Multiple sclerosis and related disorders 1

PP1216
No evident disease activity (NEDA) in the AFFIRM study: association with brain atrophy and functional outcomes

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Introduction: Analyses were conducted to investigate relationships between ‘no evident disease activity’ (NEDA) and brain atrophy and functional status in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: NEDA was defined as no relapse, no 12-week sustained Expanded Disability Status Scale (EDSS) progression, no gadolinium-enhancing lesions, and no new/enlarged T2 lesions over 2 years. Percentage changes in brain parenchymal fraction (BPF) over the second year of study, changes from baseline to 2 years in Paced Auditory Serial Addition Test-3 (PASAT), Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9-HPT), as well as rates of confirmed EDSS improvement (12-week sustained decrease of ≥0.10 point) were compared in combined natalizumab- and placebo-treated patients from the AFFIRM study.

Results: Overall, 242 of 904 patients (27%) had NEDA over 2 years. Patients with NEDA had smaller median percentage decreases in BPF than patients with disease activity (-0.15% vs. -0.28%; p=0.0055). NEDA was associated with better outcomes from baseline in PASAT scores (median change 2.00 vs NEDA: p=0.0005), T25FW (median change 0.00 seconds vs NEDA vs 0.20 seconds without NEDA; p<0.0001), and 9-HPT (median change -0.73 seconds with NEDA vs -0.24 seconds without NEDA; p<0.0001). Rates of EDSS improvement were greater in patients with NEDA than in patients with disease activity (36.9% vs 22.6%; hazard ratio 1.918 [95% confidence interval: 1.374-2.678]; p=0.0001).

Conclusions: NEDA was significantly associated with less brain atrophy, more disability improvement, and better outcomes in cognitive function, walking speed, and upper extremity function in patients with RRMS.

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PP1217
Quantitative electroencephalography in clinically isolated syndrome and relapsing remitting multiple sclerosis: correlation with cognitive functions

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Introduction: In this study, we aimed to evaluate cognitive impairment in clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS) using quantitative electroencephalography (QEEG) and neuropsychological tests.

Methods: We included 30 CIS, 30 relapsing-remitting MS patients and 34 healthy subjects as controls to the study. Patients were in remission for at least 8 weeks and did not have depression and did not take any drug. In QEEG frequency and interhemispheric coherence were calculated with Fast Fourier Transform (FFT) method in artifact free 36 second epoch of the EEG. Neuropsychological tests assessing attention, executive functions, working memory and visual memory were performed for all subjects.

Results: In RRMS group we detected decreased beta coherence in the frontal regions and decreased delta, theta and beta coherences in the central and parietal regions. We also detected increased delta coherence in the temporal regions of the RRMS patients. However, there was no difference between groups in terms of spectral power analysis. Neuropsychological tests revealed a decreased attention speed in CIS group and RRMS patients had a lower performance in executive functions, information processing speed, attention, working memory and visual memory. There was a correlation between decreased interhemispheric central beta and occipital theta, alpha and beta coherences and executive dysfunction in RRMS patients.

Conclusions: Although QEEG is a sensitive and objective method to evaluate cognitive impairment in RRMS group, it is not able to show early cognitive impairment in CIS.

Disclosure: Nothing to disclose
PP1218

Effects of siponimod (BAF312) alone and when combined with propranolol on absolute lymphocyte count decrease and recovery in healthy subjects

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Introduction: Siponimod (BAF312) is a selective sphingosine-1-phosphate (S1P1,5) receptor modulator under development for secondary progressive multiple sclerosis. We evaluated the pharmacodynamic effects of siponimod 2mg (therapeutic dose) on absolute lymphocyte counts (ALC) and subsequent recovery following treatment discontinuation.

Methods: This was a randomised, double-blind, placebo-controlled study for 20 days in 76 healthy adult subjects with four treatment arms: propranolol 80mg (10 days) on top of siponimod 2mg steady state (Group A), siponimod 2mg (10 days) on top of propranolol steady state (Group B), propranolol (Group C) and placebo (Group D). ALC was measured at baseline, Day 11, Day 21, and end of study (EOS) visit (Day 30-35). ALC was evaluated as a secondary endpoint.

Results: In Group A, mean ALC was decreased to 36% (0.69×10⁹/L) at Day 11 and 31% (0.60×10⁹/L) at Day 21 of pre-treatment levels (1.92×10⁹/L). In Group B, mean ALC was 2.10×10⁹/L at Day 11 compared to 1.91×10⁹/L at baseline. At Day 21, mean ALC in Group B was 0.79×10⁹/L (41% of pre-treatment levels). At EOS in group A and B, ALC recovered to normal levels for all except one subject (Group A). No significant change in ALC was observed in Group C or D.

Conclusion: Siponimod 2mg at steady state led to mean ALC decrease to approximately 30-40% of the pretreatment levels and was not altered by propranolol co-administration. ALC recovered to normal levels after treatment discontinuation.

Disclosure: Shibadas Biswal, Florine Polus, Atul Pawar, Uday Kiran Veldandi, and Eric Legangneux are employees of Novartis. This study was funded by Novartis Pharma AG.

PP1219

Optical coherence tomography versus visual evoked potential: which is more sensitive in detecting optic neuritis of neuromyelitis optica?

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Introduction: Detection rates of optic neuritis (ON) by optical coherence tomography (OCT) or visual evoked potential (VEP) are varying according to the number of attack or disease severity in multiple sclerosis (MS) and neuromyelitis optica (NMO). The aim of this study was to evaluate the utility of OCT and VEP for detecting and discriminating ON between MS and NMO.

Methods: We performed a cross-sectional study of 109 patients with at least 1 clinical ON episode at least 6 months prior (74 NMO and 35 MS patients).

Results: The sensitivity of OCT after ON was 57.6% and VEP sensitivity was 61.9%. For the investigation of disease specific findings without effect of cumulative damage by number of attacks, we focused on one episode ON (33 MS eyes vs 60 NMO eyes). For unaffected eyes, the sensitivity of VEP tends to be higher in MS (18.8%) than NMO (4.3%) (p=0.056) with no difference in the sensitivity of OCT. In one episode ON, the sensitivity of OCT was significantly higher in NMO (50.0%) than MS (21.2%) (p=0.007) with no difference in the sensitivity of VEP. The abnormal OCT in one episode ON may suggest more possibility of NMO (odds ratio=2.36; 95% CI, 1.17 to 4.76).

Conclusions: The sensitivity of VEP and OCT are not different in ON. However abnormal VEP in unaffected eye may be useful for the detection of subclinical ON in MS and abnormal OCT in one episode ON presents 2.4 times more possibility of NMO than MS.

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PP1220

Safety of alemtuzumab by treatment course in patients with active relapsing-remitting multiple sclerosis

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Introduction: Alemtuzumab, as 2 annual treatment courses, demonstrated superior efficacy versus subcutaneous interferon beta-1a with consistent, manageable safety in treatment-naive relapsing-remitting multiple sclerosis (RRMS) patients and those who relapsed on prior therapy. In the CARE-MS studies, approximately 20% of patients received a third alemtuzumab course in Year 3. This report examined safety by course in the alemtuzumab clinical program.

Methods: In the 36-month, phase 2 CAMMS223 (NCT00050778) and 24-month, phase 3 CARE-MS I (NCT00530348) and CARE-MS II (NCT00548405) core studies, active RRMS patients received alemtuzumab 12 mg/day intravenously on 5 consecutive days at baseline and 3 consecutive days 12 months (24 months in CAMMS223) later. All studies included an extension (NCT00930553) with patients receiving as-needed alemtuzumab re-treatment.

Results: 919, 894, and 167 patients received 1, 2, and 3 annual courses of alemtuzumab 12 mg over 3 years, respectively. Proportions of patients with adverse events (AEs; 94.7%, 89.3%, 92.2%), serious AEs (11.5%, 8.6%, 11.4%), and infections (58.8%, 53.0%, 54.5%) were similar after each course. Infusion-associated reactions were less prevalent after first course. Thyroid AE incidence was greatest in Year 3, although this is unlikely due to administration of a third course since it was also observed during Year 3 in patients not receiving a third course.

Conclusions: These data suggest that additional courses of alemtuzumab treatment were not associated with an increase in risk for AEs including infections. Robust patient education and long-term monitoring enabled early detection and treatment of autoimmune disorders.

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PP1221

Idiopathic recurrent transverse myelitis - a multiple sclerosis variant or a different identity?

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Introduction: Recurrent transverse myelitis (RTM) is a common presentation of Multiple Sclerosis (MS) and can be the only manifestation of the disease. When MRI criteria for MS diagnosis are not satisfied and other causes are excluded, Idiopathic Recurrent Transverse Myelitis (RTM-I) is assumed, but it remains in question if this is a MS variant or an independent entity.

Objective: To determine whether RTM-I can be distinguished from RTM-MS on the basis of clinical manifestations and complementary exams.

Methods: Retrospective analysis of clinical charts of patients followed at the Demyelinating Disorders Consultation with RTM as major manifestation. Patients with Neuromyelitis Optica (NMO), NMO spectrum disorders and systemic autoimmune diseases were excluded. Two subgroups were defined: RTM-MS (MS MRI criteria fulfilled), RTM-I (remaining patients).

Results: 38 patients included, 22 RTM-MS, 16 RTM-I. Median follow-up time: 92.2±65.9 months. Regarding the first episode, the RTM-I group had more frequently motor involvement (75%vs.40.9%, p=0.039), incomplete recovery (81.25%vs.22.73%, p=0.002), and prolonged recovery (81.25%vs.45.5%, p=0.028). The initial brain MRI was abnormal in 50% of both groups, only fulfilling MS MRI criteria in the RTM-MS group. Oligoclonal bands (OB) in the cerebrospinal fluid (CSF) were less common in RTM-I (31.3vs.81.3%, p=0.005). No significant difference was found in terms of gender, age, number of recurrences or final EDSS score.

Conclusions: MTR-I seems to be an entity distinct from MS, differing in its clinical presentation with motor involvement preponderance and worse recovery, and in paraclinical studies with absence of OB in CSF and MRI lesions atypical for MS.

Disclosure: Nothing to disclose
PP1222

Fampridine improves gait parameters, balance test and functional independence measurement (FIM) in multiple sclerosis

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Introduction: Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that is prevalent among young adults and usually leads to chronic disability. Ambulation is important to patients with MS, and they perceive it as a major issue for their health. Clinical trials have demonstrated that dalfampridine improves walking ability among patients with MS. We aimed to evaluate this drug’s efficacy on gait parameters, balance test, functional independence measurement retrospectively.

Methods: Datas collected from 20 patients who have MS (15 women, 5 men; aged, 32-61years) diagnosis and have been following by Kocaeli university department of neurology and also had been assessed about gait difficulties by department of physical medicine and rehabilitation before and after one month treatment of 4-aminopyridine (AP) between 2011-2012. In this retrospective pretest-posttest (one group) designed study, disease activity, temporal-spatial gait parameters (which were collected with computerized gait analysis), Berg-Balance test and functional independence measurement (FIM) data analyzed by using Wilcoxon test.

Results: We found significant difference at temporal-spatial gait parameters regarding cadence, stride length, double support and walking speed (p<0.05). Berg-Balance test results was also significantly better after treatment with 4-(AP) (p<0.05). Besides there was no significant change with FIM results (p>0.05).

Conclusions: Although we could not confirm about an improvement at functional independency, Dalfampridine seems as an effective treatment for gait and balance imperfections for MS patients.

Disclosure: Nothing to disclose

PP1223

Rituximab experience in neuromyelitis optica: data from a single center in Turkey

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Introduction: Rituximab, an anti-CD20 monoclonal antibody has been suggested as an agent for neuromyelitis optica (NMO) by EFNS guidelines. To date, variable results with this treatment have been reported. We would like to present our experience with rituximab in NMO spectrum diseases.

Methods: NMO patients who received rituximab were selected from our database. Age at disease onset, duration of disease, clinical attack rate and Expanded Disability Status Scale (EDSS) scores before and after the treatment were recorded.

Results: Seven patients were included (Median age: 33, all females). Median age at disease onset was 23 years (range 12-49) while median duration of disease was 3 years (0-39) at the time of rituximab treatment. Main reason for switching patients to rituximab was either treatment failure or intolerance with steroids or other immunosuppressants. Median clinical attack rate was 2 attacks/patients/year (range 1-3) before treatment, which was 1.5 attacks/patients/year(range 0-3) after treatment. CD20 levels were below %3 during attacks. Median EDSS score was 8.0 before (range 2-8.5) and after (range 2-10) rituximab at the end of follow up (median: 23 months, range 7-25). Post-treatment EDSS scores and attack rate was not available for one patient. Two patients were not analyzed since they were on RTX for less than a year.

Conclusions: Rituximab, despite CD20 depletion, could not perform a significant decrease in clinical - radiological attack rate or EDSS scores. In patients with already worsening disease and with lack of adequate response to other immunosuppressants, rituximab may not be able to achieve remission.

Disclosure: Nothing to disclose
PP1224

Spastic paraparesis associated with anti-aquaporin-4 antibodies in a patient infected with hepatitis C virus

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Introduction: Hepatitis C virus (HCV) infection is associated with several neurological manifestations, considered to result from neuro-immunological dysregulation, sometimes associated to interferon-alpha treatment. We report a case of a patient with spastic paraparesis, positive anti-aquaporin-4 antibodies (anti-AQP4 Ab) and non-treated HCV infection.

Case report: A 48-year-old woman, with a previous diagnosis of non-treated hepatitis C, presented with a 10-year history of progressive gait disturbance, attributed to Primary Progressive Multiple Sclerosis. She had an irregular clinical follow-up. Neurological examination disclosed a grade 4 spastic paraparesis, hyperreflexia in lower limbs, right positive Hoffmann sign, bilateral Babinsky sign and spastic gait only possible with bilateral support. Brain MRI showed an asymmetric, bilateral pontine and left mesencephalic hyperintense signal in T2/FLAIR, with no gadolinium enhancement. Spinal MRI was normal. Visual evoked potential revealed bilateral prechiasmatic hyperintense signal in T2/FLAIR, with no gadolinium enhancement. Spinal MRI was normal. Visual evoked potential revealed bilateral prechiasmatic conduction delay. Blood tests showed positive anti-HCV antibody with a viral load of 4517000 IU/mL and a positive anti-AQP4 Ab with cell-based assay test (1/1024).

Cerebrospinal fluid (CSF) analysis was normal, with no oligoclonal bands. The patient started IV methylprednisolone followed by oral prednisolone, interferon-alpha and ribavirin. There was a slight clinical improvement two weeks later.

Conclusions: We present a case of optic and brainstem demyelinating disorder associated with anti-AQP4 Ab. There are 5 case reports describing association between HCV infection and central nervous system (CNS) demyelination with positive anti-AQP4 Ab, 3 patients previously treated with interferon-alpha. Anti-AQP4 Ab should be tested in patients infected with HCV and CNS demyelination.

Disclosure: Nothing to disclose

PP1225

Vestibular evoked myogenic potentials in evaluation of brainstem involvement in multiple sclerosis

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Introduction: The aim of this study was to determine the usefulness of vestibular evoked myogenic potentials (VEMP) in the brainstem involvement in multiple sclerosis (MS).

Methods: 50 healthy controls (group 0), 50 MS patients without (group 1) and 50 MS patients with (group 2) clinical signs of brainstem involvement were enrolled. Age, gender, Expanded Disability Status Scale (EDSS) score and brainstem functional system score (BSFS) were collected from all patients. Ocular (oVEMP) and cervical VEMP (cVEMP), using acoustic clicks of 1 ms duration, intensity of 130 dB SPL and 1 Hz stimulation frequency, were performed in all participants and differences in latencies and amplitudes were analyzed between three groups.

Results: Group 1 showed statistically significant prolonged N10 and P13 oVEMP latencies bilaterally in comparison to group 0 (all p values <0.0001). In group 2 in comparison with group 0 statistical significance was reached for bilateral oVEMP latencies (all p values <0.0001) and following cVEMP latencies: waves N23 SCM right and left, P13 SCM (p=0.003, p=0.016 and p=0.018 respectively). There were no significant differences between groups 1 and 2 (all p values >0.177). No conduction block was identified in group 0, while conduction block in at least one explored wave was observed in 5 subjects (10%) in group 1 and 17 subjects (34%) in group 2, reaching statistical significance p=0.004.

Conclusions: VEMP is a reliable method in detection of symptomatic and asymptomatic brainstem involvement in MS and it is superior to clinical examination in detection of brainstem lesions.

Disclosure: Nothing to disclose
**PP1226**  
Intermittent symptomatic atrioventricular block during fingolimod initiation

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**Introduction:** Fingolimod is an oral sphingosine-1-phosphate receptor modulator used for the treatment of relapsing-remitting form of multiple sclerosis (RRMS). Although the drug is safe, certain side effects exist, with cardiac conduction abnormalities and elevation of liver enzymes being the most severe.

**Case presentation:** A 47-year-old female patient with RRMS developed an intermittent, symptomatic Weckenbach type of atrioventricular block five hours after the first dose of fingolimod that lasted five hours and resolved completely. The same reaction occurred after the second dose of the drug, which was discontinued. Magnetic resonance imaging showed demyelinating lesions in the cerebral hemispheres, at C6-C7 and C7-C8 vertebral levels and one gadolinium-enhancing lesion at T1-T2 level. Evaluation of the patient’s autonomic nervous system (ANS) function was performed by reviewing heart rate variability (HRV) from the holter’s R-R intervals and applying modified Ewing’s Tests, namely orthostatic, sustained handgrip and deep breathing test. Frequency domain analysis of HRV showed increased parasympathetic activity expressed as high frequency component and decreased sympathetic tone expressed as low frequency, implying ANS abnormalities (Fig 1B). In Ewing tests, whereas the patient reacted normally to both orthostatic (heart rate and blood pressure response) and deep breathing tests, she could not increase diastolic blood pressure during sustained hand-grip, suggesting impaired cardiac sympathetic activity.

**Conclusion:** Expression of this particular arrhythmia might be related to ANS dysfunction due to demyelinating lesions in the upper thoracic spinal cord that have been previously associated with myocardial ischemia and arrhythmias, possibly augmented by the parasympathetic effect of the drug.

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**PP1227**  
Spatial QRS-T angle is increased in MS patients possibly due to ANS dysfunction

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**Introduction:** Widening of ECG derived spatial QRS-T angle(sQRS-Ta) has been predictive of cardiovascular events in the general population. However, its significance in MS patients is not known.

**Methods:** sQRS-Ta was derived from the baseline resting 12 lead ECG of randomly selected 125 patients, aged 41.08±12.22 years old. Mean duration disease was 4.08±5.8 years and they were compared with sex and age adjusted healthy subjects. All participants were free of cardiac abnormalities with at least an ejection fraction of >50% at echocardiography. The presence of left ventricular hypertrophy (LVH), diastolic dysfunction of left ventricle (DD) as well as demographics related to therapy and comorbidities were noted. Exclusion criteria were the presence of coronary artery disease, arterial hypertension and diabetes mellitus. Heart rate, QRS duration, QT and QT corrected were calculated. 85 patients with established MS, were screened for the incidence.

**Results:** sQRS-Ta was wider in MS group compared to healthy one(17.61±10.93 vs 13.03±5.97, p<0.001 and was not associated with the age, the presence of DD or LVH, thyroid disease, smoking and/or obesity. Heart rate,QRS duration, QT and QT corrected were calculated. 85 patients with established MS, were screened for the incidence.

**Conclusions:** Ventricular repolarization heterogeneity, as reflected by wider sQRS-Ta is common in MS. Possible mechanism is Autonomic Nervous System dysfunction which is common in MS patients.

**Disclosure:** Nothing to disclose
PP1228

Delayed-release dimethyl fumarate and relapses requiring intravenous steroid use and MS-related hospitalizations: integrated analysis of the phase 3 DEFINE and CONFIRM studies

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Introduction: To evaluate the effect of delayed-release dimethyl fumarate (DMF) in reducing the number of relapses requiring intravenous (IV) steroids and MS-related hospitalizations in relapsing-remitting MS (RRMS) patients, a pre-specified integrated analysis of the Phase 3 DEFINE and CONFIRM studies was conducted.

Methods: Eligibility criteria included age 18-55, RRMS diagnosis (McDonald criteria), and EDSS score 0-5.0. Patients were randomized and received treatment with placebo, delayed-release DMF 240mg twice (BID) or three times daily (TID), or glatiramer acetate (CONFIRM only), for up to 2 years. Numbers of relapses requiring IV steroids and MS-related hospitalizations were tertiary endpoints in DEFINE and CONFIRM.

Results: The integrated analysis included a total of 2,301 patients, including 771, 769, and 761 in the placebo and delayed-release DMF BID and TID groups, respectively. At 2 years, compared with placebo, delayed-release DMF reduced the annualized rate of relapses requiring IV steroids by 48% (BID; rate ratio [95% confidence interval]: 0.519 [0.425-0.635]; p<0.0001) and 50% (TID; 0.501 [0.408-0.614]; p<0.0001), and reduced the annualized rate of MS-related hospitalizations by 34% (BID: 0.660 [0.472-0.921]; p=0.0146) and 47% (TID: 0.529 [0.372-0.752]; p=0.0004).

Conclusion: Delayed-release DMF significantly reduced the number of relapses requiring IV steroids and MS-related hospitalizations, suggesting benefits with regard to patient burden and health economic savings due to decreased resource utilization. These findings further support the efficacy results of DEFINE and CONFIRM.

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PP1229

Natalizumab in spinal relapsing-remitting multiple sclerosis

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Introduction: Multiple sclerosis (MS) with spinal involvement is associated with poor prognosis. The aim of this study was to evaluate the efficacy of natalizumab (NTZ) in patients with spinal relapses.

Methods: Multicenter, retrospective study with prospectively collected data. Relapsing-remitting (RR)-MS patients treated with NTZ for ≥1 year following a spinal relapse (SR) defined as spinal patients (S-P), were compared to a matched control group free from SR ≥2 years prior to NTZ treatment (non-spinal patients, NS-P). Patients received quarterly neurological evaluation and yearly brain MRI. Study endpoints were mean annualized relapse rate (ARR), disability progression (measured by expanded disability status score [EDSS] score), cumulative probability of EDSS progression (of at least 1 point if EDSS ≤5.5 and 0.5 points if EDSS >5.5), and new brain T2 and gadolinium enhancing lesions at year 1 and after a mean of 3 years as well as the severity of qualifying SR.

Results: 220 NTZ-treated patients were screened of which 68 S-P and 68 NS-P were included. Mean ARR was similar between groups at one year (S-P: 0.06; NS-P: 0.06; p=0.89) and after a mean of 3 years (S-P: 0.06; NS-P: 0.07; p=0.48). Mean EDSS increase and radiological parameters at 1 and 3 years were similar in S-P and NS-P as well. SR qualifying for NTZ were more disabling than non-SR (p=0.02).

Conclusions: Up to 3 years, NTZ treatment had a similar efficacy in S-P and NS-P. Attacks qualifying for NTZ treatment were more disabling in S-P compared to NS-P.

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PP1230
Clinical efficacy of delayed-release dimethyl fumarate in relapsing-remitting MS (RRMS) patients with highly active disease: integrated analysis of the phase 3 DEFINE and CONFIRM studies
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Introduction: To assess the clinical efficacy of delayed-release dimethyl fumarate (DMF) over 2 years in RRMS patients with highly active disease at baseline, a post-hoc analysis of integrated data from the Phase 3 DEFINE and CONFIRM studies was conducted.
Methods: Eligibility criteria included age 18-55 years, RRMS diagnosis (McDonald criteria), and EDSS score 0-5.0. Patients were randomized and received treatment with placebo (n=771), delayed-release DMF 240mg twice (BID; n=769) or three times daily (TID; n=761), or glatiramer acetate (CONFIRM only; n=350), for up to 2 years.
Results: 136 patients met criteria for highly active disease (defined as ≥2 relapses in the year prior to entry into DEFINE/CONFIRM and ≥1 gadolinium-enhancing lesion at baseline), including 48, 45, and 43 in the placebo and delayed-release DMF BID and TID groups, respectively. In these patients, at 2 years, ARR was reduced significantly by delayed-release DMF BID (rate ratio [95% confidence interval]: 0.397 [0.222−0.710]; p=0.0018) and borderline significantly by delayed-release DMF TID (0.599 [0.353−1.015]; p=0.0570). The proportion of patients relapsed was reduced significantly by delayed-release DMF BID (hazard ratio [95% confidence interval]: 0.368 [0.190−0.712; p=0.0030] but not TID (0.696 [0.388−1.250]; p=0.2254). There was no significant effect of delayed-release DMF on time to sustained 12-week disability progression. Other definitions of highly active will also be examined.
Conclusions: These findings suggest that delayed-release DMF 240mg BID demonstrates clinical efficacy in RRMS patients with highly active disease. However, due to the small sample size, the results should be interpreted with caution.
Disclosure: Study supported by: Biogen Idec, Inc.

PP1231
Catastrophic rebound after natalizumab treatment discontinuation
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Introduction: Natalizumab (NTZ) is a very effective drug for the treatment of relapsing-remitting multiple sclerosis (RRMS). In some patients discontinuation is needed due to the risk of progressive multifocal leukoencephalopathy (PML). After discontinuation severe clinical and radiological worsening has been described in some patients.
Methods: From a cohort of natalizumab treated patients, 25 patients were switched to fingolimod, those who had a rebound after discontinuation were selected. Clinical and magnetic resonance imaging (MRI) data were collected. Our aim is to describe the clinical and radiological characteristics these patients before and after the rebound.
Results: 4 patients were included, disease duration 9.325 yrs; mean time with NTZ of 3.1 years; all patients were positive for JCV. In the 3 following months after discontinuation all patients started with fingolimod. Despite the treatment, after stopping the patients started with neurological deterioration (mean 4.15 months with multifocal involvement: 75% presented with motor disturbances, 50% cognitive impairment, and 25% seizures. The average worsening in EDSS was of 2.75 points [1.5-5 points]. The MRI showed an increase in T2 and gadolinium lesions on MRI, with a mean of 21 enhancement-lesions [11-45]. All patients received 5 days of intravenous methylprednisolone, and one patient required plasmapheresis. After the rebound 3 patients continued with fingolimod, only one patient restarted NTZ.
Conclusions: Discontinuation of NTZ treatment can trigger a severe rebound with a marked clinical and radiological worsening. A close monitoring and a short washout period is recommended after drug withdrawal.
Disclosure: Nothing to disclose
PP1232

Intractable hiccup in multiple sclerosis treated by plasmatic exchanges

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Introduction: Intractable hiccups is rarely described with inflammatory disease; seen specifically in neuromyelitis optica (NMO), hiccups is possible in multiple sclerosis (MS).

Observation: A 28-year-old man was admitted to paraparesis associated with hiccups and vomiting. Brain MRI showed T2 and FLAIR hyperintensities; medular MRI was normal. Lumbar puncture identified an inflammatory liquid with oligoclonal bands. With a high dose of corticosteroids, spastic paraparesis was improved. A diagnosis of MS was made and a mitoxantrone treatment was started. Intractable hiccups was noted 2 months later. A new brain MRI revealed T2 weighted hyperintensities in the area postrema. Serum neuromyelitis optica antibodies (NMO Ab) were negative. Hiccups was persistent after symptomatic treatment. Finally the patient benefited from plasmatic exchanges (EP). After 2 courses of 4 EP associated with Gabapentine, hiccups and vomiting disappeared, without relapse.

Discussion: Hiccups and vomiting are more often seen in NMO. Associated with many locations, they are mainly described in medulla oblongata; this area, including the area postrema, has a high aquaporine 4 expression (AQP4). However, hiccups and vomiting are rarely described in patients suffering from MS. Thus, the clinical and cerebral MRI involvement in our patient allowed us to make this diagnosis of MS. Hiccups and vomiting are thus resistant and validate our discussion of the advantages of EP, with excellent results.

Conclusion: Hiccups and vomiting in inflammatory diseases need to be discussed regarding NMO but they can also reveal MS. These symptoms are resistant to classic treatment, but can respond to EP.

Disclosure: Nothing to disclose

PP1233

Delayed-release dimethyl fumarate and freedom from measured clinical and neuroradiologic disease activity in relapsing-remitting multiple sclerosis (RRMS) patients: integrated analysis of DEFINE and CONFIRM

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Introduction: To evaluate the effect of delayed-release dimethyl fumarate (DMF) on the proportion of RRMS patients with no measured clinical and/or neuroradiologic disease activity, a post-hoc analysis of integrated data from the Phase 3 DEFINE and CONFIRM studies was conducted.

Methods: The integrated analysis included treated patients randomized to placebo or delayed-release DMF 240mg twice (BID) or three times daily (TID). Absence of clinical disease activity (no relapses and no EDSS progression over 2 years) was analyzed in the intent-to-treat (ITT) population. Absence of neuroradiologic (no new/enlarging T2 and no gadolinium-enhancing lesions over 2 years) and overall disease activity (no measured clinical or neuroradiological disease activity over 6 months, 1 year, or 2 years) were analyzed in the MRI population. Absence of neuroradiologic (no new/enlarging T2 and no gadolinium-enhancing lesions over 2 years) and overall disease activity (no measured clinical or neuroradiological disease activity over 6 months, 1 year, or 2 years) were analyzed in the MRI cohort.

Results: A total of 2,301 patients (1,046 in the MRI cohort) were included. At 2 years, in the delayed-release DMF BID and TID vs placebo groups, the proportions of patients with no measured clinical disease activity were 69% and 71% vs 53%; the proportions with no measured neuroradiologic disease activity were 34% and 35% vs 20%; and the proportions with no measured overall disease activity were 23% and 23% vs 11% (all p<0.0001). Results for overall disease activity at 6 months and 1 year (MRI population) and at 2 years (patient subgroups stratified by age, gender, treatment history, prior relapses, and baseline EDSS score) will also be presented.

Conclusions: Delayed-release DMF significantly increased the proportions of RRMS patients free of measured clinical, neuroradiological, and overall disease activity.

Disclosure: Study supported by Biogen Idec, Inc.
PP1234
Nitric oxide synthases gene polymorphisms and multiple sclerosis
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Background: Although the role of nitric oxide (NO) in the pathogenesis of inflammation at multiple sclerosis (MS) is well documented, main of the studies are focused only on inducible nitric oxide synthase (iNOS) isoform as the high-output producer of NO. In the animal model, the level expression of iNOS correlates with severity of clinical sign. Expression of iNOS was also observed in active plaques in MS patients. A positive correlation between plasma and cerebrospinal fluid levels of nitrates/nitrites and clinical disease activity and MS course has been found.

Objectives: The aim of the study was to investigate the association between -2447 C/T and -1026 G/T iNOS polymorphism, -786T/C endothelial nitric oxid synthase (eNOS) polymorphism and -5266C/T neuronal nitric oxid synthase (nNOS) polymorphism and multiple sclerosis.

Methods: We genotyped a total of 90 unrelated patients (23 men, 67 women) with definitive MS according to McDonald criteria and 53 healthy controls matched for age and sex. Genotyping was performed using PCR with restriction analysis. Genotype frequencies were compared by Chi-square and Fisher’s exact tests.

Results: We observed no remarkable differences in genotype or allele distribution in the case-control comparison for all study polymorphisms (nNOS: Pg=0.52, Pa=0.82, eNOS: Pg=0.28, Pa=0.69, iNOS -1026G/T : Pg=0.81, Pa=0.56, iNOS -2447C/T : Pg=0.87, Pa=0.9).

Discussion: Our results did not confirm an association between genetic variations in iNOS gene and susceptibility to multiple sclerosis (although some previous studies did), neither in eNOS and nNOS genes.

Disclosure: Nothing to disclose

PP1235
Natalizumab increased the probability of clinically important confirmed walking speed improvement in AFFIRM
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Introduction: Treating walking impairment is important to MS patients. A post hoc analysis of the AFFIRM trial was performed to assess the effects of natalizumab on walking speed (WS) improvement.

Methods: WS was calculated from timed 25-foot walk assessments. Kaplan-Meier estimates of patients with 3-month confirmed ≥20% WS improvement from baseline were compared between natalizumab (N=613) and placebo (N=301) groups at years 1 and 2 of AFFIRM with subgroups defined by baseline Expanded Disability Status Scale (EDSS) scores. Patient-reported physical functioning, assessed by SF36-Physical Component Summary (PCS), was compared between those with and without ≥20% WS improvement.

Results: Natalizumab significantly increased the probability of ≥20% WS improvement at year 2 by 78% (p<0.05) (figure 1) and at year 1 by 5-fold in the subgroup with EDSS ≥4.0 (p<0.05) (figure 2). Similar trends were observed across all subgroups. Regardless of treatment, patients with ≥20% WS improvement over 2 years had a 2.7-point mean improvement in SF36-PCS, while patients without 20% WS improvement had a 0.3-point mean worsening (p<0.01). Of all patients with ≥20% WS improvement over 2 years, 24% had ≥1-point EDSS improvement.

Conclusions: In AFFIRM, natalizumab increased the probability of confirmed ≥20% WS improvement for relapsing-remitting MS patients. Treatment effects were larger for patients with higher EDSS. The association between 20% WS improvement and physical quality of life supports the clinical meaningfulness of this measure. The disparity between 20% WS and EDSS improvement suggests that this outcome captures treatment effects distinct from those measured by EDSS.

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**PP1236**

**Cognitive evolution in Tysabri (natalizumab) treated multiple sclerosis patients**

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**Introduction:** Cognitive dysfunction affects 40-60% of MS patients and progresses over time. Natalizumab has shown to be superior to placebo in preserving cognitive function for the first two years of therapy. The objectives are to understand the impact of natalizumab on cognition beyond two years of therapy and investigate whether baseline characteristics are predictive of clinical response.

**Methods:** This is a single-center, 24-month, observational study. Sixty-three patients treated with natalizumab were assessed prior to monthly infusions using the Cogstate battery and SDMT. The Beck depression questionnaire was also administered at baseline and every 4th month prior to infusion. Patient demographics, MS treatment history, EDSS, MSSS, and natalizumab treatment duration were collected at baseline. Patients with cognitive impairment from other causes were excluded. A linear mixed model was conducted with time on natalizumab (4 years, n=12) as a between-subjects factor, time point as a within-subjects factor, and age, EDSS, type of MS and number of prior drug treatments as covariates. The current data are from the 12-month interim analysis.

**Results:** Irrespective of time on natalizumab, significant improvements were observed in executive function (p<0.0001), verbal memory (p<0.0001), and working memory (p<0.0001), whereas processing speed (p=0.19) and attention (p=0.15) remained unchanged. Only one patient had clinically meaningful decline, defined as a decline of 1 or more standard deviations over three consecutive months on two or more Cogstate tests.

**Conclusions:** Interim analysis suggests that natalizumab can preserve cognitive function and the ability to learn beyond two years of continuous therapy.

**Disclosure:** Study supported by an unrestricted grant from BiogenIdec. Brian Harel, Adrian Schembri and Joanne Gale are employees of Cogstate.

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**PP1237**

**Sexual dysfunction in patients with MS**

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**Introduction:** MS may reduce the QoL of patients. One component of QoL is sexual satisfaction. Sexual function remains understudied among patients with MS in Ukraine.

**Aim:** To investigate the sexual function in patients with RRMS depending on treatment type, disease duration and frequency of attacks.

**Methods:** 90 patients suffering from RRMS were examined, 50 women and 40 men aged 18-35 years. The Female Sexual Function Index (FSFI) for women and The Male Sexual Quotient exam (MSQE) for men were used to assess sexual function. SF-36 questionnaire was used to assess the QoL, and Beck Depression Scale to assess depression. Patients were divided into groups according to their treatment; the number of attacks per year; the duration of disease; by sex.

**Results:** Sexual satisfaction was generally higher in women than in men (p=0.013). No significant differences in sexual satisfaction were found among the groups of patients receiving disease-modifying therapy and treatment-naive among both men and women (p=0.101). Intensity of sexual dysfunction was clearly correlated with the number of attacks per year (p=0.002) and with disease duration (p=0.003). Sexual dysfunction was correlated with depression (p=0.012) and with reduced QoL (p=0.015).

**Conclusions:** Sexual dysfunction can be considered as one of the symptoms of MS, requiring medical attention and leading to reduced QoL of patients. Intensity of sexual dysfunction depends on the number of attacks per year and disease duration. Depression can be both a cause and a consequence of sexual dysfunction and patients with MS.

**Disclosure:** Nothing to disclose
PP1238

Delayed-release dimethyl fumarate and health-related quality of life (HRQoL) in relapsing-remitting multiple sclerosis (RRMS) patients according to prior therapy: integrated analysis of DEFINE and CONFIRM


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Introduction: To evaluate the effect of delayed-release dimethyl fumarate (DMF) on HRQoL in RRMS patients with a history of treatment with interferon beta-1a/1b or glatiramer acetate (GA; prior ABCRE subgroup) or no prior MS treatment (treatment-naïve subgroup), a post-hoc analysis of integrated data from the Phase 3 DEFINE and CONFIRM studies was conducted.

Methods: Eligibility criteria included age 18-55 years, RRMS diagnosis (McDonald criteria), and EDSS score 0-5.0. Patients were randomized to placebo (n=773), delayed-release DMF 240mg twice (BID; n=773) or three times daily (TID; n=761), or GA (CONFIRM only; n=360), for up to 96 weeks (2 years). HRQoL was assessed using the Physical and Mental Component Summary (PCS/MCS) scales of the Short Form-36 version 1.

Results: In the prior ABCRE subgroup, there were 208 placebo patients and 196 delayed-release DMF BID patients. In the treatment-naïve subgroup, there were 377 placebo patients and 380 delayed-release DMF patients. The remaining patients had a history of non-ABCRE MS treatment. At Week 96, in the prior ABCRE subgroup, mean changes from baseline in PCS and MCS scores were significantly improved with delayed-release DMF BID vs placebo (PCS, p=0.0066; MCS, p=0.0173). In the treatment-naïve subgroup, mean changes from baseline in PCS but not MCS scores were significantly improved with delayed-release DMF BID vs placebo (PCS, p=0.0132; MCS, p>0.05). Results for delayed-release DMF TID will also be presented.

Conclusions: Delayed-release DMF demonstrated similar benefits on HRQoL over 2 years in patients with prior ABCRE treatment or no prior MS treatment.

Disclosure: Study supported by: Biogen Idec, Inc.

PP1239

Quantifying cognitive deficits in multiple sclerosis: an extensive evaluation of a short version of Rao’s Brief Repeatable Battery (BRB)


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Introduction: Cognitive impairment is frequent in Multiple Sclerosis (MS) and may be economically monitored by the Brief Repeatable Battery (BRB; Rao, 1990). Even a short version of the BRB may be highly accurate. Subtests examining cognitive processing speed, working memory and long-term memory, have been shown to display high sensitivity and specificity (Portaccio et al., 2009). To date, the latter observations rely predominantly on data testing sensitivity and specificity of a BRB subtest with respect to cognitive impairment detected by the entire BRB. In contrast, studies which use more extensive neuropsychological assessments as refined indicators of verified cognitive impairment are sparse.

Methods: Sensitivity and specificity of BRB subtests were examined in 110 MS-Patients in relation to cognitive impairment determined in a subsequent extensive neuropsychologic diagnostic procedure (2.5 hours duration). The latter involved computerized tests, which addressed the cognitive domains relevant for BRB subtests.

Results: Intercorrelations of BRB subtests and computerized tests of the extensive procedure were highly significant (all p-values <0.01). Sensitivity (range: 47-58%) and specificity (range: 86-87%) of BRB subtests resembled findings of previous work. When subtests were combined, sensitivity increased to 80%, while specificity dropped to 52%.

Conclusions: High sensitivity and specificity of BRB subtests could be confirmed with regards to an extensive diagnostic procedure for the first time. While these attributes were observed for separate subtests, the combination of subtests may foster sensitivity at the expense of specificity when considering extensively validated psychological impairment.

Disclosure: Authors of the current work received support from Bayer Vital GmbH, Biogen Idec GmbH, Boehringer Ingelheim Pharma GmbH, Genzyme GmbH, MEDA Pharma GmbH, Merck Serono GmbH, Novartis Pharma GmbH, Sanofi-Aventis GmbH and Teva GmbH.
PP1240

Peg-interferon beta-1a may improve recovery following relapses: post-hoc analyses of the pivotal phase 3 ADVANCE study in patients with relapsing-remitting multiple sclerosis

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Objective: To determine whether subcutaneous peginterferon beta-1a (PEG-IFN; 125µg) every 2 (Q2W) or 4 (Q4W) weeks improved recovery following relapses (RfR) during Year 1 of the ADVANCE study, and to examine the relationship between functional systems scores (FSS) during a relapse and following 3-month sustained disability progression (SDP).

Methods: SDP due to incomplete RfR was defined as onset of 3-month SDP (≥1.0- or ≥1.5-point increase in Expanded Disability Status Scale score, from respective baseline scores of ≥1.0 or 0.0, confirmed after 12 weeks) within 180 days of a relapse. Simultaneous FSS worsening was defined as ≥1 point change caused by a relapse, with the same FSS being part of the SDP.

Results: Overall, n=55 experienced SDP associated with relapses; n=57 experienced SDP not associated with relapses (fewer on PEG-IFN versus placebo). Relapse severities were not different between groups. Approximately 90% with SDP had ≥1 FSS with simultaneous worsening during the preceding relapse; evident in 87% within 15 days of the most recent relapse (most frequent in pyramidal [55.3-55.7%]). Q2W and Q4W reduced the proportion of patients experiencing SDP due to incomplete RfR versus placebo by 56% (p=0.012) and 41% (p=ns), respectively. Following a recent relapse, a lower proportion receiving Q2W (13.6%) and Q4W (15.2%) had SDP versus placebo (19.6%); indicating relative reductions in risk of SDP following any relapse of 30% and 22%, respectively.

Conclusions: PEG-IFN, compared with placebo, significantly improved RfR. Approximately half of patients with SDP in Year 1 of ADVANCE did not have an associated relapse.

Disclosure: Study sponsored by Biogen Idec Inc. (Cambridge, MA, USA). BCK: honoraria from Bayer Schering, Biogen Idec Inc., Merck Serono, Novartis, Roche, Sanofi Aventis, and Teva Neurosciences, and financial support for research from Bayer Schering, Biogen Idec Inc., Merck Serono, and Teva; TFS: consulting fees from Biogen Idec Inc., Novartis, Teva Neuroscience, Genzyme and Accorda; SDN: consulting fees from Biogen Idec Inc. and Genzyme; SS, SH, XY, BS: employees of Biogen Idec Inc.

PP1241

Factors influencing clinically meaningful physical deterioration in patients with relapsing-remitting multiple sclerosis: results from the ADVANCE study

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Objective: ADVANCE, a Phase 3, randomised, double-blind study, showed superior effects of peginterferon beta-1a (PEG-IFN) 125 µg every 2 (Q2W) and 4 (Q4W) weeks over placebo at 1 year in patients with relapsing-remitting multiple sclerosis (RRMS). This analysis investigated the influence of treatment and disease factors on clinically-meaningful physical deterioration (CMPD) as assessed by the Multiple Sclerosis Impact Scale (MSIS-29).

Methods: The MSIS-29 was assessed at baseline, 12, 24, and 48 weeks. A ≥7.5-point increase from baseline, obtained from literature, was used to define CMPD in the MSIS-physical subscale. A repeated measures logistic regression model was used to assess the impact of treatment, baseline, and time-dependent predictors, and interaction terms of treatment and predictors on the risk of experiencing CMPD. Significant factors at p<0.1 were retained in the final model, unless they were clinically meaningful.

Results: Data from 1,508 patients were included in the analysis. Compared to placebo, the proportions of patients with CMPD were consistently lower with PEG-IFN treatment, especially with the Q2W regimen at Week 48 (Figure 1). Relapses and disability progression were found to be the main factors influencing CMPD (Table 1). The odds of experiencing a CMPD caused by disability progression tended to be lower with PEG-IFN than with placebo (Table 1).

Conclusions: Relapses and disability progression are the key contributors to CMPD. PEG-IFN treatment incurred no additional risk of CMPD and may have the potential to lower it by reducing the risks of these events, as well as the impact of disability progression.

PP1242
Cortical activation changes following botulinum toxin treatment of leg spasticity in multiple sclerosis
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**Background:** Botulinum neurotoxin (BoNT) treatment affects multiple levels of the sensorimotor system and can relieve spasticity of lower limbs caused by multiple sclerosis. The aim of our functional magnetic resonance study was to evaluate cortical activation changes following botulinum-toxin treatment of leg spasticity in multiple sclerosis.

**Methodology:** 4 patients (1 man, 3 women, mean age 46.5, SD 9.3 years) with multiple sclerosis affected with leg spasticity were studied. Patients performed repeated knee extension-flexion movements during brain functional MRI which was acquired in three sessions: before and 4 and 12 weeks after BoNT treatment into the spastic muscles. The change of leg spasticity was assessed using the Snow scale.

**Results:** BoNT treatment decreased leg spasticity across the group. fMRI pre-BoNT treatment showed extensive bilateral task-related activation of frontoparietal sensorimotor cortical areas, whereas post-BoNT treatment caused retraction to midline and contralateral sensorimotor cortex. Third examination after 12 weeks of BoNT treatment showed re-expansion to a similar extent as seen in the pre-BoNT session.

**Conclusions and relevance:** This pilot study suggests that relief of leg spasticity may be associated with temporary partial normalization of activation in primary and association sensorimotor cortical areas. Spasticity may be contributing to the documented compensatory overactivation of the sensorimotor system in multiple sclerosis.

**Disclosure:** Nothing to disclose

PP1243
Cognitive dysfunction and the relationship of fatigue and depression in primary Sjögren syndrome
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**Introduction:** There are few studies that demonstrate cognitive dysfunction in primary Sjögren syndrome. The cognitive deficits were on attention, information processing, executive function and memory. The aim of this study is to determine the prevalence cognitive dysfunction and the relationship with fatigue and depression in PSS.

**Methods:** An evaluation was made with 33 cases in between July 2011 and August 2013, and 20 control cases with similar demographic characteristics and education levels. The clock drawing test, COWAT, PASAT, BNT, SDLT, AVLT, BJLOT and RCFT were administered. Depression was defined by using Hamilton Depression Scale and Beck Depression Inventory. SF-36, EQ-5D and FSS were applied in order to evaluate daily life activities, health status and fatigue.

**Results:** We detected a decrease in the test performance in COWAT, PASAT, SDLT, AVLT and BJLOT. It was determined that there was an impairment in the test performance of attention, information processing, short-term and long-term memory, and visual-spatial perception (p<0.05). There was an increase in the severity of fatigue and a decrease in daily life activities when compared to healthy controls (p<0.05).

**Conclusions:** Cognitive dysfunction defined in primary Sjögren syndrome was described with fronto-subcortical dysfunction. White matter anomalies detected in MRI and a hypoperfusion demonstrated by SPECT in frontal, parietal, cingulate and hippocampal areas were found to be correlated with an impairment in executive function and visual-spatial perception. The administration of the detailed neuropsychological tests is useful in identifying subclinical and clinical cognitive dysfunction.

**Disclosure:** Nothing to disclose
PP1244

Investigation of (ONO-4641) cardiac effects of ceralifimod

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Introduction: We assessed the effects of ceralifimod (ONO-4641), a selective, sphingosine-1-phosphate receptor-1 and -5 agonist, on cardiac rate and conduction at four dose levels, compared with placebo and fingolimod.

Methods: A total of 144 healthy volunteers were randomized to ceralifimod (ONO-4641; 0.01, 0.025, 0.05 or 0.10mg), placebo, or fingolimod (0.5mg) once daily for 14 days. Twenty-four-hour 12-lead Holter monitoring was performed at pre-dose (Day -1) and Days 1, 2, 4, 7 and 14 to determine heart rate (HR), PR interval and further electrocardiographic parameters at serial time points and as averaged hourly HRs (hHR).

Results: Ceralifimod (ONO-4641) showed a dose-dependent decrease in resting HR and hHR. On Day 1, the largest mean decrease from baseline HR was -3.0bpm, -3.6bpm, -5.3bpm at 6 hours post-dose with ceralifimod 0.01, 0.025, 0.05mg, respectively, and -9.4bpm at 7 hours after dosing with ceralifimod 0.10mg compared with -12.2bpm at 7 hours in the fingolimod group. In the placebo group, all mean HR changes from baseline were positive. Exposure effect analysis on Day 1 showed that the effects were concentration dependent. Throughout the study, overall maximum negative chronotropic effects occurred on different days depending on dose, being more pronounced and occurring earlier for higher doses. Treatment effects on PR interval were low, with the largest mean increases from time-matched baseline generally below 5ms compared with 9ms for fingolimod on Day 1.

Conclusions: Ceralifimod (ONO-4641) caused dose-dependent cardiac effects, which were, at the highest dose of 0.10mg, slightly less pronounced than those of fingolimod 0.5mg.

Disclosure: Study supported by: EMD Serono, Inc., Rockland, Massachusetts, USA, a subsidiary of Merck KGaA, Darmstadt, Germany

PP1245

Evaluation of atrioventricular blocks and sinus pauses at re-initiation of siponimod (BAF312) treatment after variable periods of discontinuation from continued drug therapy

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Introduction: Siponimod (BAF312) is a selective sphingosine 1-phosphate (S1P1,5) receptor modulator currently in development for the treatment of secondary progressive multiple sclerosis. We investigated the incidence of atrioventricular blocks (AVBs) and sinus pauses (SP) at re-initiation of siponimod treatment after variable periods of discontinuation from continued therapy in healthy subjects.

Methods: Siponimod doses 0.5-4.0mg, and placebo were evaluated in combination with drug discontinuation periods: 48-192h. A 12-lead Holter ECG was recorded starting 1.5h before and until 24h after single-dose re-initiation. AVBs (degree) and SPs (defined as RR >2s) were summarized by dose level, discontinuation period, and by resting (11:00 PM to 07:00 AM [8h]) and non-resting hours (remaining 16h).

Results: 138 subjects were enrolled and 117 were evaluated. After single dose re-initiation, first-degree AVBs were detected in 15 subjects (13 siponimod, 2 placebo) with no clear dose/discontinuation periods pattern; 80% occurred during resting hours. Second degree AVBs (4 events) were reported in 3 subjects (dose/discontinuation periods: 2mg/72h, 1mg/120h and placebo/48h); 2 events occurred during resting hours. Second degree AVBs (4 events) were reported in 3 subjects (dose/discontinuation periods: 2mg/72h, 1mg/120h and placebo/48h); 2 events occurred during resting periods. SPs were observed in 4 subjects (0.5mg/48h, 1mg/96h, 4mg/96h and placebo/48h); in 2 subjects only during daytime, 1 subject during resting hours only and 1 subject in both periods. The longest duration of RR was 2.26s. All detected AVBs and SPs were asymptomatic.

Conclusions: The majority of AVBs were observed during significantly shorter resting periods, which are associated with increased vagal tone known to increase the PR interval. AVBs and SPs were asymptomatic and not considered to be of clinical relevance.

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Differential methylation pattern of promoter of FAS death receptor in multiple sclerosis patients depending on response to IFN beta therapy

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Introduction: IFN beta (IFNβ) is one of the most important first-line treatments in multiple sclerosis (MS). Clinical trials demonstrate the beneficial effects of IFNβ. However, individual response is highly heterogeneous and 30-50% of patients are considered non-responders or suboptimal responders to this treatment. One of the mechanisms of action of IFNβ involves upregulation of FAS expression in antigen-specific T lymphocytes and increment of apoptosis of these cells. Apoptosis via Fas/Fas ligand may be related with the shutting-off of the immune response by in situ elimination of autoreactive lymphocytes, becoming an essential mechanism in the regulation of the inflammatory reaction. IFNβ treatment may affect the epigenetic regulation of gene expression of apoptosis related genes. Our aim in the present study was to analyze the epigenetic variations (methylation) accompanying IFNβ treatment in the Fas gene in peripheral lymphocytes from MS patients regarding the response to this drug.

Methods: 50 IFNβ treated MS patients have been included. Response to treatment was established by clinical criteria: occurrence of 1 relapse or an increase of 0.5 point in the EDSS after one year of treatment compared with the year prior to IFNβ therapy. Analysis of DNA methylation was performed by bisulfite method.

Results: Methylation pattern of a CpG island located in the Fas promoter was significantly increased in non-responder MS patients.

Conclusions: In non-responders patients, IFNβ treatment leads to a hypermethylation of Fas promoter which might be related to defects in apoptosis, with a consequent decrease in the remove of autoreactive T cells by apoptosis.

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