. Data from Gilenya assessment network clinics providing FDO were collated from July 2010 to December 2016. Extended monitoring (EM) was conducted as per product label, or if HR was ≥45 bpm at 6 hours. Cardiac safety and adverse events (AEs) were described.

Results: Data were collated from 511 in-home patients (women, 69.3%) and 15,025 in-clinic patients (women, 78.9%); the largest cohort of FDO experience reported to date. In-home mean (standard deviation [SD]) sitting HR was 73.7 (11.7) bpm at baseline and 9.4 (9.4) bpm lower at 6 hours post-dose. A similar change occurred in-clinic, mean (SD) pulse fell from 74.2 (11.3) bpm at initiation to 67.9 (10.0) bpm at discharge. Onset of first-degree atrioventricular block (AVB) during FDO was recorded for 9 in-home patients (1.8%), with no cases of second- or third-degree AVB. During in-clinic FDO, AVB was recorded in 83 patients (first-degree: n=74, 0.5%; second-degree: n=9, 0.6%; third-degree: n=0), with the majority sent home at FDO discharge (n=63, 75.9%); 4 (4.8%) were discharged to an emergency room (ER) for observation and 16 (19.3%) lost to follow up. Torsade de pointes were not observed in either program. AEs were reported for 154 in-home patients (30.1%) and 3133 in-clinic patients (20.9%); in both programs, the most common AEs were dizziness and fatigue. Few patients had palpitations (in-home: n=3, 0.6%; in-clinic: palpitations or fluttering, n=51, 0.3%). EM was required for 61 in-home patients (11.9%) and 2 patients (0.4%) were referred to an ER for overnight monitoring and released next day; 398 in-clinic patients (20.9%) needed EM, and 129 (0.9%) required ER monitoring.

Conclusions: The data support that FDO was generally well tolerated in the home setting and the safety profile was comparable with that for in-clinic FDO.

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Jamie Weiss, Xiangyi Meng and Brandon Brown: employees of Novartis Pharmaceuticals Corporation.

Background: Neuromyelitis optica Spectrum Disorder (NMOSD) is a rare, autoimmune disease that preferentially causes optic neuritis and transverse myelitis leading to blindness and paraplegy. The standard of care for treatment of acute NMOSD relapses is immunosuppression with high dose corticosteroids and/or plasma exchange. The optimal timing for initiation of treatment is thought to be “sooner than later” but data are lacking regarding the outcomes based on treatment start times.

Objective: To determine the outcome of immunosuppressive treatment of acute NMOSD relapses stratified by start time of treatment relative to relapse onset.

Methods: This is a retrospective study of 66 NMOSD relapses treated at the Johns Hopkins Hospital between 2009 and 2016. NMOSD was defined by the 2015 IPND criteria. Subjects were divided into three groups based on start time of treatment. Expanded disability status scores (EDSS) were calculated for baseline, presentation, discharge and follow up. Relapses were defined as new symptoms associated with new examination finding and a new or enhancing MRI lesion. There were no differences among the demographics or clinical characteristics among these three groups.

Results: Twenty-one NMOSD subjects were treated within 72 hours, 15 were treated between 3-7 days and 15 were treated >7 days after relapse onset. Once treatment was started for any individual, all but one subject stabilized or improved suggesting that treatment halts progression of disability from the attack. When stratified by treatment delay relative to onset of symptoms, there is no observable benefit to earlier treatment in either the discharge or long-term disability. However, when stratified by severity of presentation, there is a “point of no return” beyond which the chance of meaningful recovery drops. Among 28 patients who initially lost fewer than 2 EDSS points from baseline, 23 (82%) recovered to baseline with treatment. Among those who lost 2 or more EDSS points at presentation, only half recovered to baseline despite the same treatment (p < 0.0009).

Conclusion: These data support the idea that earlier treatment of acute NMOSD relapses is better in the sense that each relapse has a “point of no return” - when severity reaches 2+ points on the EDSS scale - beyond which the chance of recovery to baseline begins to drop.

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P756

Point of no return: outcomes from acute relapses of neuromyelitis optica depend on severity

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an induction therapy. Therapeutic attempts with mitoxantrone and cyclophosphamide failed in achieving disease stability. From 2008 she underwent 57 cycles of Alemtuzumab with complete disease control. She decided for three times to discontinue treatment due to fear of PML and invariably she experienced massive disease reactivation. After the last reactivation we administered two courses of alemtuzumab (January 2015-2016). Since then she had no evidence of clinical or MRI disease activity, and referred high quality of life. Since August 2016 she had abnormal bruising for minimal trauma and three haemorrhages: on the left palm after squats, over the dorsalis pedis after tying shoes, over the right hand after having kept her mobile tightly. She was finally admitted at our hospital for limitation in walking abilities due to popliteus muscle’s haemorrhage. At blood tests we found high PTT and absence of FVIII. The finding of anti-FVIII antibodies confirmed the diagnosis of AHA. She was treated with one single administration of rFVII and then she started therapies per os with cyclophosphamide 100mg daily for two months and prednisone 100mg daily for a month plus tapering with initial response to treatment. In January 2016, an increase of FVIII inhibitors without clinical manifestation was found. Due to relapse of AHA we stopped cyclophosphamide and started azathioprine 100 mg die per os for two months with subsequent tapering of both azathioprine and prednisone with complete clinical remission of symptoms and a progressive reduction of FVIII inhibitor title.

In MS clinical studies, alemtuzumab-treated patients experienced secondary autoimmune disease such as thyroid disorders (36%), immune thrombocytopenia (1%), nephropathies 0.3%). These findings brought to the decision of a strict monitoring of blood counts with differential and urine analysis monthly and TSH every three months in order to make an early diagnosis and to start an early treatment of such disorders. Despite AHA has not been listed among the main secondary autoimmune disorders, in the previous clinical studies on alemtuzumab AHA has been reported in 0.2% of patients. This case underlines the importance of adding PT and PTT every three months to routine monitoring after alemtuzumab initiation in order to avoid complications in optimal responders to this drug.

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P758
Is the risk of progressive multifocal leukoencephalopathy the real reason for natalizumab discontinuation in patients with multiple sclerosis?

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Background: Progressive multifocal leukoencephalopathy (PML) is one of the major risk factors of natalizumab (NTZ) therapy. Despite introduction of the currently employed PML risk stratification algorithm, the number of NTZ-associated PML cases is still increasing. To date, more than 664 PML cases in 152,500 NTZ-treated multiple sclerosis (MS) patients have been reported.

Objectives: We therefore addressed the following questions with important implications for daily practice: How do NTZ-treated MS patients with different PML risk levels and their treating physicians assess and deal with the PML risk? Is PML risk the real reason for NTZ discontinuation?

Methods: 699 NTZ-treated patients with relapsing-remitting MS and 99 physicians were included in this prospective, multicenter, non-interventional, observational cohort study. At 5 time points (at study entry, 1, 2, 6, 12 months later), patients and physicians completed questionnaires. According to the presence of PML risk factors (prior immunosuppression, anti-John Cunningham virus (JCV) antibody status, treatment duration), patients were stratified into 5 subgroups. Due to the small number of patients with prior immunosuppression (n=30, treated by n=7 physicians), those patients were excluded from statistical analyses. Using a Bayesian network and regression analysis, we examined the possible relationships between different patient- and physician-related factors and patients’ NTZ discontinuation.

Results: Patients of all subgroups and physicians assessed the PML risk as low. Overall patient adherence to NTZ was high (87%). Only 13% of patients discontinued therapy. NTZ treatment cessation was associated with different patient- and physician-related factors (physicians’ assessment of general PML risk, number of treated patients per year, NTZ treatment duration, relapses during the course of study) upon which only physicians’ opinion on continuation/discontinuation of NTZ, patients’ perception of personal PML risk, and JCV seroconversion during the observation period showed significant relationships according to the regression analysis.

Conclusion: Treatment decisions in NTZ therapy are less related to objective PML risk than previously expected, but rather guided by subjective views and experiences of patients and even more so by neurologists. Treating physicians should consider this discrepancy in their advice to improve the risk-benefit-ratio for the individual patient.

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Conclusions: The present study suggests that the safety profile of Alemtuzumab does not change after exposure to Mycophenolate, Cyclophosphamide and Rituximab in both SPMS and RRMS patients.

Disclosure

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P760

How best to communicate clinical trial information about DMD risks and benefits to MS patients?

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Background: Patients with Multiple Sclerosis (MS) are faced with complex risk-benefit profiles of disease-modifying drugs (DMDs), often involving clinical trial data. Accurately understanding DMD information from clinical trials is necessary for effective decision-making and adherence.

Goal: To identify the most effective method of communicating clinical trial data to improve treatment understanding in MS patients.

Method: 45 relapsing-remitting MS patients (mean age: 46.76, 36 females) were presented with information from two clinical trials (e.g. "150 patients taking drug A will experience risk B and 50 patients taking the placebo will experience risk B"). Clinical trial data were communicated using absolute terms (e.g. "100 more patients taking drug A will experience risk B"), relative terms (e.g. "2 times as many patients taking drug A will experience risk B") and numbers needed to treat or harm (e.g. "10 patients would have to take drug A to experience risk B"). Treatment understanding was recorded. Fatigue (FSS), depression and anxiety (HADS), numerical reasoning (VESPAR), pre-morbid IQ (WTAR); information processing speed, and verbal and visual memory (BICAMS), were also assessed.

Results: Understanding of treatment information was significantly affected by methods of communicating clinical trial data (two-way ANOVA, F(2,88)=36.49, P<.001). Pairwise comparisons revealed greater understanding for clinical trial data presented in absolute terms compared to relative terms (t(44)=2.53, p<.05), and numbers needed to treat or harm (t(44)=2.58, p<.05). Adding background information about research patients in the treatment and placebo group improved understanding for all methods of presenting clinical trial data (F(1,44)=501.96, P<.001).

There were significant correlations between understanding of clinical trial data and numerical reasoning (r=.509, p<.001), pre-morbid IQ (r=-.415, p<.001), information processing speed (r=.423, p<.01) and verbal memory (r=-.409, p<.01).

Conclusion: Clinical trial data can be communicated more effectively to MS patients by using absolute terms. Cognitive factors can influence understanding of treatment information from

P759

Safety of alemtuzumab for multiple sclerosis after exposure to chemotherapeutic agents for patients with multiple sclerosis - experience of a single MS center

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Objective: To assess the safety profile of Alemtuzumab in patients with multiple sclerosis (MS) after exposure to chemotherapeutic agents.

Background: Alemtuzumab is a humanized monoclonal antibody against CD-52 that causes rapid and prolonged lymphocyte depletion. It is used as second or third-line therapeutic drug for MS. This prospective observational study aimed to compare the safety of Alemtuzumab after exposure to the chemotherapeutics Mycophenolate, Cyclophosphamide and Rituximab in patients with both secondary progressive multiple sclerosis (SPMS) and relapsing-remitting multiple sclerosis (RRMS).

Methods: In this single-center open-label prospective study patients received a 5-day course of Alemtuzumab 12 mg intravenously (IV) daily and were monitored for adverse events (AE). After one year, patients received a second 3-day course of Alemtuzumab 12 mg IV daily. We hypothesized that the risk profile of Alemtuzumab does not vary between MS type and type of chemotherapy drug used prior to treatment initiation.

Results: Prospective analyses were performed in 36 participants, age 44.80 ± 10.56 years, 27 females, 21 RRMS, 15 SPMS, disease duration 13.54 ± 8.26 years, baseline EDSS score 3.98 ± 2.03, mean follow-up duration 600.77 ± 388.89 days. There was no difference in the mean number of AE experienced by MS type (t-test, P=0.2). Patients were divided in two groups according to treatment with chemotherapeutics vs treatment with other disease-modifying drugs. There was no difference in the mean number of AE in these groups (t-test, P=0.3). No difference was found in the mean number of AE experienced by patients not previously exposed to chemotherapeutics versus those exposed to one or more of the three agents, alone or in combination (ANOVA, P=0.8).
clinical trials. Cognition should be assessed and accommodated as part of DMD education.

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P761
Alopecia totalis following alemtuzumab treatment in relapsing-remitting multiple sclerosis

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Objective: We report a case of a patient with relapsing-remitting multiple sclerosis who developed alopecia totalis six months after the second treatment course with alemtuzumab.

Methods: Case report and review of the literature.

Results: The patient reported smooth, circular, discrete areas of complete hair loss on both thighs six months after the second treatment cycle with alemtuzumab, 18 months after first exposure. No signs of an inflammatory skin disease were observed, and hair loss was diagnosed as alopecia areata (AA). Within three months, AA progressed to complete loss of all scalp hair including eyebrows and eyelashes (alopecia totalis). Current literature rarely connects alemtuzumab with the onset of alopecia of autoimmune origin.

Conclusion: Secondary autoimmunity is the most frequent adverse event occurring in almost every other alemtuzumab-treated MS-patient. Most common autoimmune-related side effects involve autoimmune thyroiditis and Graves’ disease, immune thrombocytopenia, and anti-glomerular basement membrane renal disease. Autoimmunity typically occurs as early as 18 months after the first treatment. Here, we report a novel autoimmune disease affecting the skin, very likely being associated with alemtuzumab. This case emphasizes the necessity of careful clinical surveillance of patients treated with alemtuzumab for undescribed autoimmune diseases.

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P762
Third Japanese case of fingolimod-associated PML in natalizumab-naïve MS: coincidence or alarm bell?

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Background: Fingolimod (FTY) has been approved as a first-line disease-modifying drug for relapsing multiple sclerosis (MS) in Japan since 2011. As of 01/2017, FTY has been prescribed to 5,400 Japanese MS patients, which constitutes approximately 3% of FTY prescription worldwide (184,000). By the end of year 2016, nine FTY-associated progressive multifocal leukoencephalopathy (PML) cases had been reported in natalizumab (NAT)-naïve MS, with two of them (22%) from Japan.

Case presentation: Here we report the third FTY-associated PML case in NAT-naïve Japanese. The patient is 47-year-old male diagnosed with MS in 2002. He was treated with interferon β from 2002 to 2013, before switching to FTY in 2013, when his EDSS was 6.0. During the course, he was exposed to a single 1000mg infusion of cyclophosphamide, which was terminated due to the lack of efficacy. He had never been tested for serum anti-JC virus (JCV) antibodies. His blood lymphocyte counts maintained over 200/µl for most of the time. His biannual MRI in 11/2016 revealed a new punctate T2 lesion in left middle cerebellar peduncle and an enlarging T2 lesion in cerebral white matter near the angular gyrus, both of which lacked contrast-enhancement (CE). He remained clinically stable (EDSS=6.5) and continued FTY (for total of 44 months) until late 12/2016, when he exhibited word-finding difficulties with cognitive impairment akin to Gerstmann syndrome. FTY was discontinued immediately and the patient was admitted to hospital for further evaluations. While waiting for the JCV test result in cerebrospinal fluid (CSF), progressive hemiparesis and seizures in his right leg and ataxia in his left arm were noted concomitantly with the development of CE in the T2 lesions. PML was diagnosed upon confirmation of JCV in his CSF (25 and 423 copies/ml in 12/2016 and 01/2017, respectively). He was treated with mitrazapine, levetiracetam for seizures, repeated courses of intravenous methylprednisolone therapy with oral taper for immune reconstitution inflammatory syndrome (IRIS). JCV became negative in CSF and the patient is to be discharged in late 12/2016.

Conclusion: This is the tenth confirmed case of FTY-associated PML in natalizumab-naïve MS patients. Three of which (30%), including this case, were reported from Japan, raising a possibility that Japanese MS patients are at a greater risk of developing PML under FTY treatment.

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P763
Ozanimod has an improved nonclinical safety profile relative to fingolimod
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Background: Ozanimod is an oral, once-daily immunomodulator that selectively targets S1P1R and S1P5R. Similar receptor selectivity is seen with three active metabolites of ozanimod. Nonclinical safety for ozanimod (and metabolites) included assessments after repeated dose, reproductive and juvenile Ozanimod has an improved nonclinical safety profile relative to fingolimod toxicity. Comparative clinical safety multiples (CSM) based on exposure were calculated for each study and compared with published data for fingolimod (Pharmacology Reviews, NDA 22-527, 2010).

Methods: Good Laboratory Practice-compliant studies conducted in the rat and monkey evaluated ozanimod in repeated dose studies for 26 weeks (rat) and 39 weeks (monkey), reproductive and juvenile Ozanimod has an improved nonclinical safety profile relative to fingolimod toxicity. Comparative clinical safety multiples (CSM) based on exposure were calculated for each study and compared with published data for fingolimod (Pharmacology Reviews, NDA 22-527, 2010).

Results: In contrast to fingolimod, ozanimod did not induce cardiac toxicity or increase liver weights or proliferative lung pathology. Additionally, the active metabolites did not decrease the safety multiples relative to the parent.

Conclusion: Overall, the CSMs were enhanced with ozanimod relative to fingolimod based on exposure ratios found at the NOAEL. Importantly, the repeated dose toxicity studies with ozanimod did not reveal significant heart toxicity, increased liver weights, or proliferative lung pathology. Additionally, the active metabolites did not decrease the safety multiples relative to the parent.

Disclosure

P764
First dose effects of fingolimod: final results of an in-depth ECG and Holter study in 6,998 German RRMS patients
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Background: Fingolimod, a sphingosine 1-phosphate receptor (SIPR) modulator, activates S1P1 receptors on the surface of cardiac myocytes after treatment initiation. This activation results in a transient reduction of heart rate, and in rare cases, atrioventricular conduction blocks (usually asymptomatic).

Objectives and aims: START (A 1-week, open-label, multicenter Study to explore conduction Abnormalities during first dose administration of fingolimod in patients with relapsing-remitting multiple sclerosis, NCT01585298) is a phase IV study evaluating in detail the first-dose cardiac safety profile of fingolimod in a cohort of 6,998 RRMS patients.

Methods: The START study was a prospective, 1-week, multicenter, open-label study enrolling 6,998 RRMS patients (between June 2012 and December 2016) in more than 250 centers in Germany, according to the EU label criteria of fingolimod. The study included a screening period, a baseline visit with administration of the first dose of fingolimod, and a final visit after one week. Baseline procedures were as follows: Prior to the first intake of fingolimod, a 12-lead ECG was recorded. After the first dose, a continuous 6h Holter ECG was applied, and pulse and blood pressure were measured every hour. At the end of 6h, a 12-lead ECG was again performed. All ECG recordings were centrally evaluated by cardiologists.

Results: The previous START interim analysis was based on 4,736/6,998 patients. In this cohort, 0.8% of the patients developed asymptomatic bradycardia (< 45 bpm) during the 6h monitoring. There was no QTcF-interval prolongation beyond 500 msec. 1.5% of the patients experienced a 2nd degree AV-block of Mobitz type I or 2:1, no 3rd degree AV block was observed. Here, at the ECTRIMS, final data of the 6,998 START patients will be
presented focusing on an in-depth Holter-ECG analysis of those patients having developed bradycardia or AV-block 2nd degree or higher. In addition, the impact of co-medICATIONS with the potential to prolong QT-interval and the gender/age distribution of cardiac events will be described.

**Conclusions:** This is the largest Holter-ECG-study to date evaluating real-time ECG data to assess the cardiac safety after fingolimod initiation. Therefore, the final results of nearly 7,000 patients will be of significant clinical importance for the safety profile of fingolimod.

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**P765**

**Pregnancy outcomes in patients with multiple sclerosis and exposure to branded glatiramer acetate during all three trimesters**

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**Objective:** To evaluate pregnancy outcomes in patients with multiple sclerosis (MS) who were exposed to branded glatiramer acetate (GA, Copaxone®) during all three trimesters and compare them with reference data from the general population.

**Background:** Although MS does not increase the rate of adverse pregnancy outcomes, information regarding the potential pregnancy risks associated with MS disease-modifying therapies is insufficient. Thus, these treatments are often discontinued for women with MS who intend to become or are confirmed pregnant. However, in women with highly active MS, there is a need to continue DMT therapy throughout pregnancy. In such cases, the benefits to the mother should be weighed against the risk to the fetus. Previous analyses indicated no overall increase in malformative or fetal/neonatal toxicity or pregnancy loss among women treated with branded GA as compared with the reference rates. In those analyses, GA was discontinued in most cases once pregnancy was confirmed.

**Methods:** Data on pregnancy outcomes were sourced from Teva’s global pharmacovigilance database. Retrospective analyses were performed on prospective cases from clinical trials and solicited or spontaneous reports, including patients with known outcomes and exposure to branded GA 20 mg/mL (GA20) during all three trimesters. Rates of congenital anomalies were compared with those in EUROCAT, a European network of population-based registries for the epidemiologic surveillance of congenital anomalies.

**Results:** All 216 cases identified resulted in live births. No late-stage intrauterine deaths or stillbirths were observed. There were no abortions or early stillbirths, which may be due to the selection criteria requiring patients with exposure to GA during all three trimesters. Seven cases of congenital anomalies were reported, with an extrapolated rate of 3240.7 per 100,000 births, similar to the reference prevalence rate of 2514.6 per 100,000 births according to EUROCAT data (2010-2014). The standardized incidence ratio of congenital anomalies associated with GA20 exposure was 1.29 (95% confidence interval: 0.52, 2.66).

**Conclusions:** As compared with the general population, GA20 exposure during all three trimesters of pregnancy did not significantly increase the risk of congenital anomalies.

**Disclosure**

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**P766**

**Characterizing the cytokine profile before and after antiCD20 infusions: a comparison of rituximab versus ocrelizumab**

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**Objective:** To characterize the cytokine changes associated with antiCD20 therapies.

**Background:** Ocrelizumab was approved for treatment of multiple sclerosis (MS) in the United States on March 28th of 2017. Rituximab has been used off-label in the treatment of MS for the past decade. These two medications differ in how humanized they are, epitopes they recognize, and the mechanism of cell death of CD-20 expressing cells (mainly B cells). It has been hypothesized that this will result in differences on rates and severity of infusion related reactions (IRR) between these two medications. Here we examine how these two medications affect cytokine profiles after treatment to begin to understand how infusion reactions may differ.
Methods: Patients with MS were identified who were undergoing their first infusion with either rituximab or ocrelizumab at the Rocky Mountain MS Center at the University of Colorado. Clinical/demographic information was collected and patients were consented for collection of plasma samples before and after treatment. Plasma samples were analyzed using V-PLEX Human Cytokine 36-Plex kit (Eotaxin, Eotaxin-3, GM-CSF, IFN-γ, IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IL-1α, IL-1β, IL-2, IL-21, IL-22, IL-23, IL-27, IL-31, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8(8A), IL-10, MCP-1, MCP-4, MDC, MIP-1α, MIP-1β, MIP-3α, TARC, TNF-α, TNF-β, VEGF-A) on a meso-scale QuickPlex SQ120 imager. Paired sample T-tests were performed in SPSS.

Results: 10 patients were included in this study (7 who received rituximab and 3 who were treated with ocrelizumab). All patients were female except 1 patient who received rituximab. The mean age was 44.2 for rituximab patients and 42.1 for ocrelizumab patients. 4 (3 mild; 1 moderate) patients on rituximab had IRR while 2 (both moderate) had an IRR with ocrelizumab. Even with the low number of ocrelizumab samples, a decrease in IL-12p70 (8.4%) while an increase in TNF-β (88.3%) was observed (p< 0.05). With rituximab, an increase was seen with MIP-1β (711%), TARC (78.6%), TNF-α (123%), IL-22 (3.5%), IL-27 (87%) while a decrease was seen with Eotaxin (24%), IL-5 (22.5%); (p< 0.05). The change in IL-5 between rituximab (increased) and ocrelizumab (decreased) was different (p=0.017).

Conclusions: These findings suggest that there are differential differences in how rituximab and ocrelizumab affect cytokines after infusion. Larger sample collections and analysis to compare with infusion reactions are planned.

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Tools for detecting therapeutic response

P768
An application of a novel statistical approach to predict patient-specific treatment responses to DMTs based on a continuous score

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Background: Identifying patient subgroups that explain individual response to disease modifying therapy (DMT) is an important step in transitioning from population-level randomized clinical trials (RCTs) to personalized medicine in MS. Classical approaches for subgroup analysis use predefined or algorithm-selected cut-offs, but are often insufficiently powered. A novel modelling approach by Li et al. (Biometrics, 2016) yields a continuous patient-specific score that predicts treatment response according to baseline characteristics.

Objectives: To assess the utility of a patient-specific treatment response score to predict annualised relapse rate (ARR) in MS patients.

Methods: The DEFINE (Dimethyl Fumarate [DMF] vs placebo) RCT (n=1234) was used to build the prediction score and the CONFIRM (DMF vs placebo) RCT (n=1066) was used to validate the score. The prediction score was developed by regressing ARR on baseline age, sex, ethnicity, number of prior relapses, disease duration, time since relapse, prior treatment, EDSS, MSFC-4, Gd+ lesions, T2 and T1 lesion volume, brain volume, SF-36 PCS and MCS using negative binomial regression. Model predictions were based on a fully specified additive model; stepwise, ridge and LASSO regression; and elastic nets. Treatment-by-score interaction models were developed and cut-offs for high responders based on the top quartile of scores.

Results: The ARR risk ratios (treatment vs. placebo) ranged from 0.18 to 0.52 in DEFINE and 0.55 (95%CI 0.48-0.86) (interaction p=0.026). Significant treatment-by-score interaction models were developed and cut-offs for high responders based on the top quartile of scores.

Conclusions: This proof-of-concept application of a powerful modelling strategy successfully detected high responders, which was validated in an independent RCT. The individual response score is useful for personalized medicine, treatment response calculators, and identifying patient sub-groups for RCTs.

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P769
Minimal or no evidence of disease activity: which target to prevent long-term disability in multiple sclerosis?

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Background: The No Evidence of Disease Activity (NEDA) is a desirable outcome measure for the treatment of relapsing-remitting multiple sclerosis (RRMS) [Giovannoni et al. Mult Scler Rel Disord 2015]. However, NEDA represents a stringent goal to achieve, especially with platform therapies [Rotstein et al. JAMA Neurol 2015]. Therefore, Minimal Evidence of Disease Activity (MEDA) has been proposed as a more realistic target that can be tolerated without any significantly increased risk of future disability worsening.

Objective: To investigate the effect of early NEDA or MEDA status on long-term disability outcome in patients with RRMS.

Methods: We collected data of patients with RRMS regularly attending 3 Italian MS Centres. Patients were considered eligible if they started Interferon Beta or Glatiramer Acetate as first treatment, had an Expanded Disability Status Scale (EDSS) score ≤4.0 and were followed for ≥5 years. They were classified in subgroups according to level of disease activity after the first year of treatment [Rio J et al. Mult Scler 2017].

(i) NEDA, i.e. absence of relapses, of confirmed EDSS worsening and of magnetic resonance imaging (MRI) activity;
(ii) MEDA, i.e. either “1 relapse with ≤2 new T2 lesions” or “< 3 new T2 lesions or < 2 gadolinium-enhancing lesions”, in the absence confirmed EDSS worsening;
(iii) Evidence of disease activity (EDA), i.e. occurrence of ≥1 relapse with either confirmed EDSS worsening or ≥1 gadolinium-enhancing lesion or ≥3 new T2 lesions.

We ran a multivariable Cox regression model (stratified by Centre) to explore the long-term risk of reaching the disability milestone of EDSS≥6.0 according to one-year status (NEDA, MEDA or EDA).

Results: We analyzed 987 patients with mean age of 33.3±9.7 years and median EDSS score of 1.5. They were followed for a median time of 10 years (range 5 to 23). Of them, 423 (43%), 389 (39%) and 175 (18%) were classified at one year as having NEDA, MEDA and EDA, respectively. Overall, 182 (18%) patients reached EDSS≥6.0 after a median time of 9 years (range 2-22). The risk of reaching EDSS≥6.0 was higher in the event of
Background: Subcutaneous interferon β-1a (scIFNβ-1a) has been commercially available since 1998, with approximately 1.44 million patient-years of exposure. scIFNβ-1a reduces relapse rates and delays disability progression in patients with multiple sclerosis (MS). This post-hoc analysis examined the association of the Magnetic Resonance Imaging in MS (MAGNIMS) score at Year 1 (Y1) with long-term clinical disease activity free (CDAF) status and disability progression in patients treated with scIFNβ-1a using data from 15 years of PRISMS.

Methods: In PRISMS-2 relapsing-remitting MS patients were randomised to scIFNβ-1a 22 µg (n=189) or 44 µg (n=184), or placebo (n=187), three times weekly for 2 years. At the start of Year 3 placebo patients were randomised to scIFNβ-1a 22/44 µg; scIFNβ-1a patients continued their initial regimen. Patients were followed to 15 years post-randomisation (scIFNβ-1a 22 µg n=95; 44 µg n=95; placebo n=100). We classified scIFNβ-1a patients by MAGNIMS score at Y1: 0 (0-2 new T2 lesions+0 relapses), 1 (0-2 new T2 lesions+1 relapse or >3 new T2 lesions+0 relapses) or 2 (0-2 new T2 lesions+≥2 relapses or ≥3 new T2 lesions+1 relapse). CDAF was defined as no relapses or disability progression (an increase of 1 point vs baseline in the Expanded Disability Status Scale [EDSS] score, or 1.5 points in patients with EDSS 0).

Conclusions: Disease activity as assessed by the MAGNIMS Score predicts long-term clinical disease activity free status and disability progression in patients treated with subcutaneous interferon beta-1a.

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P771
Defining areas of cognitive impairment in relapsing-remitting multiple sclerosis (RRMS) - baseline analysis of a longitudinal multicenter study in 15 German practice centers


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Background: Cognitive dysfunction is considered one of the most important non-motor deficits of MS representing an essential predictive factor for MS-associated the quality of life (QoL) and disease progression.

Objective: Baseline analysis of cognitive profiles of RRMS patients starting therapy with dimethylfumarate (DMF, deNovo) or switching from other MS medications (switchers) with respect to the following questions:

1) Which areas define differences in the cognitive profile of RRMS patients and healthy controls?
2) Does cognitive profile distinguish between deNovo and switchers?
3) Which are the vulnerable domains affected by the MS disease process?

**Methods:** Baseline analysis of a prospective, non-interventional, multicenter (15 German practices) study of 24 months with assessments at baseline/T0 and after 6,12 and 24 months follow-up (T6, T12, T24).

**Inclusion:** 18-60 yr, RRMS/McDonald, EDSS: 0-6.0.

**Groups:** 210 RRMS patients compared to 129 healthy controls, among the latter 136 switchers and 74 deNovo patients.

**Assessments:** clinical status (EDSS, ambulation index, functional status), behavioral (CGI, fatigue/FSS/FSMC, daytime sleepiness/ESS, self-rated attention/FEDA, depression/BDI, QoL/EQ5D) and cognitive domains (executive function, i.e.verbal and non-verbal fluency/RWT,RFFT, interference control/Stroop; working memory/WMSr-BS/ZS, information processing/SDMT, learning & memory (non-verbal/BVMT and verbal/CVLT domains).

**Results:**

1) When comparing the RRMS group vs. controls, significant cognitive impairment was shown among the patients in the domains of information processing (SDMT: p< .0001), executive function as represented by verbal fluency (RWT; lexical (p< .01) and semantic category change (p< .0001) and design fluency (RFFT; p< .0001), as well as verbal working memory (WMS-ZS: p< .007).

2) Subgroup analysis showed significant deficits for switchers concerning information processing (SDMT: p< .0001) and verbal (RWT, semantic category change p< .01) as well as design fluency (RFFT: p< .003).

**Conclusion:**

1) Data provide evidence that the MS disease process primarily affects information processing speed, executive function, fluency and verbal working memory which have to be considered as vulnerable cognitive domains due to a network insufficiency.

2) Switchers are more affected by information processing and working memory deficits suggesting that these areas may be particularly vulnerable in case of medication failure and longer disease duration.

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P772

Long-term disease outcomes in multiple sclerosis patients categorised by baseline brain volume and with no disease activity over 2 years

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**Background:** Baseline (BL) magnetic resonance imaging (MRI) activity predicts subsequent brain volume loss (BVL), while normalised brain volume (NBV) at BL and BVL over time predict future disability in studies with patients with relapsing–remitting multiple sclerosis (RRMS). However, the predictive value for clinical outcomes of NBV categories, in the absence of MRI lesion activity and clinical symptoms, remains to be explored.

**Objective:** To study long-term (up to 8 years) MS outcomes of patients with low vs high NBV at BL and no disease activity during the first 24 months (M).

**Methods:** The Normative Brain Volumes: application in Multiple Sclerosis (NoViMS) dataset of 600 healthy subjects was used to generate an age-based NBV percentile chart. The BL NBV of patients with RRMS from the FREEDOMS and FREEDOMS II trials of fingolimod were plotted against this normative dataset and a quantile regression analysis was performed. Patients were categorised into four subgroups based on percentiles: ≤P10 (N=540), >P10 to ≤P25 (N=556), >P25 to ≤P50 (N=605), and >P50 (N=631). At M24, patients on placebo were switched to fingolimod and treatment effects by NBV percentiles were assessed. Outcomes of patients with no disease activity, defined as no relapse, no disability progression and no gadolinium-enhancing T1 lesions at M24, were assessed at M96 for each NBV category.

**Results:** At BL, patients in lower percentiles had higher MS disease burden (p< 0.0001 for most measures). Low BL NBV correlated with increased T2 lesion volume (T2LV) and annualised rate of brain volume loss (ARBVL) at 2 years (p<0.0001 for both). Compared with placebo, fingolimod treatment improved outcomes in all NBV percentiles at 2 years. At 8 years, patients with no disease activity at M24 had consistently worse outcomes if they had low vs high NBV at BL: change in Expanded Disability Status Scale score (0.5 vs −0.2), 6M-confirmed disability progression (CDP) (27 [32.1%] vs 17 [13.8%]), change in T2LV (1565.8 vs 450.4 mm3) and ARBVL (~0.28% vs −0.22%). Overall, risk of 6M-CDP at 8 years was higher in patients with low NBV compared with high NBV at BL (hazard ratio [95% CI]: 1.64 [1.30; 2.07]; p< 0.0001).

**Conclusions:** Despite the initial absence of clinical and radiological disease activity, patients with low brain volume at baseline were at a higher risk of future disease progression. NoViMS, a healthy subject brain volume normative dataset, is a useful tool to identify such at-risk patients based on their NBV.

**Disclosure**

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**P773**

Comparison between central and whole brain atrophy in multiple sclerosis measured by structural image evaluation using normalization of atrophy (SIENA)

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**Background:** Artifacts and partial volume effects in the superior and inferior parts of the brain may affect the measurement of whole brain atrophy when applying Structural Image Evaluation using Normalization of Atrophy (SIENA). To overcome this issue, some pivotal multiple sclerosis (MS) trials (e.g. FREEDOMS) used a central slab instead of the whole brain as input for SIENA but others did not (e.g. INFORMS). It is not clarified how this different approach influences the variability of atrophy measures.

**Objective:** To compare the variability of central and whole brain atrophy in MS using SIENA and their association to clinical outcomes longitudinally.

**Methods:** SIENA was performed in 105 MS patients with a five-year follow-up (67% female, 23/105 progressive MS; mean age 43.8±10.9 years; median disease duration 12 years, median Expanded Disability Status Scale score (EDSS) 3.0) on 3D T1-weighted MPRAGE images (spatial resolution 1x1x1 mm³) with and without using a central slab (-10 mm to +60 mm Montreal Neurological Institute atlas coordinates) to assess percentage brain volume change (PBVC). The statistical analysis included Cronbach’s alpha, coefficient of variation (CV), Bland-Altman plots and a sample size calculation. Clinical outcomes at 5 years comprised the EDSS, Multiple Sclerosis Functional Composite (MSFC) and Symbol Digit Modalities Test (SDMT).

**Results:** Mean annualized (a) PBVC was higher using the central slab compared to the whole brain (-0.55±0.43% vs. -0.33±0.31%; p< 0.001). The difference was most pronounced in patients with an aPBVC higher than 0.4% (n=50, mean PBVC difference 1.63±1.32 [range: -1.48;+6.16]) compared to patients with an aPBVC of less than 0.4% (n=55, mean PBVC difference 0.57±0.67 [range: -0.86;+1.92]). The CV was lower for central compared to whole brain atrophy (78% vs. 92%). Cronbach’s alpha between the two methods was 0.89. Central and whole brain volume change over 5 years similarly correlated with EDSS, SDMT and MSFC at 5 years (Spearman rho range: 0.26-0.40; all p<0.007). Based on five-year follow-up data, sample size calculations estimate 29% fewer patients per arm required to detect a treatment difference of 20% for PBVC with 80% power when using the central slab instead of the whole brain as input for SIENA.

**Conclusions:** The variability of atrophy measures was lower when using the central slab compared to the whole brain as an input for SIENA. Both methods provided similar associations with clinical outcomes.

**Disclosure**

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**P774**

Association of brain volume loss and NEDA outcomes in patients with relapsing multiple sclerosis in the OPERA I and OPERA II studies


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Background: Brain volume loss (BVL) occurs in patients with multiple sclerosis (MS), reflecting irreversible tissue damage. No evidence of disease activity (NEDA), a composite measure assessing absence of clinical and MRI disease activity, has emerged as an important treatment goal in MS and may be associated with preservation of brain tissue and prevention of BVL.

Objective: To examine the association between BVL and NEDA status in patients with relapsing MS from OPERA I (NCT01247324) and OPERA II (NCT01412333).

Methods: Patients in OPERA I and II received ocrelizumab 600 mg via intravenous infusion every 24 weeks or subcutaneous interferon beta-1a (IFN β-1a) 44 µg three times weekly for 96 weeks. Brain magnetic resonance imaging (MRI) assessments were completed at baseline and at Weeks 24, 48 and 96. Brain volume normalized for head size was measured using SIENAX software. Percent change in whole brain volume (WBV) was determined using SIENA software, while changes in cortical grey (GMV) and white (WMV) matter volumes were measured using validated, locally developed Jacobian integrator atrophy software. NEDA was defined as the absence of relapses, 12-week confirmed disability progression, T1 Gd-enhancing lesions and new and/or enlarging T2 lesions. Changes from baseline in brain volume were examined in patients with NEDA and those with evidence of disease activity (EDA), irrespective of treatment and by treatment group, using the mixed-effects model for repeated measures method.

Results: The analysis included 1,520 patients (ocrelizumab, 761; IFN β-1a, 759). Over 96 weeks, 569 (37%) patients (ocrelizumab, 363 [48%]; IFN β-1a, 206 [27%]; p<0.001) had NEDA. Compared with patients with EDA, those with NEDA had significantly less WBV loss from baseline (30% reduction; p<0.001). In the NEDA group, ocrelizumab patients had significantly less WBV loss (32% reduction; p<0.001), WMV loss (34% reduction; p=0.044) and GMV loss (30% reduction; p<0.001) from baseline than IFN β-1a patients. In the EDA group, ocrelizumab patients had significantly less WBV loss (11% reduction; p=0.047) and GMV loss (21% reduction; p<0.001) but not WMV loss (1.03% increase; p=0.90) than with IFN β-1a patients.

Conclusions: These findings highlight the importance of NEDA as a treatment goal with respect to brain tissue preservation regardless of treatment choice. Ocrelizumab may confer additional benefits in patients who achieve NEDA beyond what is observed with IFN β-1a.

Disclosure
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P775
Permeability of the blood-brain barrier predicts no evidence of disease activity at two years after natalizumab or fingolimod treatment in relapsing-remitting multiple sclerosis
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Background: Early detection of sub-optimal treatment response in relapsing-remitting multiple sclerosis (RRMS) is important for effective treatment escalation. Previously we demonstrated an association between blood-brain barrier (BBB) permeability as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and cerebrospinal fluid cellularity. We hypothesized that DCE-MRI predicts sub-optimal treatment response after two years of treatment with fingolimod or natalizumab, drugs with a common effect of decreasing lymphocyte trafficking and again three and six-months post treatment. We calculated the influx constant Ki, a measure of BBB permeability, during the conduct of the study; and grants and personal fees from Biogen, F. Hoffmann-La Roche Ltd, Sanofi Genzyme, Chugai, Novartis and Teva, outside the submitted work.
Results: 13 out of 33 (39%) subjects lost NEDA status after one year of treatment and 15 out of 33 (45%) lost NEDA status after two years. Subjects who lost NEDA status at two years had a 51% higher mean Ki in normal-appearing white matter (NAWM) measured after six months of treatment, when compared to the group who maintained NEDA status (p=0.0003), while there was no difference in Ki, before treatment initiation or after three months of treatment. We found no such difference for NEDA status at one year. A ROC curve analysis found Ki, in NAWM, to be a good predictor of loss of NEDA status at two years (AUC 0.84, p=0.003). Values of NAWM Ki, at six months above a cut-off of 0.136 ml/100/g/min yielded an odds ratio of 11.5 for loss of NEDA at 2 years (positive and negative predictive values of 73% and 81%, respectively). A one-way repeated measures ANOVA with Ki as a surrogate marker of the state of health of the BBB, with a predictive threshold for disease activity, which is remarkably identical in clinically, isolated syndrome and established RRMS.

Conclusions: We show that BBB permeability as measured by DCE-MRI is a good predictor of sub-optimal treatment response after treatment with natalizumab or fingolimod. We provide evidence that Ki, as a surrogate marker of the state of health of the BBB, with a predictive threshold for disease activity, which is remarkably identical in clinically, isolated syndrome and established RRMS.

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P776
Patient reported disease modifying therapy adherence in the clinic: a reliable metric?
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Introduction: A number of studies have assessed patient adherence to multiple sclerosis (MS) disease modifying therapy (DMT). Such studies have typically been based on claims data or patient completed research questionnaires. We decided to investigate patient reported DMT adherence in the clinic and its relationship to clinical outcomes.

Methods: The Knowledge Program is a Cleveland Clinic database that electronically captures patient reported outcomes and clinician entered data at each clinic visit. Collected outcomes include the Performance Scales (PS, a measure of MS related disability), European Quality of Life 5 Dimensions (EQ5D), Patient Health Questionnaire 9 (a depression scale), and the timed 25-foot walk. Patient reported DMT adherence over the prior three months is recorded as part of our standard follow-up progress note. The KP was queried for patients with relapsing-remitting MS who had been on DMT for ≥6 months. The primary outcome was the association between baseline adherence and PS scores at 6, 12, 24, and 36 months. Secondary outcomes included the association of adherence with the other metrics listed above. Adequate adherence was defined as taking ≥80% of DMT doses. Adjusted and unadjusted linear regression models were constructed to assess the outcomes. Important covariates were adjusted for including age, gender, race, and DMT.

Results: There were 1,148 patients available for analysis of which 94.9% were defined as adherent. There was adequate data to assess the primary outcome in 501 patients at 6 months, 544 patients at 12 months, 331 patients at 24 months, and 247 patients at 36 months. In the unadjusted models, adherence was only significantly associated with lower PS scores (less disability) at 2 years and lower EQ5D scores (lower quality of life) at one year. In the adjusted models, adherence was not significantly associated with any outcome at any time point.

Conclusions: The proportion of patient who reported adequate adherence to DMT in our study was much higher than in studies based on administrative data or questionnaires, which typically estimate adherence at about 75%. This suggests that patients may not be forthright when reporting DMT adherence to their clinicians, possibly due to a desire to avoid disappointing their care team. The minimal observed effect of adherence on outcomes in our study further supports the notion that patient reported DMT adherence may not be a reliable metric.

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P777
Overall response score: a novel disability endpoint that allows for the integrated assessment of improvement and worsening over time in patients with MS
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Background: Disability in MS has been evaluated using confirmed worsening/improvement on several measures (EDSS, MSFC), or multicomponent endpoints with established change thresholds (EDSS, T25FW, 9HPT). Worsening/improvement are rarely examined jointly; current multicomponent endpoints do not tend to reflect changes on >1 disability measure. The patient population is typically classified by these criteria into binary categories (changed or not); data are usually censored after reaching the endpoint with subsequent disability worsening/stabilisation/improvement information lost. An endpoint integrating clinically relevant worsening/improvement across domains could provide a more complete assessment of disability trajectory and a sensitive tool to evaluate new therapies.

Objectives: To describe the overall response score (ORS), a novel endpoint measuring disability improvement and worsening simultaneously, and to evaluate its sensitivity to changes over time and relationship to established disability progression endpoints.

Methods: The ORS has 4 components: EDSS, T25FW, 9HPT (dominant and non-dominant), and a range of +4 to -4. At each visit, each component is scored vs baseline: -1 (threshold for worsening met), 0 (no change met threshold), or +1 (threshold for improvement met). Component thresholds are based on commonly used definitions. Patients are scored against baseline repeatedly over time. ORS was evaluated with different therapies and types of MS using historical data in RRMS (natalizumab, AFFIRM; dimethyl fumarate, DEFINE, CONFIRM), SPMS (natalizumab, ASCEND), and PPMS (rituximab, OLYMPUS). Comparisons were quantified by overall disability status (area under curve), trajectory of decline (slope), and difference at 2 years. Sensitivity analyses explored different thresholds or weighting for components and the relationship with conventionally defined confirmed improvement/worsening.

Results: ORS over time for each therapy vs placebo captured the treatment efficacy observed with established disability progression endpoints (AFFIRM: N=942; DEFINE: N=818; CONFIRM: N=722; ASCEND: N=887; OLYMPUS: N=439) and displayed lower variability. Differences by type of MS were observed in the endpoint’s utility.

Conclusions: This novel endpoint includes well-established components and was sensitive to change, allowing assessment of worsening/improvement over time without censoring.

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P778
The effect of dimethyl fumarate treatment on hippocampal metabolite levels in RRMS using 1H-MR spectroscopy
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Background and aims: The systemic anti-inflammatory action of Dimethyl fumarate (DMF) is hypothesized to be partly due to its modulation of glutathione levels. Its impact on neurometabolite profiles and anti-inflammatory status of the brain is less understood. In this study we applied non-invasive 1H-MRS to evaluate hippocampal neurometabolite changes in RRMS patients compared to healthy controls(HCs) and then assessed changes associated with DMF treatment over time.

Methods: 1H-MRS was undertaken on 20 RRMS patients prior to treatment onset (baseline) and at 1, 6 and 12 months post-inception of DMF treatment and 20 age and sex-matched healthy controls, using a Siemens Prisma 3T MRI scanner. Spectroscopic data were acquired by using single voxel spectroscopy (6.75mL, PRESS, TE 30ms). Hippocampal metabolite to total creatine ratios of 5 neurometabolites of interest were derived using LCModel(v6.2-2B), this included: N-acetylaspartate(NAA), glutamine-glutamate, glutathione(GSH), myo-inositol(mI), and phosphocholine.

Comparisons of mean metabolite levels between controls and the RRMS group at baseline were undertaken using T-tests. In the patient group at baseline, bivariate correlation analysis evaluated association of clinical covariates with each metabolite. Changes in
Conclusions: Our findings suggest that DMF treatment is associated with a modification in the level of glutathione in the hippocampus. Further studies with larger patient numbers and longer treatment durations are warranted to investigate the impact of DMF on metabolic changes in the MS brain.

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P779
Silent lesions on MRI - shifting goal post for treatment decisions in MS
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Background and aims: Magnetic resonance imaging (MRI) plays an indispensable role in monitoring treatment in multiple sclerosis (MS). As new lesions on cerebral MRI scans represent a validated biomarker for disease activity and prognosis, clinicians are increasingly using MRIs to assess subclinical activity that might prompt earlier change of disease-modifying therapies (DMTs) in the absence of clinical relapses. ≥3 new cerebral lesions in patients treated with interferon-beta for ≥1 year have been linked to worse prognosis. The practical use of MRIs for treatment failure determination is unknown. Using real world data, we assessed the relationship between MRI lesion count and DMT change, taking into account different treatment types.

Methods: MRI lesions counts were extracted from MSBase in December 2016, and analyzed using univariable logistic regression. We included all relapsing-remitting multiple sclerosis (RRMS) patients on DMT, aged ≤55 years, with at least one clinical assessment, followed by DMT change within 12 months of the index scan. Those with DMT alterations due to clinical relapses, EDSS change, documented side effects or pregnancy were excluded. DMTs at time of index MRI were subdivided into ‘orals’, ‘injectables’ or ‘infusions’.

Results: A total of 8311 MRI brain scans of 4232 patients were identified. 26% of MRIs with ≥1 new T2 lesion resulted in starting a new DMT, whilst 50% of MRIs with ≥6 new T2 lesions resulted in a change of DMT. The mean time for DMT change after the index MRI was 4.65 months irrespective of lesion count. For every additional new T2 lesion, the odds of changing DMT were 1.25 (p<0.001). DMT changes were more frequently observed with initial ‘orals’ and ‘injectables’, than with ‘infusions’. The odds ratio for additional T2 lesions was 1.39 (p<0.001) in the ‘oral’ group compared to 1.24 (p<0.001) in the ‘injectables’ group. New Gadolinium-enhancing (Gd+) T1 lesions were 2.43 times more likely to result in a DMT change, irrespective of country. Patients who were on injectables were most likely to change DMTs (OR 2.86; p<0.001) with a new Gd+ T1 lesion. DMT changes were more frequently observed with initial ‘orals’ and ‘injectables’, than with ‘infusions’. The odds ratio for additional T2 lesions was 1.39 (p<0.001) in the ‘oral’ group compared to 1.24 (p<0.001) in the ‘injectables’ group. New Gadolinium-enhancing (Gd+) T1 lesions were 2.43 times more likely to result in a DMT change, irrespective of country. Patients who were on injectables were most likely to change DMTs (OR 2.86; p<0.001) with a new Gd+ T1 lesion.

Conclusions: Clinicians have low thresholds in making decisions on DMT change with new T2 or Gd+ T1 lesions despite clinical stability. The probability of changing DMTs is highest in patients treated with ‘injectable’ DMTs. This study suggests that no evidence of disease activity (NEDA) 3 has become a target for MS treatment in various countries.

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Dr. Spelman received honoraria for consultancy, funding for travel and compensation for serving on scientific advisory boards from Biogen Idec Inc; speaker honoraria from Novartis.
Dr. Sola reports no disclosures.
Purpose: Changes to the guidelines for the diagnosis and follow-up of patients with multiple sclerosis (MS), which previously recommended routine use of gadolinium (Gad) in brain magnetic resonance imaging (MRI), are proposed. In this consensus statement, we consider concerns about the risk of Gad accumulation in the brain, and propose changes to current clinical guidelines.

Material and Methods: A consensus conference was convened in early 2017 to review the literature on the retention and safety of gadolinium (GBCA) in MS.

Results: The association of GBCA with nephrogenic systemic fibrosis in patients with severe renal disease (eGFR < 30) is well known. Recent literature has shown that all GBCA lead to retention of very small amounts of Gad in the brain (predominantly dentate nucleus and globus pallidus), bone, skin, and elsewhere in the body. In the brain, Gad is retained at different rates/in different regions, and the health effects of Gad deposition are unknown, the need for...
contrast-enhanced studies must be clearly indicated. Consideration of GBCA and dose should depend on sensitivity of the agent to detect new inflammatory lesions versus the likelihood of tissue deposition, as GBCA also vary in the degree to which they induce lesion enhancement per administered dose. Group consensus: To demonstrate inflammatory MS lesion activity, GBCA remains essential in the diagnostic evaluation of a patient suspected of having MS. For the routine follow-up monitoring of patients with MS, the use of GBCA may be useful in the following circumstances: suspicion of or obvious clinical disease activity for which confirmation may modify therapy, confirmation of lack of disease activity, and facilitating selection of disease-modifying therapies.

Conclusion: Because all GBCA lead to retention of very small amounts of Gad in the body (including the brain) and as the health effects of Gad deposition are unknown, even in the absence of documented evidence of clinical neuro-toxicity, the need for Gad-enhanced studies in MS, must be balanced with well supported clinical indications.

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Treatment of progressive MS

P781

A comparative-effectiveness analysis applying a 3 way propensity matching to real-world data from MSBase Registry in preparation for a cost effectiveness model: patients switching within firstline agents or to natalizumab or fingolimod in active RRMS


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Background: In MS patients experiencing relapses on first-line interferon-beta (IFN), glatiramer acetate (GA) Dimethylfumarate or teriflunomide (BRACETD) therapy, switching to natalizumab or fingolimod is a common strategy, however in some jurisdictions the switch is stratified according to level of disease activity.

Objectives: To compare in a real world data setting the treatment effectiveness measured by annualized relapse rate (ARR), 6 month confirmed disability progression and regression in patients switching to either natalizumab, fingolimod or within BRACETD from initial treatment on BRACETD. The results of this

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comparative effectiveness analysis were applied to an economic model (subject of a companion paper).

**Methods:** Patients included were registered in MSBase, experienced relapse/s on BRACETD within 12 months prior to switching within BRACETD (97% pre and 80% post switch were on GA or IFN) or natalizumab or fingolimod. An application of 3-way multinomial propensity score matching on predefined clinical variables was used. Pairwise comparisons of the matched switch treatment groups have been conducted with the reference group switch within BRACETD. The primary outcome ARR was analysed using a GEE Poisson regression model. Secondary outcomes time to 6 months confirmed disability progression (CDP6M) respective regression (CDR6M) were analysed using a Kaplan-Meier approach and Cox marginal regression model. The clustered nature of the matched design was taken into account. Non-simultaneous censoring was applied.

**Results:** 897 patient triplets were matched. ARR (95% CI) for BRACETD to natalizumab was 0.21 (0.19,0.23), to fingolimod was 0.30 (0.28, 0.33) and within BRACETD was 0.33 (0.31,0.36). There was a statistical significant reduction for natalizumab in ARR (RR = 0.64; 95% CI 0.57,0.72; p= 0.001) and no evidence for difference for fingolimod (RR = 0.91; 95% CI 0.81,0.1; p=0.133). No evidence for a difference in CDP6M was observed however a statistical significant increase on CDR6M was seen for switching to natalizumab (HR = 1.67,95% CI 1.30,2.15;p< 0.001) and an almost statistical significant increase for fingolimod (HR = 1.30; 95% CI 0.99,1.72; p=0.058).

**Conclusion:** This novel triple propensity matched analysis suggests that patients experiencing disease activity on BRACETD clearly benefit from therapy escalation to natalizumab as compared to switching among BRACETD. The benefit was less marked for the therapy escalation to fingolimod.

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Tomas Kalincik: Served on an advisory scientific board from Merck-Serono, has received conference travel support and speaker honoraria from Novartis, Biogen, Sanofi-Aventis, Genzyme,
Efficacy of siponimod on disability progression in SPMS patients with and without on-study relapses

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Background: In EXPAND, a randomised, double-blind, parallel-group, placebo-controlled, variable-treatment duration study in patients with secondary progressive multiple sclerosis (SPMS), siponimod reduced the risk of 3-month (3m) and 6-month (6m) confirmed disability progression (CDP) by 21% (p = 0.013) and 26% (p = 0.006), respectively. Siponimod also reduced the annualised relapse rate by 55.5%. However, on-study relapses (OSRs) may impact CDP results. Analyses for the subgroups of non-relapsing (n=1430) and relapsing (n=215) patients classified by occurrence of OSR favoured siponimod over placebo for 3mCDP and 6mCDP. However, subgroup analyses based on on-study findings may be confounded since the allocation to such subgroups may be affected by treatment effects.

Objective: To investigate the impact of OSRs on CDP in patients with SPMS receiving siponimod.

Methods: Impact of OSR on CDP was explored by an exploratory multi-state time-to-event model. In the model all patients start in a Baseline state. From there CDP may be reached without prior OSR, (1) transitioning from Baseline to CDP without prior OSR, (2) transitioning from Baseline to OSR without prior CDP, and (3) transitioning to CDP following OSR.

Results: Annualised transition rates (number of transitions divided by number of patient-years of follow-up for the respective transition) were calculated. The transition rate to 3mCDP without prior OSR was 0.20 for placebo and 0.17 for siponimod patients. For transition from Baseline to OSR state, the rates were 0.14 for placebo and 0.07 for siponimod patients. For transition from OSR to 3mCDP in these relapsing patients, rates of 0.74 for placebo and of 0.48 for siponimod patients were found. Similar results were observed for 6mCDP. Based on the model, siponimod reduced the risk of 3mCDP and 6mCDP in patients with OSR by 31% and 19%, respectively, and by 13% and 22% in patients without OSR, respectively. The risk reduction for 6mCDP in patients without OSR reached nominal statistical significance (HR 0.78 [95%CI (0.61; 0.98)]).

Conclusions: The exploratory multi-state model indicates that siponimod reduces the risk of CDP independently from OSRs. For both, 3mCDP and 6mCDP, HRs for CDP without prior OSR favoured siponimod over placebo.

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Background: Treatment options in primary progressive multiple sclerosis (PPMS) are scarce and, with the exception of ocrelizumab, anti-inflammatory agents have failed to show efficacy in ameliorating disability progression in randomized controlled trials. Still, such drugs are currently used to treat PPMS in clinical practice.

Objective: Our aim was to investigate a potential effect of anti-inflammatory disease modifying treatment on short-term disability outcomes in PPMS.

Methods: Using MSBase, a large, international, observational, prospectively acquired database, we identified patients with PPMS that were either never treated or treated with one of the following drugs: Interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, mitoxantrone, or rituximab. Propensity score matching was used to select subpopulations with comparable baseline characteristics. Disability outcomes were compared with an intention-to-treat and an as-treated approach in paired, pairwise-censored analyses, adjusted for visit density. Several sensitivity analyses were performed.

Results: Of the 1419 included patients, 546 were matched (treated, n=173; untreated n=373). Median on-study pairwise-censored follow-up was 3.0 years (quartiles 1.9–4.7) for the treated and 2.8 years (1.8–3.8) for the untreated patients. Most patients were treated with interferon beta (51%), followed by mitoxantrone (18%), glatiramer acetate (16%), fingolimod (9%), natalizumab (4%), rituximab (2%), and teriflunomide (< 1%). No difference in the risk of experiencing 3-month confirmed disability progression events was observed between the groups (HR [hazard ratio] 0.9, 95%CI [confidence interval] 0.5–1.7, p=0.79) in the intention-to-treat analysis. We also did not find significant differences in the risk of reaching a confirmed Expanded Disability Status Scale step ≥7 (HR 1.3, 95%CI 0.7–2.4, p=0.41) or confirmed disability reduction (HR 1.0, 95%CI 0.6–1.6, p=0.98). The as-treated analysis and sensitivity analyses confirmed the results of the primary analysis.

Conclusion: Our pooled analysis of the currently available disease modifying agents suggests that, on average, these therapies have no substantial effect on short-term disability outcomes in PPMS. However, separate evaluations of the newer, potentially more effective disease modifying drugs in PPMS are needed.

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Dr. Duquette has served on editorial boards and has been supported to attend meetings by EMDSerono, Biogen-Idec, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen-Idec, Novartis, and Genzyme.

Dr. Girard has received speaker honoraria and has been on advisory board for Novartis, Biogen Idec, Teva Neuroscience, EMD Serono and Genzyme. He has received research grant from CIHR and the MS Society of Canada.

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Dr. Grammond is a Novartis, Teva-neuroscience, Biogen Idec and Genzyme advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis.

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Dr. Pucci served on scientific advisory boards for Genzyme, Merck-Serono and Biogen-Idec; he received honoraria and/or congress and travel/accommodation expense compensations from Sanoﬁ Aventis, Novartis, Biogen-Idec, Merck-Serono, Genzyme, Teva and Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche.

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Dr. Van Pesch has received travel grants from Biogen, Bayer Scherling, Genzyme, Merck, Teva and Novartis Pharma. His institution receives honoraria for consultancy and lectures from Biogen, Bayer Scherling, Genzyme, Merck, Roche, Teva and Novartis Pharma as well as research grants from Novartis Pharma and Bayer Scherling.

Dr. Butzkueven has served on scientific advisory boards for Biogen Idec, Novartis and Sanoﬁ-Aventis and has received conference travel support from Novartis, Biogen Idec and Sanoﬁ Aventis. He serves on steering committees for trials conducted by Biogen Idec and Novartis, and has received research support from Merck Serono, Novartis and Biogen Idec.

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Dr. Kalincik served on scientific advisory boards for Roche, Genzyme-Sanoﬁ, Novartis, Merck and Biogen, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanoﬁ, Teva, BioCSL and Merck and has received research support from Biogen.

P784

Contribution of inflammation to disability accrual in primary progressive multiple sclerosis


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**Background:** Primary progressive multiple sclerosis (MS) may present with or without superimposed relapses. The role these relapses play in disability accumulation remains contested.

**Objective:** To examine the effect of superimposed relapses in progressive-onset MS on disease outcomes.

**Methods:** 1427 patients with progressive-onset MS from MSBase, an international prospective cohort, were analyzed. Inclusion criteria consisted of primary progressive MS (with or without relapses), adult-onset disease, at least three visits with Expanded Disability Status Scale (EDSS) recorded, first and last visit a minimum of 3 months apart and availability of minimum dataset. Multivariable regression models were used to compare effect of superimposed relapses on cumulative hazard of 3-month confirmed EDSS progression events and EDSS score 4, 6 and 8. Three sensitivity analyses for data from high quality centres, 12-month relapse-free EDSS progression and exclusion of bout-onset progressive MS were performed.

**Results:** 1427 eligible patients were identified for the analysis of the cumulative hazard of confirmed EDSS progression events. Progressive onset patients with recorded relapses were younger at disease onset (median 39 vs. 43 years) and baseline visit (median 46 vs. 51 years), and demonstrated a lower baseline EDSS (median 4.0 vs. 4.5 years) compared to those without relapses, respectively. The likelihood of confirmed disability progression was lower in patients with superimposed relapses (HR: 0.83, p<0.01). In the cohort with active progressive MS, we observed an association between the proportion of the follow-up time spent on immunotherapy and the hazard of confirmed disability progression events (HR: 0.996, p=0.01). This association was not seen in the progressive MS without relapses (HR: 1.00, p=0.21). Three subcohorts were analyzed for cumulative hazard of EDSS 4 (n=504), 6 (n=965) and 8 (n=1399). Likelihood of reaching EDSS 4 (HR: 0.78, p=0.07), 6 (HR: 0.81, p=0.07) and 8 (HR: 0.64, p=0.06) was not significantly associated with superimposed relapses.

**Conclusion:** In patients with primary progressive MS, superimposed relapses are associated with a lower risk of confirmed disability progression. This is most likely attributed to the preventative effect of immunotherapy on disability accrual in patients with active primary progressive disease. The findings of this study suggest that disease-activity is an important modifier of disability in primary progressive disease.

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Francois Grand Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals.

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Helmut Butzkueven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck, Novartis and Biogen.
Tomas Kalincik served on scientific advisory boards for Roche, Genzyme-Sanoﬁ, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanoﬁ, Teva, BioCSL and Merck and received research support from Biogen.

**P785**

**Safety and clinical improvement in a phase I trial of autologous Epstein-Barr virus-specific T-cell therapy in patients with progressive multiple sclerosis**

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**Background:** Increasing evidence indicates a role for Epstein-Barr virus (EBV) infection in the pathogenesis of multiple sclerosis (MS). EBV-infected autoreactive B cells might accumulate in the central nervous system because of defective cytotoxic CD8 T-cell immunity.

**Objective:** To determine the safety of treating progressive MS patients with autologous EBV-specific T-cells.

**Methods:** This 26 week phase I trial is designed to treat 5 patients with secondary progressive MS (SPMS) and 5 patients with primary progressive MS (PPMS) with autologous EBV-specific T cells targeting EBV nuclear antigen-1, latent membrane protein 1 (LMP1) and LMP2A. Four escalating doses are administered biweekly.

**Results:** To date (May 2017), 8 patients (5 SPMS and 3 PPMS) have received the full course of therapy, including one SPMS patient who had been treated 4 years earlier (compassionate use) and was treated on study owing to worsening symptoms after 3.5 years of sustained improvement. Five of these patients have experienced clinical improvements. Exploratory analyses suggest that clinical improvement correlates with the levels of EBV-specific reactivity and polyfunctionality (IFNγ/TNFα/IL2/CD107a expression) of the administered CD8 T cells. No significant adverse events have been observed. One treatment-related adverse event, transient grade 1 dysgeusia likely related to DMSO, was observed.

Of the first six patients, three experienced symptomatic and objective clinical improvement, commencing 2-8 weeks after the first infusion. Marked improvement occurred in one SPMS patient, with resolution of fatigue, increased manual dexterity, increased walking distance and improvement in lower limb tone, power, reflexes, sensation and coordination. A second SPMS patient had reduced fatigue, increased productivity and improved balance. A third patient (PPMS) had improved colour vision, visual acuity and manual dexterity and reduced fatigue, lower limb spasms and urinary urgency. The seventh (PPMS) and eight (SPMS) patients were most recently assessed at 6 weeks following their first T cell infusion and reported reduced fatigue and improved cognition. The ninth patient (PPMS) has so far received one T cell infusion.

**Conclusion:** Our findings, to date, of safety and clinical improvement set the stage for further clinical trials with autologous and allogeneic EBV-targeted T cell therapy in MS. Updated data for all 10 patients will be presented at the meeting.

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Rajiv Khanna serves as a consultant and Member of the Scientific Advisory Board of Atara Biotherapeutics and has received a licence fee payment and research funding from Atara Biotherapeutics; he is the Editor-in-Chief of *Clinical & Translational Immunology.*

**P786**

**Effect of MD1003 (High-Dose Biotin) for the treatment of progressive MS: 36-month follow-up data**

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Objective: MS-SPI was a 12-month (M) double-blind study where patients (pts; n=154) with non-active progressive multiple sclerosis (PMS) were randomised to MD1003 (n=103) or placebo (n=51). In the open-label extension phases, all pts received MD1003. Here, we present the 36M results (shown as MD1003>MD1003 [MM] vs placebo>MD1003 [PM]).

Methods: The extension phase included 133 pts (MM: 91; PM: 42). At M12, M24 and M36 we analysed: confirmed Expanded Disability Status Scale (EDSS) or timed 25-foot walk (TW25) improvement; mean EDSS change from baseline (mEDSS); TW25 evolution; and Clinician and Subject Global Impression of Change scale (CGI and SGI).

Results: EDSS or TW25 improvement was significantly higher for MM vs PM pts at M9 (13% vs 0%, P=0.05; confirmed at 3M); the trend was similar at M18 (13% vs 7%) and M30 (10% vs 2% both confirmed after 6M).

mEDSS slightly decreased in MM and worsened in PM pts at M12 (−0.03 vs 0.13; P=0.01). When all patients were treated with MD1003 after M12, mEDSS remained stable and there was no significant difference between groups (M24: 0.04 vs 0.15, P=0.13; M36: 0.09 vs 0.18, P=0.35). However, the 2 mEDSS evolution curves remained parallel suggesting that earlier treatment leads to a lower disability at M36.

The proportion of pts unable to complete TW25 (or with time >180 sec) increased in both groups before M12, with a trend for less increase in MD1003 treated pts (baseline: 1% vs 2%; M12: 6% vs 19%). This proportion remained quite stable in all pts in year 2 (M24: 13% vs 20%) and in MM patients in year 3, but increased again in PM pts in year 3 (M36: 13% vs 30%).

CGI and SGI results were significantly better in favour of the MD1003 group at M12 (CGI: 4.05 vs 4.62, P<0.0001; SGI: 4.27 vs 4.76, P=0.009). After M12, scores remained stable for MM pts and improved for PM pts, and the difference was no longer significant at M24 (CGI: 4.17 vs 4.21, P=0.93; SGI: 4.47 vs 4.41, P=0.75) or M36 (CGI: 4.11 vs 4.09, P=0.88; SGI: 4.11 vs 4.03, P=0.86).

At M36, adverse events were experienced by 67% vs 79% of pts in MM and PM groups.

Discussion: These results indicate that: MD1003 effects seem sustainable over time; disease progression halts when pts switch from placebo to MD1003; delayed treatment in PM pts results in higher disability over time; and MD1003 is well tolerated over 36M.

These data suggest that targeting neuronal metabolism in PMS might represent a new class of long-term disease-modifying therapy.

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P787

Effect of MD1003 (High-Dose Biotin) in spinal progressive multiple sclerosis (MS-SPI): subgroup analyses

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Objective: MS-SPI was a 12-month (M) double-blind, randomised, placebo-controlled study evaluating the effect of MD1003 on non-active progressive multiple sclerosis (PMS) patients (n=154), followed by an open-label extension phase where all patients received MD1003. The results indicated at 9 months a statistically significant 3 month confirmed improvement of patients in the MD1003 as compared to placebo, using the Expanded Disability Status Scale (EDSS) score. Here we present the results of subgroup analyses in the main phase of the study.

Methods: The global population (n=154) was split into the following subgroups of interest: EDSS score/fampridine use/PMS type/DMT use: 0.0866, 0.0304; PMS type: 0.0056, 0.0407; DMT use: 0.0098, 0.0407; concomitant use of fampridine (n=72) or not (n=82); primary progressive MS (PPMS; n=55) or secondary progressive MS (SPMS; n=99); concomitant use of disease-modifying therapy (DMT; n=61) or not (n=93); and undergoing new intensive physical therapy during the study (n=29) or not (n=125). Analyses of both observed and imputed data were performed on these covariates using van Elteren tests and mixed models. A forest plot analysis of the treatment’s effect in different subgroups using a mixed model has been performed.

Results: When adjusting for different baseline covariates, MD1003 effect is statistically significant for the whole population. The P-values for the change in EDSS from baseline to M12 in the intention-to-treat population (observed data, imputed data) were: EDSS score: 0.0181, 0.0604; fampridine use: 0.0083, 0.0304; PMS type: 0.0056, 0.0407; DMT use: 0.0098, 0.0407; undergoing physical therapy: 0.0092, 0.0390; mixed model analysis of EDSS score/fampridine use/PPMS type/DMT use: 0.0866, 0.0733; and mixed model analysis of MS type/DMT/physical therapy: 0.0438, 0.0345.

The forest plot analysis showed that whatever the subgroup studied the results systematically favoured the MD1003 over the
placebo group. Although the relatively small numbers of patients in some of the subgroups precluded statistical significance, the same trends were observed among all different subgroups. **Discussion:** There is no evidence that a specific subgroup did not benefit from MD1003 treatment in patients included in the MS-SPI trial.

**Disclosure**

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**Others**

**P788**

**A multicentre, randomized, double-blind, non-inferiority clinical trial to compare the clinical and radiological efficacy of 625 mg versus 1250 mg of oral methylprednisolone in patients with relapse of multiple sclerosis: the Oral-CORTEM trial**

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**Objectives:** To compare the clinical and radiological efficacy of two doses (1250mg/day vs 625mg/day) of oral methylprednisolone (oMP) given for three days for the treatment of acute relapse of multiple sclerosis (MS).

**Background:** MP is the mean treatment for acute relapse of MS. Our group have demonstrated that 1250mg oMP or intravenous MP have similar efficacy in clinical and radiological response after a relapse. High-dose corticosteroids have side effects short and long-term, so it is important to consider decreasing dose without affecting efficacy.

**Methods:** A non-inferiority, double-blind, clinical trial randomised 49 patients who had moderate to severe MS relapse in 9 different MS-specialized hospital units. The primary endpoint was the improvement in EDSS at 29 and 90 days, adjusted for baseline values. A predefined margin of non-inferiority of 1 point was applied. The main analysis was done in the per-protocol (PP) subset, imputing missing data with 90th percentile of EDSS. Pre-specified sensitivity analyses in both PP and intention to treat (ITT) subsets included: LOCF imputation, non-parametric approach and mixed models for repeated measurements. Secondary variables included results from imaging (MRI), safety and quality of life.

**Results:** Mean EDSS improvements [95CI%] at D29 were -0.78[-1.11;-0.46] and -1.21[-1.53;-0.88], and at D90 were -0.94[-1.32;-0.56] and -1.18[-1.55;-0.82] (n=22/23), for oMP-625 mg and oMP-1250mg, respectively; the differences between treatments were not significant and excluded differences equal or higher than the pre-specified delta (-0.42[-0.88;0.04]), thus concluding non-inferiority. All sensitivity analyses led to the same conclusion. The number of patients with more than 9 lesions at D29 injuries was 14 (70%) and 22 (96%) (p = 0.02), and contrast enhancement 10 (50%) vs 12 (52%) (p=0.99), respectively. Overall, Physical and Mental MUSIQoL-54 score comparisons were not statistically different (p=0.51, p=0.35, p=0.12). Both treatments were well tolerated and there were no serious related adverse events.

**Conclusions:** This study showed that oMP-625mg is non-inferior to the oMP-1250mg in the clinical and radiological response with a good profile for safety, and quality of life assessments.

**Disclosure**

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Other authors declare no conflicts of interest.

**P789**

**MS FIRST - utilising a longitudinal, prospective, comparative drug safety module for use in everyday MS clinical practice to evaluate and track incidence and characteristics of safety outcomes in MS patients on therapy over the long term**


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Objects: To compare the clinical and radiological efficacy of two doses (1250mg/day vs 625mg/day) of oral methylprednisolone (oMP) given for three days for the treatment of acute relapse of multiple sclerosis (MS).
Objective: MS FIRST is a prospective, longitudinal study, recruiting since 1st January 2012. The primary objective of this study is to track and compare the incidence of safety outcomes in MS patients who either receive DMD or who are on no treatment.

Methods: Rates of adverse events by treatment group including fingolimod (FINGO), natalizumab (NAT), interferon (IFN), glatiramer acetate (GA) or no treatment group were calculated as the number of events per 100 person-years of follow-up. The relative risk of SAE’s by treatment was estimated using a longitudinal Poisson regression model offset by DMD exposure time and clustered at the level of the individual patient, adjusting for age, sex and disease duration.

Results: As per 1st December 2016 there were 3360 patients enrolled contributing to a total of 6033.59 person-years of follow-up at a mean (SD) of 520.17 days per patient. A total of 1632 adverse events have been observed. A total of 87 immunosuppression related or severe infection events were observed with an incidence rate of 1.44 infections per 100 person-years of follow-up: 89 herpes zoster, 72 non-melanoma skin cancer (NMSC) and 66 malignancy events observed at an incidence rate of 1.48, 1.19 and 1.09 events per 100 person-years respectively. Compared to a No DMT MS control group, there was a increase in observed infection for NAT (RR 1.52) 0.0011 and FINGO (RR 1.87), p<0.001. There was an increased risk of NMSC in FINGO (RR 1.75, p<0.001). All other cancer rates were lower in NAT treated patients (RR 0.42, p<0.001) and tended lower in FINGO (RR 0.79, p=0.06). Herpes Zoster events were increased only in FINGO treated patients (RR 1.47, p<0.009) and reported significant medical conditions had a slightly lower rate of reports in NAT (0.47, p<0.001) and FINGO (RR 0.70, p<0.001) than untreated group.

Conclusions: The establishment of a large, prospective multi-drug safety module for use in routine practice has been successful to date in Australia. Long term monitoring in clinical practice could provide important insights into incidence and timing of treatment-associated SAE’s. This data will be updated for the ECTRIMS meeting.

Disclosure

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P790 Effect of early switch to fingolimod from other oral therapies in patients with relapsing-remitting multiple sclerosis

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Background: Patients with relapsing-remitting multiple sclerosis (RRMS) who switch between multiple disease-modifying therapies (DMTs) accumulate disease activity due to suboptimal treatment response, and become increasingly difficult to treat. Early disease control with high-efficacy DMTs may reduce disease burden in the short and long term.

Objective: To compare the effect of fingolimod in RRMS patients who switched from first-line oral DMTs (oDMTs) vs patients who switched directly from injectable DMTs (iDMTs) using data from two independent real-world observational studies, PASSAGE (USA and Europe) and PANGAEA 2.0 (Germany).

Methods: In the present analysis, patients were divided into two cohorts: patients who switched to fingolimod 0.5 mg from dimethyl fumarate or teriflunomide (oDMT cohort; PASSAGE N=157, PANGAEA 2.0 N=72) and those who received fingolimod as their first therapy or after iDMTs (iDMT cohort; PASSAGE N=3484, PANGAEA 2.0 N=270). The annualised relapse rate (ARR) was recorded at months (M)12 and 24.

Results: In the PASSAGE study, patients in the oDMT cohort had a higher ARR at baseline (BL; the year before the switch to fingolimod) vs the iDMT cohort (1.45 vs 1.15, p=0.0006). At M12, fingolimod treatment resulted in an overall ARR reduction to 0.30 in the oDMT cohort and 0.26 in the iDMT cohort that was constant at M24. When compared by their number of prior DMTs, patients whose first therapy was an oDMT had a higher ARR compared with those starting fingolimod as their first therapy (1.34 vs 1.02, p=non-significant). Increasingly higher ARR were observed in the oDMT cohort patients who had received two DMTs (ARR=1.47) or three DMTs (ARR=1.53). Fingolimod treatment reduced the ARR at M12 and 24. Similarly, in the PANGAEA 2.0 study, patients in the oDMT cohort had a higher BL ARR vs the iDMT cohort (1.59 vs 1.29, p=0.02). Although fingolimod treatment reduced the ARR at M12 in both cohorts, it was higher in the oDMT than in the iDMT cohort (0.19 vs 0.10, p=0.01). The BL ARR in the oDMT cohort increased with the number of failed DMTs prior to the fingolimod switch (two DMTs, 1.58; three DMTs, 1.86) and was reduced with fingolimod treatment at M12 (two DMTs, 0.18; three DMTs, 0.21).

Conclusions: Fingolimod treatment is an effective option to control disease activity in patients who switched from other oDMTs. Patients exposed to multiple oDMTs showed higher ARR. Early switch to fingolimod results in better relapse control within 1 year of initiation.

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Stanley Cohen has received speaking honoraria, served on steering committees or advisory boards and has received research support from Biogen, Novartis, SanofiGenzyme, Roche, Acorda, Opexa, MedDay and Mallinckrodt.

Diego Silva, Jennie Medin and Christian Cornelissen are employees of Novartis.

P791

The rapid efficacy of natalizumab vs fingolimod in patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a randomised, head-to-head phase 4 study


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Background: REVEAL was designed as a 1-year, multicentre, randomized, rater-blinded, prospective phase 4 study comparing natalizumab and fingolimod in patients with active relapsing-remitting multiple sclerosis (RRMS). Although the study closed early (for non-safety/ non-efficacy reasons), data permitted comparison of effects occurring shortly after treatment initiation.

Objective: To compare onset of efficacy with natalizumab and fingolimod in REVEAL.

Methods: Patients were assigned to open-label intravenous natalizumab 300 mg every 4 weeks (n=54) or oral fingolimod 0.5 mg once daily (n=54). Magnetic resonance imaging was scheduled every 4 weeks for the first 24 weeks and then at weeks 36 and 52; relapses and adverse events (AEs) were assessed at scheduled visits. Analyses included Kaplan-Meier and Cox regression for time to event; negative binomial regression for annualized relapse rate (ARR) and number of T1 gadolinium-enhancing (Gd+) lesions; and a negative binomial generalized estimating equation for cumulative Gd+ lesions over time.

Results: As expected for a randomized study, demographics, disease characteristics and follow-up time (median 39 weeks) were generally similar between groups. Natalizumab patients were less likely than fingolimod patients to develop new Gd+ lesions, with a cumulative probability of 40.68% vs 57.99% (hazard ratio [HR]=1.678 [95% confidence interval [CI]: 0.865-3.255]; P=0.1258) of developing ≥1 lesion and 11.54% vs 48.48% (HR=4.053 [95% CI: 1.474-11.144]; P=0.0067) of developing ≥2 lesions. The natalizumab group consistently had 63%-72% fewer Gd+ lesions, with between-group differences apparent within 4 weeks and reaching significance by week 16 (P=0.0251). ARR was 83% lower with natalizumab than with fingolimod (0.05 vs 0.29; P=0.0236), and cumulative probability of relapse was 1.85% weeks and reaching significance by week 16 (P=0.0006).
with natalizumab vs 22.28% with fingolimod (HR=12.184 [95% CI: 1.552-95.634]; P=0.0174). AEs were consistent with known safety profiles.

**Conclusions:** These results extend previous work showing that natalizumab has benefits soon after initiation, demonstrating that onset of reduced disease activity occurred more rapidly, and to a greater extent, with natalizumab than with fingolimod in patients with active RRMS. However, given early study closure, available data did not permit primary endpoint evaluation, so these results should be interpreted with caution.

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**Disclosure**

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DLA: has served on advisory boards for, received speaker honoraria from, served as a consultant for, or received research support from Bayer, Biogen, Coronado Biosciences, the Consortium of Multiple Sclerosis Centers, Eli Lilly, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, Merck Serono, MS Forum, NeuroRx Research, Novartis, Opexa Therapeutics, Roche, Teva, the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada, the S.A. Serono Symposia International Foundation; holds stock in NeuroRx Research.

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JGG: serves on the editorial boards of *Multiple Sclerosis Journal* and *Neurology*; has received speaker honoraria from Biogen, Genzyme, Merck Serono, Novartis, Teva; has received research support from Biogen; has served on the boards of the Dutch MS Research Foundation and the Progressive MS Alliance.

**P792**

Probiotic VSL3 induces changes in the gut microbiome function and promotes an anti-inflammatory peripheral immune response in multiple sclerosis patients

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**Background:** The gut microbiome plays an important role in autoimmunity including multiple sclerosis (MS). Probiotics represent an oral, non-toxic immunomodulatory agents that could be used in combination with current MS therapy.

**Methods:** Relapsing remitting MS subjects on glatiramer acetate (N=7), or untreated (N=2) and healthy controls (N=13) were orally administered VSL3 twice daily (total 3,600 billion CFU/day) for two months. Stool specimens were collected prior to, at discontinuation of therapy and 3 months thereafter. Frozen peripheral blood mononuclear cells (PBMCs) were used for immune cells profiling and immune genes expression profiling in monocytes by Nanostring. Stool samples were used for 16S profiling by Illumina MiSeq and stool metabolomics profiling.

**Results:** VSL3 administration was associated with increased abundance of many taxa including streptococcus species in both groups. Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) analysis revealed decreased in many pathways following VSL3 administration in both groups. Stool metabolomics profiling revealed changes in the concentration of several stool metabolites following VSL3 administration in both groups. At the immune level, VSL3 administration was associated with decreased frequency of intermediate monocytes (9.07% vs 7.58%, p=0.039) as well as decreased HLA-DR mean fluorescence intensity (MFI) on dendritic cells (1890 vs 1510, p=0.0156) in MS patients and decreased CD80 MFI on monocytes (88 vs 80.6, p=0.035) in controls. Following discontinuation of VSL3, increased frequency of pro-inflammatory monocytes (4.68% vs 7.08%, p=0.039) and decreased frequency of IL-10 T regulatory cells (2.25% vs 1.63%, p=0.0269) were observed in controls. We noted decreased latency-associated peptide (LAP) MFI on PBMCs (65.9 vs 52.2, p=0.0156) in MS patients and decreased expression of pro-inflammatory genes HLA.DQA1 (479.4 vs 391.6, p=0.0117) and IL6ST (423.1 vs 365.3, p=0.0039) in monocytes following VSL3 administration in controls. We observed increased expression of anti-inflammatory genes IL-10RA (479.4 vs 391.6, p=0.0117) and IL6ST (423.1 vs 365.3, p=0.0039) in monocytes following VSL3 administration in MS patients.

**Conclusion:** VSL3 administration induces changes in the gut microbiota composition and function that are associated with an anti-inflammatory peripheral immune response in healthy controls and MS patients.

**Disclosure**

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TG1101-RMS201 is a 52-week, phase 2, placebo-controlled, multicenter study of ublituximab (UTX), a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis.

Patient characteristics, safety, and preliminary results of a placebo controlled, phase 2a multicenter study of ublituximab (UTX), a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis

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Objective: To assess the safety, B cell depletion dynamics, and clinical efficacy of UTX in patients with RMS.

Background: UTX is a novel mAb targeting a unique epitope on the CD20 antigen and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, demonstrating greater antibody-dependent cellular cytotoxicity activity (ADCC) than rituximab. UTX has demonstrated robust efficacy and favorable safety profile in multiple phase 3 trials for treatment of hematologic malignancies. The enhanced ADCC potency of RTX may offer a benefit over currently available anti-CD20s in terms of lower doses and shorter infusion times.

Design: TG1101-RMS201 is a 52-week, phase 2, placebo-controlled, multicenter study that is designed to assess the optimal dose and infusion time as well as safety/tolerability of UTX in RMS subjects. Subjects are randomized to UTX or Placebo for 28 days, encompassing the first two infusions on Day 1 and Day 15. Subjects initially randomized to placebo are subsequently given UTX after the 28-day observational period and followed for 52 weeks. Optimal dosing is determined by B cell depletion, defined as percentage of CD19⁺ B cells present following UTX administration, and assessed at multiple timepoints throughout the treatment period. Radiological and clinical analyses are also performed.

Results: To date, B cell data from 16 subjects have been analyzed up to Week 24 of the 52-week study, encompassing two infusions of UTX. At Week 4, median B cell depletion was 99% from baseline in UTX treated subjects and maintained to Week 24. No relapses have been reported in any subjects during the first 24 weeks (83% of subjects had ≥1 relapse in the year prior to screening). Mean EDSS at baseline was 2.7 (±1.3) and at Week 24 the Mean EDSS was 1.9 (±1.5) with a change of -0.8. No Gd lesions were found in any patients at Week 24. No SAEs or clinically significant lab abnormalities have been observed. Most commonly reported AEs were infusion related reactions (IRR; Grade ≤2). Faster infusion times, as low as 1 hour for 450mg UTX, did not result in an increased frequency of IRRs.

Conclusions: Ublituximab, a novel glycoengineered anti-CD20 antibody demonstrates rapid and robust B cell depletion, a profound reduction in Gd enhancing lesions, with clinical stability observed at week 24. Unlike other IV administered anti-CD20s, UTX has been delivered in shorter infusions, providing a potential convenience benefit for future patients.

Disclosure
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9. Wendy Su, PhD is employed by TG Therapeutics, Inc
P794
Variability in adverse event reporting and reasons for discontinuations with dimethyl fumarate: results from a generalized linear mixed model
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Background: Adverse event (AE) reporting and associated treatment discontinuations are often analysed in terms of patients’ characteristics. The impact of clinical site variability on AE reporting and treatment discontinuations is generally underestimated. The assessment of both patient- and site-level variability is crucial to a better understanding of AE reporting and discontinuation.

Objectives: To assess the unique contributions of patients’ baseline characteristics (case mix) and clinical site variability in the occurrence of overall and GI tolerability-related AEs, and AE-related treatment discontinuation in dimethyl fumarate (DMF) clinical trials using generalized linear mixed models (GLMMs).

Methods: Pooled DEFINE and CONFIRM clinical trial data (n=2300) were used to model overall and gastro-intestinal (GI) tolerability-related AEs and related GI-AE discontinuation. Baseline predictors were age, sex, MS duration, ethnicity, smoking, alcohol consumption, BMI, prior treatment, number of prior relapses, EDSS, MSFC-4, SF-36 PCS and MCS. GLMMs were used to determine patient-level predictors and assess the variability and site-level correlation between endpoints. Residual intra-class correlation coefficients (ICC) captured the proportion of variability still attributable to sites.

Results: AEs and discontinuation were poorly predicted by patients’ case mix. Site-level variability was present for both endpoints after adjusting for case mix (ICC 0.29 and 0.09). Higher GI-related AE risk was predicted by female sex, smoking, alcohol use and MSFC-4, while discontinuation from GI-related AEs was predicted by female sex and smoking. Case mix adjusted percentages (DMF vs. placebo) were 42.3 vs. 31.7 for GI-related AEs, and 1.8 vs. 0.2 (both p< 0.0001) for discontinuation due to GI-related AEs. Site-level variability was present for both these endpoints after case mix adjustment (ICC 0.12 and 0.20). Site-level residual correlations between endpoints were 0.54 for overall AEs and discontinuation, and 0.71 for GI-related AEs and discontinuation due to GI-related AEs.

Conclusions: GLMMs are a modelling tool suitable to benchmark variability and correlation between adverse events and discontinuation in MS. After adjusting for case mix, residual site level heterogeneity indicated significant variation of AEs and discontinuation by site. Site characteristics should be explored to better understand their influence on AE reporting and treatment discontinuation.

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P795
Overcoming therapeutic inertia in multiple sclerosis care: a pilot randomized trial evaluating an educational intervention
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Introduction: Therapeutic inertia (TI) is a common phenomenon in multiple sclerosis (MS) care defined as the lack of treatment escalation despite evidence of disease progression. The consequences of TI include poorer patient’s outcomes and diminished quality of life.

Objective: To evaluate the feasibility of an educational intervention (traffic light system - TLS) designed to overcome TI among neurologists managing MS patients.

Design: A pilot, double-blind, randomized study. Neurologists were assigned to receive the educational intervention (n=11) or standard of care (n=14). Participants answered questions regarding the management of 20 simulated case-scenarios commonly encountered in clinical practice. The intervention consisted of introducing the TLS to help participants identify patients at high-risk of progression. TI was defined according to best practice guidelines based on clinical/radiological activity to escalate therapy. Primary outcome (feasibility): completion rate and the proportion of participants who correctly identified the traffic light (red for high-risk, yellow for moderate-risk) according to the simulated case-scenarios.

Results: TI was present in 72.0% of participants in at least one case scenario. There were no significant differences between groups at baseline (responses with TI in the interventional group 23.9% vs. 26.8% in the control group; p=0.74) (Figure). The completion rate of the study was 100% (25/25 participants). Overall, 77.4% of participants correctly identified the ‘red traffic light’ for clinical-scenarios with high-risk of disease progression. Similarly, 86.4% of participants correctly identified the ‘yellow traffic light’ for cases that would require a reassessment within 6-to-12 months. We found a 43% trend of reduction in odds of TI in the interventional group compared to controls (22.6% vs. 33.9%; OR 0.57; 95%CI 0.26-1.22).

Conclusions: TI is a common phenomenon in MS care affecting 7 out of 10 neurologists. TLS is a feasible educational intervention

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that when applied to neurologists may help overcome TI and improve MS outcomes.

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P796
Siponimod pharmacokinetics, safety and tolerability in combination with the CYP2C9/3A4 inducer, rifampin in healthy subjects
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Background: Siponimod, a modulator of sphingosine 1-phosphate receptor subtypes 1 and 5 (S1P 1,5) is primarily metabolised in the liver by CYP2C9 and CYP3A4. Rifampin is one of the most potent inducers of CYP2C9/3A4 enzymes. This study evaluated the effect of a simultaneous induction of both metabolising enzymes on siponimod pharmacokinetics (PK) to support the development of clinical recommendations for siponimod co-administration with CYP2C9/3A4 inducers.
Objective: To investigate the PK, safety and tolerability of multiple doses of siponimod 2mg od and its selected metabolites (M3 and M5) when administered with or without rifampin in healthy subjects.
Methods: This was a confirmatory, open-label, multiple-dose, two-period study in healthy subjects aged 18-45 years. In Period 1 (Days 1-12), siponimod alone was administered orally in multiple doses, up titrated from 0.25 to 2mg over 6 days and 2mg od from Days 6-12. In Period 2 (Days 13-24), siponimod 2mg od was co-administered with rifampin 600mg od. Primary assessments included PK of siponimod (Days 12 and 24; Cmax,ss, Tmax,ss, AUCtau,ss) and selected metabolites (M3 and M5). Data are presented as geometric mean, except Tmax,ss as median (range). Key secondary assessments included PK of M3 (glucuronidation) and M5 (hydroxylation) metabolites and safety/tolerability of siponimod. Change in absolute lymphocyte count (ANC) was also measured.
Results: Of the 16 subjects enrolled, 15 completed the study. Mean±SD age was 31±8.3 years; 94% were men. When siponimod was administered alone, Cmax,ss of 28.6 ng/mL was achieved in 4h (Tmax,ss range 1.5-8) and AUCtau,ss was 546 h*ng/mL. When co-administered with rifampin, Cmax,ss and AUCtau,ss decreased to 15.7 ng/mL and 235 h*ng/mL, respectively. Tmax,ss remained the same (4h). In the presence of rifampin, Cmax,ss of M3 increased (53%), while AUCtau,ss showed minor change; the Cmax,ss of M5 remained the same, while AUCtau,ss decreased (37%). Siponimod mean trough levels in Period 2 suggest the maximum induction conditions by Day 24. No severe or serious adverse events (AEs) were reported. Higher incidence of AEs was reported in Period 2 (86.7%) vs Period 1 (50%). Mean ALC slightly increased in rifampin’s presence but remained below 1.0×109/L. Conclusions: Siponimod Cmax,ss and AUCtau,ss decreased by 45% and 57%, respectively, in rifampin’s presence. Despite significant reduction in siponimod exposure, rifampin or any other potent CYP2C9/3A4 inducer can be co-administered with siponimod for a short period (up to 1 month).

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P797
No evidence of disease activity status among patients with relapsing-remitting multiple sclerosis on long-term natalizumab treatment: data from a real-world cohort in the Czech Republic
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Background: No Evidence of Disease Activity (NEDA) is a composite assessment of disease activity that may be used to define treatment goals in MS; however, long-term NEDA outcomes are still needed. Natalizumab is efficacious in improving clinical, MRI, and NEDA outcomes in relapsing-remitting MS (RRMS) patients, but reports of combined long-term clinical and MRI outcomes as measured by NEDA in real-world cohorts are limited.
Objective: To investigate long-term natalizumab effects on clinical and MRI outcomes as measured by NEDA in a single-center cohort of RRMS patients from a retrospective real-world study.
Methods: Patients were continuously treated with natalizumab for ≥24 months and were assessed regularly for clinical and MRI outcomes (NEDA-3=no new/enlarging fluid-attenuated inversion-recovery [FLAIR] lesions, no relapses, and no 6-month confirmed Expanded Disability Status Scale [EDSS] progression); clinical NEDA=no relapses and no 6-month confirmed EDSS progression.

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Results: Patients (N=193) had a median natalizumab exposure of 2.95 (range 1.18-6.72) years, with 92% having received a prior disease-modifying therapy. At natalizumab initiation, patients had a mean of 1.8 (SD 0.95) relapses in the past 12 months and a median EDSS score of 3.5 (range 1.0-6.5). NEDA-3 was achieved by 52.2% (n=186; 95% CI 44.7-59.5) of patients at year 0-1; by 69.2% (n=172; 95% CI 61.7-76) at year 1-2; 75.2% (n=105; 95% CI 65.9-83.1) at year 2-3; 70.3% (n=64; 95% CI 57.6-81.1) at year 3-4; and 87.5% (n=32; 95% CI 71-96.5) at year 4-5. Clinical NEDA was achieved by 67.7% (95% CI 60.5-74.4) of patients at year 0-1; 70.9% (63.5-77.6) at year 1-2; 75.2% (65.9-83.1) at year 2-3; 71.9% (59.2-82.4) at year 3-4; and 87.5% (71-96.5) at year 4-5. Sensitivity analyses with 3-year completers demonstrated similar effects. A full analysis of NEDA-3 and the relationship between percentage of brain volume change and NEDA will be presented.

Conclusion: In this pretreated RRMS patient cohort, the percentages of natalizumab-treated patients who achieved annual NEDA-3 are consistent with 2-year results from controlled clinical trials and demonstrate that NEDA rates remain high for patients treated with natalizumab for >2 years in a real-world setting. These findings are limited by natalizumab discontinuation, which was primarily due to safety concerns.

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Objective: To examine the effect of ublituximab (UTX) on the development of new Gd-enhancing lesions and new or enlarging T2 lesions at 24 weeks in subjects with relapsing multiple sclerosis (RMS).

Background: Focal inflammatory lesions are responsible for the occurrence of relapses in MS, and demyelinating axons are more susceptible to neurodegeneration, which, in turn, leads to irreversible disability. Patients with RMS have shown significant reduction in MRI and clinical disease activity after B cell depletion with an anti-CD20 antibody. UTX is a novel, chimeric mAb which targets a unique epitope on the CD20 antigen and has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, demonstrating greater antibody-dependent cytotoxicity activity (ADCC) than rituximab.

Methods: TG1101-RMS201 is a 52-week, phase 2, placebo-controlled, multicenter study that is designed to assess the optimal dose and infusion time as well as safety/tolerability of UTX in RMS subjects. Laboratory, clinical and MR analyses are also performed. Number of total/new Gd-enhancing lesions and total/new or enlarging T2 lesions are evaluated on brain MR scans performed at baseline, 24 and 48 weeks. Change of T2 lesion volume over time is also calculated.

Results: To date, MRI data from 16 subjects have been analyzed up to week 24 of the 52-week study, encompassing two infusions of UTX. No SAEs have been reported, including subjects receiving rapid UTX infusions. At baseline, the 38 enrolled patients showed a total number of 104 Gd-enhancing T1 lesions (mean 7, SD 5) and a total T2 lesion volume of 16.1 ± 21.8 mL. 16/38 enrolled patients (42%) completed 24 weeks of the study. In this subgroup, at baseline, total number of Gd-enhancing T1 lesions was 51 (mean 3, SD 4) while T2 lesion volume was 19.2 ± 26.3 mL. At week 24, total number of Gd-enhancing T1 lesion was 0, with a 100% decrease compared to baseline (95% CI 1-5, p = 0.004); the number of new or enlarging T2 lesion was 5 (mean 0.3, SD 0.5) and T2 lesion volume showed a 6% decrease compared to baseline (95% CI 0.3-2, p = 0.01). [Additional analysis including placebo patients will be reported at the conference.]

Conclusions: Ublituximab is well tolerated and this preliminary data shows high efficacy in reducing MRI activity at 24 week. Unlike other anti-CD20s, ublituximab can be delivered in shorter infusions, providing a convenience benefit for patients.

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P799
Treatment of neuromyelitis optica spectrum disorders with methotrexate: experience of a specialist center in Brazil
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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) is a recurrent autoimmune inflammatory disease which lead to early disability mainly caused by severity of relapses. The cornerstone of relapse prevention is immunosuppression and the most commonly prescribed include azathioprine, rituximab and mycophenolate mofetil. Adverse events, failure with first-line medications and financial restrictions may prompt the use of methotrexate (MTX), although there are only few reports so far.

Objective: To review our experience using MTX as long-term therapy in NMOSD, evaluating effectiveness and tolerability of MTX in patients with NMOSD aquaporin-4 antibody (AQP4-IgG) seropositive.

Material and Methods: We retrospectively assessed data of 167 NMOSD AQP4-IgG positive (CBA method) seropositive.

Background and Methods: There was no report of MTX inter-rupt due to adverse events.

Results: 10 met inclusion criteria, 6 were female and median age of onset was 39y (range 22-61). Median treatment duration was 19 months (range 7-120 months), with a median dose of 10mg/week (range: 10-20 Mg/week). In 8 patients MTX was initiated following adverse events or failure with azathioprine; in 1 it was introduced due to stability of the disease and prolonged use of azathioprine; in 1 it was the first choice. 80% of the patients were relapse-free and 90% had EDSS stability. 1 patients failed with MTX, switching to rituximab. There was no report of MTX interruption due to adverse events.

Conclusion: MTX maintained stability in most patients and was well tolerated in our sample. We believe that MTX is a reasonable choice in patients who had adverse events with azathioprine, considering the context of restricted financial resources.

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P800
Pilot results of a web-based patient decision aid for first-line treatment of relapsing-remitting multiple sclerosis patients
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Background: Most patients with relapsing-remitting multiple sclerosis (RRMS) wish to be actively involved in their care (1). With the emergence of new disease-modifying therapies (DMTs), treatment decision-making is increasingly complex. Patient decision aids (PDAs) can help match therapies with individuals’ characteristics and values, potentially facilitating treatment decision-making (2).

Objective: To assess the usability and usefulness of a prototype web-based PDA for first-line therapies in patients with RRMS.

Design: The PtDA was developed following international standards and consisted of
1) background information about RRMS and available first-line DMTs;
2) interactive questions based on 6 issues previously identified as influencing decision-making (3) used to clarify patients’ characteristics and treatment preferences;
3) a knowledge quiz and 1 page summary. Treatment naïve patients in the process of initiating a first-line DMT were recruited from the local MS clinic. After trialing the PtDA, they completed the System Usability Scale (SUS) (4) and the Preparation for Decision Making scale (5) to determine overall usability and preparation.

Results: 18 RRMS patients participated in the usability testing. For the PrepDM scale: overall, 76% of patients affirmed the
PtDA “greatly” or “quite” helped their decision-making process with nearly all patients suggesting it increased their desire for involvement and awareness of the importance of their personal preferences. Perceived benefit on the understanding of each treatment option was also high (89%). Moreover, 70% felt “greatly” or “quite” better prepared to discuss treatment options with their care provider. 89% considered the information they got from the PtDA was consistent with previous discussions involving healthcare professionals. In terms of usability, the majority (78%) stated they would like to use the PtDA frequently and 94% found it was easy to use. The mean SUS score was 80.6 [range 50-100].

Conclusions: The results suggest our web based PtDA is promising, usable and useful in preparing and engaging RRMS patients in treatment decision-making.

2. Stacey et al. Cochrane database of systematic reviews. 2017

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P801
U.S. payers’ views on expansion of patient access to disease-modifying therapies (DMTs) for multiple sclerosis
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Background: In the U.S., pharmacists and physicians in payer organizations play pivotal roles in making formulary decisions about DMTs for MS. However, patient access to the full range of DMTs is limited.

Objective: To assess the extent to which payer organizations provide access to the full range of MS DMTs and to identify MS-related practice barriers and education needs and outcomes among U.S. pharmacist and physician payers.

Methods: Surveys were administered to pharmacist and physician payers (n = 657) before and after they participated in 3 accredited continuing education (CE) programs: a symposium at a national conference and 2 national webinars. Held between 9/3/2016 and 4/5/2017, the CE programs focused on MS pathophysiology, DMT mechanisms of action, and recent research and clinical trial evidence on B-cell-targeted DMTs for relapsing and progressive MS. The survey items assessed knowledge, barriers, and competence in these areas. The impact of the CE program was assessed by comparing pre- and post-education response frequencies to survey items.

Results: On the pre-education survey, only 23% of participants reported that their payer organizations strongly facilitated patient access to the full range of approved DMTs for MS. Participants reported that, other than costs, their main challenges in MS patient management were lack of established guidelines (50%) and uncertainty about when to initiate and switch DMTs (36%). Only 12% of participants indicated a good or excellent understanding of the roles of B- and T-cells in MS pathogenesis. There were significant pre- to post-education increases in the proportions of participants who anticipated that the education would promote greater patient access to DMTs (+20%, p< .001); understood the roles of B-cells and T-cells in MS pathogenesis (+22%, p<.001); correctly identified relationships between CD20 and B-cell subsets (+18%, p< .001); and would recommended switching DMTs for patients with disability progression by EDSS (+19%, p<.001), lesion progression by MRI (+14%, p<.001), or to improve tolerability (+14%, p<.001) and adherence (+12%, p<.001).

Conclusion: Among U.S. payers, participation in a series of CE programs enhanced intentions to expand patient access to MS DMTs and improved understanding of MS pathophysiology and competence in decision-making regarding treatment for relapsing and progressive disease.

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Treatment of specific symptoms

P802
The effect of fampridine treatment on cognition: two year prospective study
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Multiple sclerosis (MS) is a degenerative disease that results in impairments in multiple domains including cognition. Fampridine has been approved to improve walking in persons with MS.
(PwMS). It is plausible that Fampridine could improve cognition through the same mechanisms. We aim to examine effects of Fampridine treatment on cognitive function in two years period. The patients included in this multi-centre, examiner-blinded, and prospective study were the adults with MS who initiated fampridine treatment at the MS clinic of Dokuz Eylül University Hospital. They were followed up at three centres in Turkey. Patients with Expanded Disability Status Scale (EDSS) scores between 4 and 7 enrolled in the study. To maintain treatment blinding, we used the two-physician principle: a treating neurologist was responsible for overall care of the patient; and an evaluating neurologist assessed patients at scheduled visits and performed cognitive tests, but was not otherwise involved in patient care. Neurological evaluations and cognitive tests were performed at baseline, at the end of the third month, sixth month and then every six months for 2 years. Age, sex and education-matched healthy control people were also evaluated cognitively at the same scheduled visits. For cognitive evaluation The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery, which included the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-2 (CVLT-2) and the Brief Visuospatial Memory Test-Revised (BVMT-R) used. A total of 148 patient (106 female, mean age: 43.4±9.1) and 79 healthy control (51 female, mean age: 41.8±7.5) included in the study. SDMT score improved at month 3 vs baseline (38.1 vs. 40.7, p= 0.007. BVMT-R score also improved at month 3 (18.3 vs. 21.9, p=0.008). CVLT2 improved from 40.4 to 42.1, p=0.031). 59 patients (39.9%) were found to be cognitively impaired at study entry on the basis of SDMT under -2 SD. At follow-up 45 patients were cognitively impaired (p=0.008). Number of cognitively impaired patients decreased from 61 to 43 on the basis of CVLT, and 64 to 51 on the basis of BVMT at month 3. Patients were stable at month 6, month 12, month 18, and month 24. There was no difference between baseline and 24th month in terms of cognitive functions in healthy controls. The results of this study have indicated that fampridine treatment could improve cognitive functions and improvement could be stable up to two years in PwMS.

Discussion

Serkan Ozakbas: nothing to disclose
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P803 Efficacy of an internet-based program (MS Intakt) to promote physical activity after inpatient rehabilitation in persons with multiple sclerosis - a randomized controlled study

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Background: Multimodal rehabilitation improves symptoms in persons with multiple sclerosis (PwMS), but these effects diminish with time, despite the well-known positive impact of exercise on fatigue and mobility.

Objective: We evaluated the efficacy of a 3-month, internet-based program (MS Intakt) on fatigue and mobility in PwMS after inpatient rehabilitation.

Methods: PwMS admitted to inpatient rehabilitation, age > 18 years, EDSS ≤ 6.0, fatigue (WEIMuS score ≥ 32) and willingness to participate were randomized into the intervention (IG) and control (CG) group. The IG underwent a 3-month home training program that was supervised via internet by sport therapists directly after rehabilitation, whereas the CG received usual care alone. The primary outcome was fatigue after 3 months (WEIMuS questionnaire). Secondary outcomes were quality of life (MSIS-29, EQ-5d), mobility (EDSS, 2min walking test, 10m walking test, Tinetti score), neuropsychological parameters (TAP alertness, TAP executive control) and questionnaires for physical activity. Measurements were done within the first week (T0) and at the end of rehabilitation (T1), at follow-up after 3 months (T2), and via mail after 6 months (T3). In addition, an economic evaluation was performed in both groups.

Results: 84 PwMS were included (41 IG, 43 CG), of whom 64 completed the study (33 IG, 64 % female, mean age 48.0 ± 6.5 yrs, disease duration 10.5 ± 4.7 yrs, median EDSS 4.5; 31 CG, 58 % female, age 45.8 ± 10.4 yrs, disease duration 9.1 ± 5.8 yrs, EDSS 4.0). At baseline, median WEIMuS scores were higher (indicating a higher degree of fatigue) in IG than in CG, but decreased similarly at T1 in both groups (IG: 45 vs. 31; CG: 39 vs. 26). However, WEIMuS scores increased in CG to 36 at T2 and remained there at T3, whereas in IG, fatigue further improved at 3 and 6 months (WEIMuS 29 and 27); the improvements at 3 months were significantly different between both groups (p< 0.0001). Similarly, MSIS-29 scores were better in both groups at T1, but remained stable at T2 only in IG. The improvements in gait parameters were also more pronounced in IG.

Conclusion: The results of our study demonstrate that the effects of rehabilitation on fatigue, quality of life, and mobility can be maintained with an internet-based home training program for up to 3 - 6 months. Further studies are needed to investigate whether longer-lasting programs may have sustained effects on these disabling symptoms of PwMS.

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P804 Aspirin improves exercise endurance in multiple sclerosis: pilot findings from a double-blind randomized placebo-controlled crossover trial

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Background: Persons with multiple sclerosis (PwMS) are often symptomatically limited during exercise, often as a result of fatigue. The effects of aspirin on exercise endurance in PwMS have not been extensively studied. This pilot trial investigated the effects of aspirin on exercise endurance in PwMS.

Methods: PwMS were randomized to aspirin (150 mg daily) or placebo for 6 weeks. Exercise endurance was measured using an incremental cycle ergometer protocol. Percent change in exercise endurance between baseline and week 6 was the main outcome. The sample was stratified by age (≤ 45 vs. > 45) and sex (male vs. female) and balanced across groups with respect to EDSS. A two-sided t-test was used to test the main outcome. Clinically relevant increases in exercise endurance were defined as at least a 15% increase.

Results: Twelve PwMS were randomized; six in each group. Eight completed the study. No serious adverse events occurred. Aspirin was well tolerated. There were no differences in exercise endurance between groups at baseline. At week 6, aspirin increased exercise endurance by 15.6% compared to placebo (p=0.03). The effect was larger in women (18.0% vs. 12.2%, p=0.03) and those aged ≤ 45 (18.9% vs. 10.0%, p=0.04) compared to those ≥ 45 (12.5% vs. 13.7%, p=0.17).

Conclusion: Aspirin improves exercise endurance in PwMS. Larger studies are needed to confirm these findings and to investigate the effects of aspirin on exercise endurance in other populations.
Background: Exercise holds many benefits for persons with multiple sclerosis (MS), but exercise is only beneficial if people do it. Many patients are deterred by exercise-induced overheating, exhaustion, and symptom worsening (“Uhthoff’s phenomenon”). We conducted a double-blind crossover-design randomized placebo-controlled pilot study of aspirin (ASA) to improve exercise performance and attenuate exercise-related body temperature increase in persons with MS.

Methods: Twelve MS patients participated. At enrollment, 8 of 12 participants reported overheating during exercise, i.e., “heat-sensitive.” All participants completed two maximal aerobic exercise sessions. At each session, participants were administered a standard dose (650 mg) of ASA, or placebo. After one hour, participants performed a progressive ramped exercise test with lower body cycle ergometer. Test was terminated when volitional exhaustion was reached. Paired samples t-tests were conducted to evaluate differences in a) time-to-exhaustion (TTE) between ASA and placebo (primary outcome) and b) change in body temperature from pre- to post-exercise between ASA and placebo (secondary outcome).

Results: Exercise performance (TTE) improved after pre-treatment with aspirin compared to placebo (mean TTE difference = 16.4 ± 23.7 seconds; 95% CI: 1-31 sec); t(11) = 2.405, p = 0.035 (Cohen’s d = 1.45). In self-identified heat-sensitive patients, the effect of ASA was larger: t(7) = 3.321, p = 0.013 (Cohen’s d = 2.51; 95% CI: 7-44 sec). Exercise-induced body temperature increase did not differ across treatment in the full sample. However, in the heat-sensitive subgroup, there was a 56% attenuation of body temperature increase after exercise with ASA (mean increase = 0.41°F ± 0.55) compared to placebo (mean increase = 0.88°F ± 0.63); t(7) = -1.494, p = 0.178 (Cohen’s d = 1.13).

Conclusions: Prior exercise work in MS has shown efficacy for cooling treatments, although tested treatments involved obtrusive and/or non-standardizable methods of peripheral cooling such as cold bath pre-cooling and vacuum hand-cooling chambers. ASA, selected for its antipyretic effect, is convenient, inexpensive, readily accessible, and unobtrusive. This pilot study suggests that aspirin may represent an easy, economical treatment to enable people with MS to access the many benefits of exercise.

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Background: Fatigue is known for being one of the most debilitating and common symptoms of multiple sclerosis (MS). Despite its prevalence, though, reliable treatment options are lacking. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation treatment that uses low amperage (2.0 mA) electric current to stimulate cortical regions. tDCS has been shown to improve fatigue in MS following consecutive daily treatment sessions. We have recently developed and shown the feasibility of a remotely supervised tDCS (RS-tDCS) protocol to ease the burden of daily sessions and allow patients to complete the treatment at home. We aim to evaluate the efficacy of RS-tDCS in fatigue management for patients with MS.

Methods: We enrolled n = 31 patients with MS (all subtypes) into a remotely controlled, double-blind trial; n = 27 patients provided data for analysis with n = 15 randomized to the active group and n = 12 in the placebo or “sham” group. Participants came to the clinic for baseline and follow-up measures including self-report forms on fatigue. At baseline they were also trained in operating the tDCS headset. Participants then took the device home where they complete 20 sessions of tDCS (20 minutes, 2.0 mA, dorsolateral prefrontal cortex montage, left anodal) paired with cognitive training.

Results: Our primary outcome measure was the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue scale. When comparing change in PROMIS Fatigue between the active and sham tDCS groups we found that active tDCS participants had significantly greater reductions in fatigue (mean change in Active = -5.6 ± 8.9 vs. Sham = 0.9 ± 1.9, p = 0.02 conditions). We analyzed the within-subject effect tDCS had and found a significant, beneficial effect in the active group (pre-treatment mean = 26.6 ± 9.2, post-treatment mean = 21.0 ± 6.4, p = 0.04) and no such effect in the sham group (pre-treatment mean = 22.9 ± 7.9, post-treatment mean = 23.8 ± 8.4, p = 0.15). Finally, we calculated Cohen’s d effect size (Active d = -0.71, Sham d = 0.11).

Conclusions: These data suggest that RS-tDCS provides significant reduction in MS-related fatigue.

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P807 Walking economy, as measured by decreased oxygen demand, is improved in multiple sclerosis patients responding to fampridine
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Background: Impairment in walking ability is a hallmark feature of Multiple Sclerosis (MS). Fampridine (FAM) has been reported to improve walking ability, as measured by 25 Foot Walk Test (25FWT) time, in MS patients who respond to this therapy. However, the improvement in economy of walking, as measured by expired gas analysis, in responding subjects has not been reported. Accordingly, it is the objective of this study to determine if, and to what extent, walking economy is improved in MS patients who respond to FAM.

Methods: Ethical approval was obtained for this study. Inclusion criteria: Expanded Disability Status Score between 3.5 and 5.5 and responders to FAM therapy (defined as improvement in 25FWT time of 10% or greater). Subjects responding to FAM discontinued their therapy and were scheduled for 3 subsequent treadmill (TM) sessions. TM1 and TM2 were performed between 7 and 14 days after discontinuation of FAM to allow for washout. TM1 familiarized the subject to the treadmill test and metabolic measurement equipment and determined a constant speed the subject could walk at for 6 minutes. TM2 involved connecting the subject to the metabolic measurement system and recording resting data for 4 minutes. Subjects then walked for 6 minutes at the predetermined speed before sitting and resting for 4 minutes. Data for the last three minutes of exercise was averaged and used for analysis. After TM2, subjects resumed FAM therapy. TM3 repeated the protocol performed in TM2 and occurred 3–4 weeks after resuming FAM.

Results: Data are presented as (mean±SD). 59 subjects were recruited, 39 responded to FAM (27 female) with an average age of 52.3(±9.9) years. Pre and post treadmill tests were compared using Repeated Measures ANOVA. Subjects showed an improvement in relative oxygen consumption (VO2) (Pre: 11.39±2.92 vs. Post: 10.75±3.16 mL/kg/min, P=0.057) with significant improvements observed in: Absolute VO2 (Pre: 0.90±0.35 vs. Post: 0.84±0.35 L/min, P<0.05), ventilation (Pre: 28.16±10.55 vs. Post: 25.89±10.10 L/min, P<0.05), carbon dioxide production (Pre: 0.80±0.31 vs. Post: 0.75±0.32 L/min, P<0.05) and mean exercising heart rate (Pre: 108.6±5.9 vs. Post: 104.9±13.7 bpm, P<0.05).

Conclusion: Subjects responding to FAM show a significantly lower oxygen requirement and heart rate for walking at a constant speed. Further research into the benefits and mechanisms of these improvements needs to be further investigated.

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P808
A systematic review of everyday memory measures in multiple sclerosis
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Background: Cognitive problems are common in people with Multiple Sclerosis (MS), with Everyday Memory (EM) being one of the most affected. EM refers to memory functions associated with daily life. The measurement of EM problems is vital for monitoring the impact of memory deficits on an individual’s daily life and to evaluate the effectiveness of interventions that aim to improve cognitive functions. There is currently no gold standard EM measure, but several measures are available.

Aims: To systematically review the research literature on EM measures used with people with MS, describe the types of measures used, summarise their psychometric properties, and to describe how these measures have been used and what they have been used for.

Method: Empirical studies of cognitive function in MS utilising standardised EM measures were included. Online databases (MEDLINE, PsycINFO, PsycARTICLES and Embase) were searched from their inception until 2 May 2017. Additional measures identified were searched with Google Scholar (24 February 2017). Papers obtained were screened by four reviewers independently against the inclusion criteria, and relevant data were extracted using a customised data extraction form. A narrative approach was used to synthesise the extracted data.

Results: A total of 44 papers were included in the review involving 4402 participants with MS. A total of 12 measures were identified, with varied uses and administration methods. The majority of papers (33) did not report the psychometric properties of the measures. The few papers that did, reported that the measures have good reliability and appear to have good face, concurrent and ecological validity.

Conclusion: EM measures have been used for a variety of reasons with people with MS of different ages and diseases types. These measures are often versatile self-administered questionnaires or objective tests with prescribed activities. EM questionnaires and tests have been used as outcome measures in trials of cognitive rehabilitation. Although the measures appear to have acceptable psychometric properties, they need to be evaluated further. This review presents researchers and clinicians with an overview of the various EM measures used in studies with people with MS, to help them choose the appropriate measure for their evaluations.

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P809
MS relapse treatments and relapse resolution: retrospective study results from a US health plan
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Background: Relapse resolution in multiple sclerosis (MS) is critical, given relapses may last a few days to several weeks or months and leave residual deficits. Our goal was to identify patients with MS relapse and to evaluate unresolved relapses from the Humana Research Database. Humana policy considers corticosteroids (CS) to be first-line relapse therapy; other therapies include repository corticotropin injection (RCI; H.P.Acthar® Gel), intravenous immunoglobulin (IVIG), or plasmapheresis (PMP). Since oral CS are often used first, we focused on intravenous CS (IVMP), RCI, IVIG, and PMP.

Methods: Retrospective analyses were conducted using Humana’s Commercial and Medicare Advantage claims data from 1/1/08 - 7/31/15. An MS relapse event was defined as a hospitalization with a principal diagnosis of MS (ICD-9-CM 340.xx) or outpatient visit with MS diagnosis and a medical or pharmacy claim for treatment (CS, RCI, IVIG, PMP) within 30 days. The first relapse event and treatment in the study period were considered the index event and treatment. Relapse events were unresolved if >1 relapses occurred within 30 days. No minimum enrollment was required. Proportions and annualized rates of relapse (ARR) were calculated.

Results: 9,574 patients with ≥1 relapses were identified. Per year, 74.0% patients had <2 relapses, 20.6% had 2-4 relapses, and 5.4% had ≥4 relapses (ARR). 3,532 patients (36.9%) had ≥1 unresolved relapses. A total of 25,162 relapses were identified; 51.8% of relapses were treated with oral CS, 38.6% with IVMP, 6.0% with IVIG, 2.2% with RCI, and 1.5% with PMP. Patients usually continued with their first observed treatment for subsequent relapses. In index event analyses, 47.8% of patients treated with IVMP had no unresolved relapses; 96.9%, 50.7%, and 43.9% of patients treated with RCI, PMP, and IVIG had no unresolved relapses, respectively.

Conclusions: Relapse rates and unresolved relapses remain a challenge in MS. 26.0% of patients had ≥2 relapses per year. Among those with ≥1 relapses, 36.9% had unresolved relapses. Of treatments evaluated, RCI had the lowest proportion of unresolved relapses. Relapse resolution is an important indicator of treatment effectiveness. Limitations apply: claims reflect treatment-seeking behavior and lack clinical detail, IVMP may be followed by an oral CS taper by design, index events were first observed not incident, and unrestricted enrollment was used. Our study should be repeated with fixed enrollment.

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Fampridine effects on upper limbs motor function and quality of life
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Introduction: Fampridine is a drug approved for the treatment of walking disability in patients with multiple sclerosis (MS). It causes an increment in the velocity of electric transmission through the demyelinated axon.

Objective: To analyze the effect of fampridine on the upper limbs motor function and quality of life.

Material and Methods: Observational, prospective study of patients with MS on treatment with fampridine. Timed 25 Foot Walk (T25FW), MS Walking Scale-12 (MSWS-12), 9 Hole Peg Test (9-HPT) and EuroQol 5-Dimension (EQ-5D) were done before and 14 days after treatment start. Patients with a good response to fampridine (reduction of at least 20% in T25FW and 6 points in MSWS-12) were also evaluated at 3 and 6 months.

Results: 68 patients were included in the study. A significant improvement (p<0.001) was obtained at day 14, month 3 and 6 in 9-HPT (dominant hand: -8.65%, -13.14% y -0.8%; non-dominant hand: -5.44%, -7.98 y -11.92%) and in the EQ-5D (20.24%, 18.93% y 47.82%). Differences in 9-HPT were correlated with the changes in T25FW (0.438, p=0.001) and in MSWS-12 (0.542, p<0.001). However, the differences in EQ-5D were independent of the tests T25FW, 9-HPT and MSWS-12.

Conclusions: Fampridine causes an improvement of upper limbs motor function and in the quality of life. Changes in quality of life are independent of motor function, therefore it is possible that other benefits not detected with these test would happen in these patients.

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Mental processing velocity in patients on treatment with fampridine
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Introduction: Fampridine blocks the voltage-dependent K channels increasing the velocity of conduction in nerves. It is a drug approved for the treatment of walking difficulties in patients with multiple sclerosis (MS).

Material and Methods: Observational, prospective study of patients with MS on treatment with fampridine. Timed 25 Foot Walk (T25FW), MS Walking Scale-12 (MSWS-12) and Symbol Digit Modalities Test (SDMT) were done before and 14 days after treatment start. Patients with a good response to fampridine (reduction of at least 20% in T25FW and 6 points in MSWS-12) were also evaluated at 3 and 6 months.

Results: 68 patients were included. The rate of responders was 55.9% at 14 days, 33.8% at month 3 and 29.4% at month 6. A significant improvement (p<0.001) in SDMT was obtained at day 14, month 3 and 6 (5.49%, 13.62% y 2.83%). The changes in SDMT were not related with age, EDSS or the basal results of this test. Differences in SDMT were independent of changes in T25FW (0.168, p=0.226) and MSWS-12 (0.212, p=0.128).

Conclusions: An improvement in the velocity of mental processing was detected in patients on treatment with fampridine. These results were independent of the effect on walking scales. It is possible that several patients get a benefit of treatment with fampridine even when they do not achieve the actual criteria for response.

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Intrathecal baclofen is an effective treatment for ambulatory subjects with MS related spasticity
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Background: Spasticity is a disabling symptom in people with Multiple Sclerosis. Intrathecal baclofen (ITB) is effective, but has been viewed as a last resort, traditionally reserved for wheelchair users.
Study aim: Evaluate efficacy and utility of ITB in a cohort of ambulatory people with MS-related spasticity.

Methods: A single centre observational cohort study was performed between 2009 - 2017. Subjects were admitted for ITB trial and subsequent pump implantation. Data collected prospectively at baseline, at peak trial effect and longitudinally after pump implant. Data: baseline demographics, EDSS, spasticity scores (Ashworth), spasm score (Penn), 10m timed walk seconds (10MTW), mobility aids, other spasticity treatment, ITB dose.

Results: 23 people were ambulatory at ITB trial. Females to males 13:10, mean age 47.3 years [26-64]. All patients were EDSS 6.5/7. All were taking oral anti-spasticity treatment and seven patients on disease modifying drugs. 22 subjects responded to ITB trial with significant reduction in Ashworth (pre 1.35; post 0.67, p< 0.05) and Penn (pre 3.2; post 1.20; p< 0.05). 10MTW pre-trial was 56.3s [40-158] and post-trial 31s [43-107] (p=0.055). Fourteen subjects (61%) proceeded with pump implantation and nine (39%) did not. Mean 10MTW in those who proceeded to pump was: pre-trial (58.1s) and post-trial (54.1s) (p = 0.37). Six subjects significantly improved their walking speed post-pump. After dose stabilisation, Mean 10MTW at 3 months was 31s [12.2 - 64] (p=0.055). Mean lower limb MRC power grade pre-trial was 3.8 (1.7-5) in those who proceeded to pump and 2.5 (1.4-3.7) in those who did not (p< 0.05, 95% CI 0.32-2.2). Thirteen subjects discontinued other spasticity treatments post-pump. Eleven subjects (84%) were ambulatory at 1 year. At review, ten patients (77%) were ambulatory (mean follow up 3.5 years, maximum 8). Mean time to inability to walk was 1.75 years (0.5-4). Two people have remained ambulatory with one stick for 7 years (EDSS pre pump 6.5 and 7).

Conclusions: Although ITB may increase/unmask lower limb weakness in people with MS, it may preserve and in some cases improve mobility. People with better baseline walking ability and lower limb power are most likely to benefit.

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P813 Comparative effectiveness of natalizumab and fingolimod treatment on cognitive outcomes in relapsing multiple sclerosis patients

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Background: To date no comparisons between second-line treatments have been performed to evaluate their effect on cognition in relapsing multiple sclerosis (RRMS).

Objective: to compare the effect on cognition of 1-year Fingolimod (FIN) or Natalizumab (NTZ) treatment.

Methods: All consecutive RRMS scheduled for NTZ or FIN treatment in 2 MS centers underwent neuropsychological evaluations using the Brief Repeatable Battery, Stroop Test, Fatigue Severity Scale (FSS) and Beck Depression Inventory (BDI) at baseline and after 12 months. A test was considered failed if the corresponding z-score was 2 standard deviation (SD) below the mean Italian normative values. The Cognitive Impairment Index (CII) as a measure of global cognitive function was calculated for each patient. Patients were propensity score (PS)-matched on a 1-to-1 basis at the time of treatment start using the following covariates: sex, age, relapses prior the treatment, number of gadolinium enhancing lesions at the MRI, EDSS score, school education and BDI score. A generalized linear mixed model for repeated measures with an autoregressive variance-covariance structure was applied to evaluate changes in each cognitive test score, the CII, the mean number of tests failed and FSS score at year 1.

Results: the effect of treatments on the cognitive functions was evaluated in 114 PS-matched RRMS patients receiving NTZ (n=57) or FIN (n=57). The CII significantly improved in both treatment arms (NTZ 12.3±7.2 vs 9.8±7.2, p<0.001; FIN 16.1±6.6 vs 12.8±6.9, p< 0.001), but there was not a significant interaction between group X time. The mean±SD number of cognitive tests failed was significantly reduced only in FIN-treated patients (2.1±2.1 vs 1.4±1.9, p=0.003) and the delayed recall of verbal memory was more significantly improved in FIN-treated patients in comparison with those treated with NTZ (Estimate mean=0.807, Standard error=0.3524, p=0.02). The FSS was unchanged in both groups.

Conclusions: Overall the results indicate that both NTZ and FIN treatments significantly ameliorate cognitive functions in RRMS in the short-term. This effect could be due to their anti-inflammatory properties. The greater impact of FIN on the reduction of the number of tests failed and on the improvement of delayed recall of verbal memory than NTZ could be also related to an associated beneficial effect of FIN on brain atrophy. A longer follow-up is needed to confirm these findings.

Disclosure

Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec and Novartis, and has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Merck-Serono, Teva and Novartis.
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Angelo Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec, Novartis, Teva; received honoraria for speaking form Merck Serono, Biogen Idec, Genzyme, Almirall, and Novartis; received research support from Sanofi Genzyme, Biogen Idec and Merck Serono.
Quality of life

P814
Comparing patient and healthcare professional perceptions on multiple sclerosis management and care - where do their priorities differ? Results from a qualitative survey
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Background: The MS in the 21st Century initiative is led by a steering group (SG) of international multiple sclerosis (MS) specialists and patient advocates with a current focus of improving education and communication between healthcare professionals (HCPs) and people with MS.

Objective: To compare the priorities of the MS clinical community and patients on MS management and care. Particular emphasis was on patient support at diagnosis, treatment decisions, and communicating the concept of disease progression.

Method: An electronic survey was developed to gain insight into HCPs’ opinions on unmet needs in MS management. This was conducted at two international neurology congresses (2016 and 2017). An equivalent patient survey was developed and conducted at a patient meeting in 2017. Multiple answers were solicited in response to 10 questions.

Results: A total of 101 HCPs and 54 MS patients completed the survey, with 98.4% and 93.6% reporting at least one communication challenge at diagnosis, respectively. The most frequently reported challenge for HCPs was lack of time with the patient (26.6%). Patients reported a lack of time (14.5%) but also difficulty understanding their treatment options (20.2%) and disease status (19.4%). Whilst 60.0% of patients felt they guided disease progression discussions, only 15.9% of HCPs reported that this was the case. Both HCPs and patients agreed the most important treatment consideration for patients was that it slows disease progression (26.2% and 31.5%, respectively). Although 31.8% of HCPs thought patients preferred to focus more on the benefits than risks of treatments, only 9.3% of patients agreed; 68.5% of patients reported they have equal interest in treatment benefits and risks. HCPs felt the biggest barrier to effective communication was in helping patients to understand complicated information (31.3%). Patients also expressed difficulty in understanding MS (19.4%) but felt HCPs’ misunderstanding of patient priorities (21.8%) was a barrier.

Conclusion: HCPs and patients reported a lack of time and resources, particularly at diagnosis; however, there were distinct variations in priorities and perceptions surrounding treatment decisions. Both groups reported a number of barriers to effective communication, which supports the need for joint education related to communication.

Disclosure
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P815
Intensive social-cognitive program (Can Do Treatment) in patients with relapsing remitting multiple sclerosis and low disability: a randomized controlled trial
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Background: Can Do Treatment (CDT) is an intensive, multi-disciplinary, 3-day, social-cognitive program for patients with multiple sclerosis (MS). CDT’s primary goal is to improve patients’ self-efficacy.

Methods: In a 6-month randomized controlled trial (RCT) we investigated the effectiveness of CDT in relapsing remitting (RR) MS patients with Expanded Disability Status Scale score ≤ 4.0. Control patients received care as usual and had the option to receive CDT after the controlled study phase. Primary outcome: self-efficacy control (MS Self-Efficacy Scale [MSSES]-Control, range 90-900). Self-efficacy function, health-related quality of life (MSQoL-54), autonomy and participation (Impact of Participation and Autonomy-32), anxiety and depression (Hospital Anxiety and Depression Scale) were secondary outcomes. Tertiary outcome: care-related strain to support partners (Caregiver Strain Index). Assessments were at baseline and at 1, 3 and 6 months. Three ANCOVA models were built to analyze differences between
the two groups for the primary outcome, with the assessments at 1, 3 or 6 months as dependent variables and baseline assessment as independent variable. Analyses were performed according to the intention-to-treat principle.

**Results:** One-hundred-and-fifty-eight patients were included and randomized to CDT (n=79; 70 female, 9 male) or the control group (n=79; 69 female, 10 male). Mean (standard deviation) age was 41 (8.7) and 40 (9.4) years and EDSS score was 2.3 (1.03) and 2.3 (1.13), respectively. Mean self-efficacy control in the CDT group at baseline, Month 1 (M1), M3 and M6 were 468 (162), 597 (114), 561 (160) and 578 (166), and in the control group 477 (136), 491 (131), 514 (143) and 540 (135). Mean changes at M1, M3 and M6 compared to baseline were +27.6%, +19.7% and +23.5% in the CDT group and +2.9%, +7.6% and +13.0% in the control group. The difference between CDT and control groups was statistically significant at M1 (p = 0.000) and M3 (p = 0.019), but not at M6 (p > 0.05). The secondary and tertiary outcomes are being analyzed and results will be presented at the congress.

**Conclusion:** CDT effectively improves self-efficacy control in RRMS patients with low disability. The fact that at M6 the difference between the study groups was not statistically significant most likely relates to the control group experiencing a gradual increase in self-efficacy control during the study period, which can be interpreted as a waiting list effect.

**Disclosure**

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**P816**

**Octogenarians with MS: a study describing lifestyle factors of the oldest old living with multiple sclerosis**

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**Background:** Due to advancements in treatment and disease modifying drugs, people with multiple sclerosis (MS) are living longer and healthier lives, with a select few individuals reaching their 80th year of life and beyond. We hypothesized that octogenarians with MS may demonstrate greater neuroprotective lifestyle behaviors that helped them reach the 80th decade of life.

**Methods:** Data was obtained from “The Canadian Survey of Health, Lifestyle and Ageing with Multiple Sclerosis”. Participants were recruited if they were older than 55 years of age, and had self-reported MS symptoms for greater than 20 years. The Simple Lifestyle Indicator Questionnaire (SLIQ) was administered to examine physical activity, diet, alcohol use, smoking and stress of respondents. All individuals who completed the survey who were 80+, or who were turning 80 that calendar year, were included in the Octogenarians group (n=23). To compare to a younger group of individuals living with MS, we created a matched Young Old group of respondents aged between 60 and 69 years of age (n=61).

To compare to a healthy population, we compared our octogenarians sample to healthy octogenarians using data from the 2012 Canadian Community Health Survey (CCHS) accessed via the University of Toronto Data Library Service.

**Results:** The MS Octogenarians group had a mean age of 81.9 years (SD = 2.9 years) and had been diagnosed with MS 34.2 years (SD = 10.5 years). There were no differences between the MS Octogenarians and MS Young Old group with regards to physical activity, diet, alcohol and smoking; however the MS Octogenarians group reported higher levels of stress compared to the MS Young Old (F = 9.40). The MS Octogenarians reported a greater percentage of healthy lifestyle factors of physical activity (87.0% vs 30.9%), diet (regular fruit consumption: 21.7% vs 10.9%), alcohol (regular consumption: 47.5% vs 54.5%) and smoking (smokers: 0% vs 5.2%) in comparison to the CCHS sample. However, a greater percentage of MS Octogenarians report their lives as stressful (69.6%) compared to healthy Octogenarians (10.6%).

**Conclusion:** MS Octogenarians live a healthier lifestyle that other people their age. However six times more MS Octogenarians described their lives as stressful compared to healthy Octogenarians. Those in the MS Young Old group also display similar healthy lifestyles as the MS Octogenarians suggesting that healthy lifestyle practices are likely a habit.

**Disclosure**

M.B. Downer: nothing to disclose
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M. Ploughman: nothing to disclose

**P817**

**Laughing matters: the role of humor on psychological well-being, health & quality of life in multiple sclerosis (MS)**

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**Background:** Humor has been purported to play a role on stress, psychological well-being (PWB), and health, including immune function. Individuals who utilize humor have also been shown to have greater self-esteem and social functioning. We previously found that among a host of other disease and person factors, the use of humor played a large role in distinguishing individuals with MS who were considering leaving work and those staying employed.

**Objective:** The purpose of the present study was to further examine the role of humor on perceived stress, PWB, health, self-efficacy/locus of control (LOC), and social functioning in MS. We also examined whether individuals who utilized humor as a coping mechanism were more likely to engage in other behaviors related to cognitive health such as diet/exercise and social/intellectual activities that may also assist in maintaining overall functioning.

**Method:** 172 individuals with MS were administered a comprehensive battery assessing perceived stress, PWB, health, self-efficacy/LOC, social functioning, and health behaviors. A median split was utilized to divide the groups into high and low use of humor. Multivariate analyses were used to compare the two groups.

**Results:** There were no differences between the groups on gender, age, education, or disease duration. Surprisingly, there were no differences between perceived stress. Despite this, individuals...
with high use of humor reported greater PWB, physical health, general and MS self-efficacy, LOC, and social support. In contrast, they endorsed lower levels of depression and anxiety (p's < .05). Individuals who reported using humor as a coping mechanism also reported engaging in more social and intellectual activities with a trend for diet and exercise, suggesting that they also engage in other tangible activities that can foster cognitive health.

Conclusions: Use of humor has been considered complementary therapy in some medical populations for the reasons stated above. Little attention has been given to the use of humor in MS, despite many anecdotal experiences from patients. Further investigations into the role of humor on well-being and health in MS are warranted and may suggest the use of humor as an intervention to improve well-being and health.

Disclosure
Lauren Strober, Ph.D.: Nothing to disclose

P818
Combined T25FW and MSWS12 response improves identification of persistent response to PR-Fampridine in people with MS
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Background: Walking impairment is frequently reported by people with Multiple Sclerosis (PwMS). PR-Fampridine has been shown to improve walking in MS. Translating responder status from clinical trials to clinical practice is challenging. Pivotal Phase III trials defined response as a ≥20% improvement in Timed 25 Foot Walk (T25FW), while the ENHANCE trial proposed using a ≥8 point improvement on the 12-Item MS Walking Scale (MSWS12).

Objectives: To determine responder criteria in a clinical setting and to assess the long-term impact of PR-Fampridine on walking, quality of life and goal attainment.

Methods: PwMS were assessed in a specialist clinic. Responder status was defined as T25FW improvement of ≥20 %. MSWS12 response was a ≥6 point improvement. Additional measures included EQ-5D-5L, VAS walking and individualised treatment goals. Outcomes were recorded at baseline, 2 weeks, 4 months and 4 monthly thereafter up to 4 years. Data was analysed with SPSS V24. Paired T-tests were used to compare responder and non-responder data. Longitudinal changes were analysed using repeated measures analysis of variance (ANOVA). Multiple imputation was used for missing data.

Results: 560 patients were assessed. 231 were trialled; 162 (70.1%) females and 69 males (29.9%). Mean age 54 [28-82] years. Mean EDSS 6.45 [6.0-7.0]. T25FW response alone identified 166 responders (72.4%),76.5% of which were responders at 1 year. 90 subjects (40.5%) had MSWS12 response. Combining T25FW and MSWS response identified 85 responders (38.1%); 81.3% were responders at 1 year. Median change in T25FW speed was 69.1%[20.1-472%] in responders versus -0.4%[-57.6-18.7%] in non-responders (p<0.0001). Responders walked faster than baseline at 3 years (60.8%, p< 0.05). MSWS-12 improved in TW responders (-14.0) but not in non-responders (+5.0) (p=0.001). EQ-5D-5L index changed by +0.123 in responders and -0.02 in non-responders (p=0.028), this was sustained at 16 months (+0.514, p<0.003). 82% achieved their goals by 4 months. 34 T25FW responders discontinued drug due to recognised side effects or lack of ongoing efficacy.

Conclusions: Defining response to open label PR-Fampridine treatment is challenging. Combining objective and self-reported measures is likely the most reliable method. Exact thresholds need further evaluation. It is clear, however, that PwMS who receive PR-Fampridine in an open-label clinical setting experienced sustained improvements in their walking ability and quality of life.

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Renee Ewe, Hannah Louissaint, Joanne Allen, Joanne Johnson, Nicola Hare: Nothing to declare

P820
High levels of alexithymia may contribute to the complex affective traits found in patients with multiple sclerosis
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Introduction: Alexithymia is a personality trait characterized by difficulties in identifying and describing feelings, with an externally oriented thinking style. While studies on traumatic brain injury, stroke and epilepsy show that these neurological patients have high rates of alexithymia, there are remarkably few reports on alexithymia in patients with MS. The objective of the present study was to further characterize findings of alexithymia in MS.

Materials and Methods: This cross-sectional case-control study included 180 patients with MS and a gender, age and schooling-matched control group of 180 individuals. They were all assessed using tools validated for traits of depression, anxiety and alexithymia. Demographic and clinical data were obtained during individual interviews.

Results: There were 126 women and 54 men in each group, with median age of 37 years and median schooling of 16 years. The median disease duration was eight years. Patients with MS presented higher degrees of depression (p< 0.01), anxiety (p<0.01) and alexithymia (p< 0.01) than did control subjects. For individuals with MS, depressive traits (p< 0.01), anxious traits (p<0.03), higher age (p<0.02), lower education level (p<0.02), higher degree of disability (p< 0.01) and not being part of the working
force (p=0.03) had a significant influence on higher rates of alexithymia. Control subjects with higher age (p<0.01) and lower schooling level (p<0.01) had higher rates of alexithymia, although the participation in the working force did not affect their results.

**Conclusion:** Alexithymia was an important finding in patients with MS and should be addressed when psychological testing and care are considered for these individuals. Further studies will consider whether certain areas of brain lesions and volume loss might be relevant to the findings of alexithymia in MS.

**Disclosure**
Yara Dadalti Fragoso, Audred Cristina Biondo Eboni, Mariana Cardoso, Felipe Moreira Dias, Paulo Diniz da Gama, Sidney Gomes, Marcus Vinicius Magno Goncalves, Suzana Costa Nunes Machado, Adauto Wanderley da Nobrega Jr, Monica Fuiza K. Parolin, Sonia Castero Paz, Heloisa Helena Ruocco, Claudio Scorcíne, Fabio Siquinelli, Caroline Vieira Spessotto, and Carlos Bernardo Taui declare no disclosures or conflicts of interest in this study. No financial support of any kind, no drugs or procedures involved.

**P821**
Validation of MUSIQOL among Arabic-speaking MS patients treated with high dose INF-β 1a sc injection New Formulation
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**Background and Objective:** Validated quality-of-life (QOL) tools are not available for Arabic-speaking MS patients. SF36 and MUSIQOL have been validated for other languages. The objective of this study was to prospectively assess and correlate MUSIQOL with disease activity and progression among Arabic-speaking MS patients treated with INF-β 1a sc injection New Formulation over 12 months.

**Methods:** The subjects comprised a prospective multinational, multicenter cohort study of Arabic-speaking MS patients treated with RNF for at least 6 months prior to entering the study. Their average age was 32.44(±0.34) years, 71.5% were female, and 63.1% were educated to university level or above. The subjects had an average MS duration of 4.13(±0.12) years, an average age at first attack of 27.35(±0.26) years, and baseline EDSS of 2.05±0.04. Overall QOL measured using SF36 remained generally unchanged over time (P=0.215). However, QOL change overtime measured by using MUSIQOL was statistically significant (P=0.00015). Several aspects of subjects’ QOL, including daily living activities, physical wellbeing, symptoms, and coping improved. Sentimental & sexual life decreased overtime (p=0.0072).

**Conclusion:** The study suggests that the use of MUSIQOL among Arabic-speaking MS patients is a valid tool, and may capture changes in several aspects of their clinical status over 12 months. Periodic assessment of QOL is recommended for management of MS patients. INF-β 1a sc = Interferon beta 1 a subcutaneous

**Disclosure**

**P822**
Equivalence of the electronic versus paper-based short version of the MSQOL-54 (MSQOL-29)
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**Background:** We recently developed a short version of the Multiple Sclerosis Quality Of Life-54, named MSQOL-29 (25 items grouped in seven subscales, plus four single items) also available in electronic, self-administered form, with automatic scoring (eMSQOL-29).
Objective: To assess the acceptability of the eMSQOL-29 and its equivalence to the paper-based version.

Methods: Equivalence of the eMSQOL-29 was assessed on 223 adult patients with a confirmed MS diagnosis (revised McDonald criteria). Patients with exacerbations in the previous month, overt cognitive impairment, or any physical compromise precluding participation were excluded. We adopted a crossover design with random test order, by which patients completed both MSQOL-29 versions, in an interval of 2-4 weeks. After the second administration, they completed a short, ad hoc questionnaire assessing the acceptability and usability of the eMSQOL-29. For each of the 11 MSQOL-29 subscale scores equivalence was assessed by (a) the intraclass correlation coefficient (ICC, with 95% confidence interval); and (b) mixed effect model. The latter included the following independent variables: version (paper, electronic), order of administration, sequence (order per version), center (Milan, Orbassano), sex, age, Expanded Disability Status Scale (EDSS ≤2.5, >2.5) and disease course (relapsing-remitting, primary or secondary progressive). We also tested for the first-order interaction term sequence per age.

Results: Of the 223 MS patients enrolled, 210 (94%) completed the questionnaire in both modes (13 did not return the paper MSQOL-29). All the patients found the eMSQOL-29 well-accepted and user friendly.

Eight of the 11 of the ICCs were ≥0.70, with higher values for the multi-item subscales (median ICC 0.87, range 0.84-0.95) compared to single-item subscales (median ICC 0.63, range 0.52-0.76). MSQOL-29 version, order and sequence of administration did not affect subscale mean score in the linear mixed models (p>0.05, data not shown).

Conclusions: Equivalence of the eMSQOL-29 was supported by our findings, with slightly lower (but above threshold) ICC values for the single-item subscales. Acceptability of the tool was also good.

Disclosure

Conflicts of interest:

All the authors declare that they have no competing interests.

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P823

Cladribine tablets treating multiple sclerosis orally (CLARITY): an independent analysis of the quality of life data

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Background: Oral cladribine (cladribine) is currently under consideration for licensing with the European Medicines Agency (EMA). However, a number of elements of the pivotal Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial have remained unpublished.

Objective: To report the impact of cladribine on health-related quality of life (QoL) in people with relapsing MS (pwRMS).

Methods: QoL data from CLARITY, a randomized, double-blind, placebo-controlled trial of two different doses of cladribine (3.5mg/kg and 5.15mg/kg over 96 weeks) were extracted from the CLARTIY dataset acquired from the EMA through Freedom of Information. Spearman’s rank correlation was used to analyse the relationship between baseline QoL scores and baseline Expanded Disability Status Scale (EDSS) scores. Responses of the Euro Quality of Life 5 dimension (EQ-5D) and MS Quality of Life 54 (MSQOL54) questionnaires were compared between treatment and control groups using univariate analyses of covariance.

Results: In total n=5,148 EQ-5D responses and n=894 MSQOL54 physical, mental-health and dimension scores were extracted. Baseline EQ-5D indices correlated with EDSS scores. After two years, pwRMS taking 3.5mg/kg (p=0.001) and 5.25mg/kg (p=0.022) reported significantly improved EQSD index scores compared with placebo. Positive, yet non-significant, differences were detected in MSQOL54 scores between cladribine and placebo.

Conclusion: Analysis of the CLARTIY dataset indicates that, overall and above its excellent clinical efficacy and tolerability, cladribine leads to improved QoL over 96 weeks. ClinicalTrials.gov identifier, NCT00213135.

Disclosure

DA, CA, DRA and LZ have nothing to disclose. DB is shareholder and consultant to Canbex therapeutics and has received research funds from Sanofi-Genzyme. KS has been a PI of trials sponsored by Novartis, Roche and Teva and involved in trials sponsored by Biogen, Sanofi-Genzyme, BIAL, Cytokinetics, and Canbex and has received honoraria and meeting support from Biogen, Merck, Novartis, Teva, Merck.

P824

Coping strategies, health-related quality of life and life satisfaction among persons with multiple sclerosis

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Background: A vast literature attests to the relation between coping strategies and illness adjustment among persons with multiple sclerosis (PWMS). Particularly, avoidance strategies were pervasively associated with lower health-related quality of life (HRQoL), while mixed findings were obtained about problem- and emotion-focused strategies and illness adjustment among persons with multiple sclerosis.
coping, depending on personal and clinical characteristics. Little however is known about the relationship between illness-related coping strategies and more general well-being dimensions such as life satisfaction, if the same strategies apply as for HRQoL and if they are adaptive or maladaptive.

**Aim:** To investigate the relation between coping strategies, health-related quality of life (HRQoL) and satisfaction with life among PwMS.

**Methods:** Questionnaires assessed participants’ HRQoL in its physical and mental health composite dimensions (MS Quality of Life-54), life satisfaction (Satisfaction with Life Scale) and coping strategies (Brief COPE-28; avoidance: self-distraction, denial, behavioral disengagement; problem-focused: active coping, planning, instrumental support; emotion-focused: emotional support, positive reframing, humor, acceptance, religion).

**Results:** Data were analyzed for 680 participants from 8 MS centers in Italy. Regression analyses revealed that, over and above demographic and clinical variables, both the physical and the mental health composites were positively predicted by positive reframing (respectively, B=0.09, p<0.05; B=0.14, p<0.01), and negatively by emotional support (B=-0.10, p<0.01; B=-0.17, p<0.001), denial (B=-0.08, p<0.05; B=-0.16, p<0.001), and behavioral disengagement (B=-0.11, p<0.01; B=-0.20, p<0.001). Life satisfaction was positively predicted by positive reframing (B=0.17, p<0.001) and humor (B=0.10, p<0.01), and negatively by behavioral disengagement (B=-0.15, p<0.001). Problem-focused strategies were not predictive of any well-being dimension.

**Conclusions:** The ways PwMS cope with disease are associated with both HRQoL and general life satisfaction. While some strategies - be they adaptive or maladaptive - were related to both (positive reframing and behavioral disengagement), others were specific to HRQoL (denial and emotional support) or life satisfaction (humor). Intervention targeting PwMS’ coping efforts should thus broaden its scope of action by enhancing adaptive strategies and reducing maladaptive strategies, taking into account patients’ health-related well-being and lives as a whole.

**Disclosure**


**P825**

Patient satisfaction and quality of life during treatment with fingolimod in multiple sclerosis: results from the ‘DIAMOND’ non-interventional, prospective, observational study in Greece

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**Background:** Fingolimod is the first approved oral disease-modifying therapy for patients with relapsing multiple sclerosis (MS). Real-world evidence on long-term treatment satisfaction (TS) and impact of fingolimod on the patients’ quality of life (QoL) remains limited.

**Methods:** This non-interventional 24-month study evaluated TS and QoL in 498 fingolimod-treated MS patients, using the Greek version of the validated TS questionnaire for medication (TSQM) v.1.4 and the EuroQol 5-dimension 3-level (EQ-5D-3L) instrument, which were completed at enrolment and at 6, 12, 18 and 24 months post-enrolment.

**Results:** At enrolment, 6, 12, 18 and 24 months post-enrolment, the median EQ-VAS score was 65.0, 70.0, 71.0, 70.0 and 74.5, and the EQ-5D index score was 0.78, 0.80, 0.80, 0.79, and 0.80, respectively. Pairwise comparisons revealed significant increases from enrolment at 6, 12, 18 and 24 months for the EQ-VAS (p<0.001 for all) and at 6, 12 and 18 months for the EQ-5D index score (p<0.05 for all). At enrolment, 6, 12 and 24 months the percentage of patients that reported ‘problems’ in EQ-5D-3L dimensions were: 74.2, 66.9, 64.0, and 64.0% for ‘mobility’; 56.6, 49.2, 50.3, and 50.0% for ‘usual activities’, 66.9, 64.0, and 64.0% for ‘anxiety/depression’, 65.7, 62.0, 62.2 and 61.3% for ‘pain/discomfort’; and 65.7, 62.0, 62.2 and 61.3% for ‘mobility’. Intervention targeting PwMS’ coping efforts should thus broaden its scope of action by enhancing adaptive strategies and reducing maladaptive strategies, taking into account patients’ health-related well-being and lives as a whole.

**Disclosure**

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D.D. Mitsikostas has received grants and honoraria from: Allergan, Amgen, Biogen, Genesis Pharma, Electocore, Eli Lilly, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, Teva.
E. Zafeiropoulou is currently a Novartis (Hellas) S.A.C.I employee.
A. Kyriasis has nothing to disclose.
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All authors, except of E.Z are Principal Investigators of the study.

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Claes Martin has received honoraria from Bayer, Biogen, Genzyme, Merck, Novartis, Sanofi and Teva.
Stefan Hau has received honoraria from Merck.
Dimitri Guala is working at Merck.
Lillemor Jansson has no disclosures.

**P826**

RebiQoL: A telemedicine patient support program on health related quality of life and adherence in MS patients treated with Rebif

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**Introduction:** RebiQoL is a phase IV multicenter randomized study to assess the impact of a telemedicine patient support program (Min Support Plus, MSP) on health-related quality of life (HRQoL) through intervention of lifestyle style factors (e.g. stress management and physical activity) in patients with relapsing-remitting MS (RRMS) being administered with Rebif® with the RebiSmart device.

**Objectives:** The primary endpoint was to assess the impact of MSP compared to patients only receiving technical support for RebiSmart on HRQoL at 12 months, using the psychological scale of Multiple Sclerosis Impact Scale (MSIS-29), in patients administered with Rebif.

The secondary endpoints were to assess the impact of MSP on HRQoL, (MSIS-29, EuroQoL-5 Dimension Questionnaire (EQ5D)), fatigue (Fatigue severity scale (FSS)), Modified Fatigue Impact Scale (MFIS), depression and anxiety (Hospital Anxiety and Depression Scale (HADS)), at 6 and 12 months. Impact regarding adverse events, patient satisfaction and lifestyle goals were assessed, at 12 months and the adherence was measured at 6 and 12 months. The potential impact of gender, education and disability level as measured by Expanded Disability Status Scale (EDSS) > 4.0 vs. < 4.0 and HRQoL at baseline, were also evaluated.

**Methods and patients:** The telemedicine intervention consisted of 13 calls related to MSP including lifestyle interventions. A total of 97 patients diagnosed with RRMS were screened for participation in the study of which 3 patients did not fulfill the eligibility criteria and 1 patient withdrew consent. Of the 93 randomized patients, 46 were randomized to MSP and 47 to Technical support only.

**Results:** The demographic characteristics of the patients were well-balanced in the two arms. There were no statistical differences (linear mixed model) in any of the primary (p=0.91) or secondary outcomes.

Although the study was slightly underpowered, there was a trend towards better adherence in the MSP group. (p=0.08). No unexpected adverse events occurred.

**Conclusion:** This study did not show a statistical significant effect of teleintervention on HRQoL as compared to traditional hospital based health care.

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Sten Fredrikson has received honoraria from Bayer, Biogen, Genzyme, Merck, Novartis, Sanofi and Teva.
Claes Martin has received honoraria from Bayer, Biogen, Genzyme, Merck, Novartis, Sanofi and Teva.
Stefan Hau has received honoraria from Merck.
Dimitri Guala is working at Merck.
Lillemor Jansson has no disclosures.

**P827**

Physical activity impacts positively on depression and objective sleep in patients with MS

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**Background:** There is growing evidence that regular physical activity has a favorable effect on psychological functioning and sleep. However, as regards patients with MS, evidence is still scarce. The aim of the present study was therefore to investigate the impact of a regular physical activity program on psychological functioning and subjective and objective sleep in patients with MS.

**Methods:** A total of 14 patients (mean age about 40 years; EDSS: 2-5) took part in this longitudinal and four weeks lasting intervention study. At baseline and 4 weeks later, patients completed self-rating scores covering depression, mental toughness and subjective sleep. Further, sleep was assessed via sleep-EEG-recordings at both time points. Patients had physical activity programs every weekday for 1 to 4 hours.

**Results:** Compared to baseline, at the end of the study symptoms of depression and sleep complaints decreased. Objective sleep onset latency decreased, slow wave sleep increased and the number of awakenings decreased, resulting in a more stable objective sleep.

**Conclusions:** In patients with MS, regular physical activity has the potential to impact positively on psychological functioning and subjective and objective sleep.

**Disclosure**

All authors declare no conflicts of interest. The entire study has been performed without external funding.
P828
Profiles of patient-reported outcomes as predictors of treatment type in multiple sclerosis: a discriminant function analysis of disease modifying treatment
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Objective: To characterize how patients with relapse-remitting MS (RRMS) using one of two drug classes of disease modifying treatments (DMTs; orals, including fingolimod and dimethyl fumarate, or infusibles, including natalizumab and rituximab) respond to each of the Quality of Life in Neurological Disorders (Neuro-QoL) Measures

Background: Measures of patient-reported outcomes (PROs) have been shown to be effective for tracking treatment outcomes in multiple sclerosis (MS). Neuro-QoL is a validated series of self-report questionnaires for assessing physical function and symptoms, emotional and cognitive health, and social abilities in clinical populations. Discriminant function analysis (DFA) is a multivariate procedure used to classify groups by determining linear dimensions of observed predictor variables.

Methods: PRO data from 594 patients (age = 44±11.1 years; disease duration = 8.5±7.40; 78.3% female) with RRMS were collected between 2014 and 2017 using the Neuro-QoL Short Forms (SF). A stepwise linear DFA procedure was used to evaluate individual SF scores contributing to the overall discrimination between treatment groups.

Results: Patients were equally distributed between DMTs (Orals=297, Infusibles=297). A single discriminant function was extracted, comprised of only two SF variables and accounting for 100% of variance in DMT group. Overall Chi-square test was significant, Wilks’ λ = 0.982, χ² (2) = 10.566, p=0.005, indicating goodness of fit with the data. Ability to Participate in Social Roles as well as Emotional/Behavioral Dyscontrol were identified as significant function coefficients; the oral group was characterized as having worse self-reported emotional/behavioral dyscontrol, but greater ability to participate in social roles compared to the infusion group. SF scores related to fatigue, sleep disturbance, upper and lower extremity mobility, and cognition were not significantly predictive of DMT group.

Conclusions: These findings suggest that individuals with relapse-remitting MS treated with an oral DMT may differ from those treated with an infusion DMT on self-reported concerns of participation in social activities as well as emotional and behavioral regulation symptoms. As classes of DMTs are now getting more clearly differentiated into distinct delivery types, namely oral versus infusibles, their impact on PROs is more important to identify. Future research can examine differences among individual DMTs.

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