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ACTRIMS 2018 - POSTERS

Biomarkers

P001

Regulator of Oligodendrocyte Maturation, Mir-219, a Potential Biomarker for MS

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Background: Multiple sclerosis (MS) is a demyelinating and degenerative disease of the central nervous system. Normally, demyelination is followed by remyelination, which requires repopulation of a demyelinated area by oligodendrocyte precursor cells. Although large numbers of precursor cells are present in MS lesions, remyelination often fails, in part by the inability of precursor cells to differentiate into mature myelin-forming cells. In mouse and rat, miR-219 is required for this differentiation. Previously, we identified decreased miR-219 expression in brain tissue of MS patients compared to controls. Cell-free miRNAs have been detected in many different bodyfluids including cerebrospinal fluid (CSF), and may reflect disease processes going on in the central nervous system. This prompted us to investigate the biomarker performance of CSF miR-219 for MS diagnosis.
Objectives: To assess the biomarker performance of CSF miR-219 for MS diagnosis
Methods: Quantitative PCR was performed measuring miR-219 levels in CSF of MS patients and controls in three independent cohorts (cohort 1: n=24; cohort 2: n=115; cohort 3: n=46). Using cross tabulation, the incidence of MS and/or Clinically Isolated Syndrome (CIS) patients with undetectable miR-219 expression was compared with that in controls by calculating odds ratios (OR) with 95% confidence intervals (CIs) and its p-value (two-tailed Fisher Exact test).
Results: All three cohorts of MS patients and controls revealed that the absence of miR-219 detection in CSF is consistently associated with MS. In the first cohort the OR for a diagnosis of progressive MS versus a control was 20.8 (p=0.03) times higher if CSF miR-219 was undetectable. We next sought to validate these findings in a larger, independent second cohort of MS patients versus controls. In this cohort the OR for a diagnosis of MS or CIS versus controls was 2.6 (p=0.03) times higher if CSF miR-219 was undetectable, and the OR for a diagnosis of progressive MS versus non-MS was 3.6 (p=0.02) times higher if CSF miR-219 was undetectable. In the third cohort the OR for a diagnosis of MS versus controls was 39.7 (p=0.0002) times higher if CSF miR-219 was undetectable
Conclusion: We have been able to identify and validate absence of miR-219 detection in CSF of MS patients compared to controls, suggesting that it may emerge as a candidate biomarker for MS diagnosis.

P002

Can Treg Migratory Signature Predict MS Disease Progression?

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Background: Multiple Sclerosis (MS) is thought to be provoked by pathogenic T effector cells (Teff) migrating into the central nervous system (CNS). Upon reactivation by antigen presenting cells (APC) they cause damage to the myelin sheet, as well as orchestrating an immune response against myelin. Regulatory T cells (Treg) are one of the key components of immune tolerance, protecting against autoimmune disease. In MS patients Treg presence and function within the CNS has been a matter of debate. Previous work demonstrated that Treg are present in a subset of patients and are capable of producing anti-inflammatory IL-10, thus leaving open the possibility Treg might be functional. Currently, relatively little is known about how Treg enter the CNS, ie which cellular adhesion molecules (CAMs) and/or chemokine receptors are involved.
Objectives: Unravel the mechanisms by which Treg cross the BBB into CNS and investigate whether this Treg migratory signature can predict disease progression (ie are Treg less capable of migrating when the disease progresses? Do patients with fewer active relapses have Treg with a migratory signature resembling healthy individuals?). To this extent various markers for Treg functionality, CAMs and chemokine receptors were studied with flow cytometry and correlated with patient data (retrospective and prospective clinical parameters reflective of MS disease course e.g. EDSS, lesion load, annual relapse rate, responsiveness to therapy).
Methods: The expression of cellular adhesion molecules LFA-1, VLA-4, ALCAM, CD6, MadCAM, MCAM, integrin alpha 8, DICAM, P-selectin, L-selectin and αvβ3 has been studied on Treg present in the peripheral blood and CSF of MS patients (RRMS, CIS, SPMS, PPMS) using FACS. Using the same methods, the expression of chemokine receptors CCR2, CCR3, CCR5, CCR6,

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CXCR4 and CX3CR1 and Treg functional markers ST2L, PSGL-1, CD147 have been investigated. Subsequently these data have been correlated with patient data

Results: Preliminary data shows that VLA-4, MCAM, CD6, ST2L, CD147, PSGL-1, CCR3, CCR6, CXCR4 and CX3CR1 are differentially regulated in MS patients compared to healthy control individuals. Further results of ongoing analysis will be presented at the meeting.

Conclusion: The migratory signature of Treg is different in MS patients compared to healthy individuals, which may have an effect on dampening down the ongoing immune response in lesions.

P003

Exploring the Relationship between Endothelin-1 and Peripheral Inflammation in Multiple Sclerosis

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Background: There is a pressing need to identify biomarkers that might unlink neuroinflammatory and neurodegenerative pathways to better understand and prevent disability progression in people with MS. Endothelin-1 (ET-1) is a potent vasoconstrictor thought to contribute to cerebral hypoperfusion and tissue damage in MS. Its link with the neuroinflammatory process remains poorly investigated.

Objectives: To determine the amplitude of plasma ET-1 changes in people with MS, and the relationship between ET-1 and peripheral immune mediator levels.

Methods: This study included 35 patients with MS and 35 sex- and age-matched controls. None of the patients were on disease-modifying therapy at time of the study, and all were free from steroids for at least 4 weeks. ET-1 levels were measured by enzyme-linked immunosorbent assay (ELISA), and multiple cytokines [interleukin (IL)-1beta, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12(p70), IL-13, interferon (IFN)-γ and tumor necrosis factor (TNF)-α] were simultaneously measured by Multiplex assay in plasma samples.

Results: ET-1 levels were significantly increased in MS patients compared to controls [(1.64±0.43) and (1.44±0.34) pg/mL, respectively; p=0.034]. We found no significant difference in cytokine levels, but a significant increase in IFN-γ/IL-4 ratio was observed in patients with MS in comparison with controls (p=0.009) suggestive of Th1 skewed response. Binary logistic regression was performed to ascertain the effects of age, sex, ET-1 and cytokines levels on the likelihood of MS diagnosis. In the final model, ET-1 (OR=3.908), IL-4 (OR=0.735), and IFN-γ (OR=1.037) levels remained as predictors of MS (model area under the curve= 0.702). There was no significant correlation between ET-1 and cytokines levels.

Conclusion: Patients with MS presented increased levels of ET-1 and an immune response biased towards a Th1 profile. Although both ET-1 and Th1 cytokine profile were associated with MS diagnosis, ET-1 levels were not associated with peripheral immune markers, suggesting that these changes may occur independently.

P004

Aging Influences MS Immune Profile

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Background: Biological aging is associated with alterations of the immune profile called immunosenescence. Repeated antigen encounter accelerates this process, and as such recent studies have hinted to accelerated immunosenescence in Multiple Sclerosis (MS). Age is the strongest predictive factor for onset of progression in MS; we therefore hypothesize that age-sensitive immune markers could represent relevant biomarkers for progression in MS.

Objectives: To compare the expression of age-sensitive immune markers in the peripheral blood of MS subjects and of age and sex-matched healthy controls.

Methods: We have measured by flow cytometry the proportion of T cells, B cells, NK cells and monocytes expressing CD27, CD28, CD57 and CD70 in the peripheral blood of 80 MS patients and 50 healthy controls between 20 and 75 years old. We have assessed levels of IL-10, IL-18, TNF, leptin and BDNF in their sera. Results are correlated with age, disease duration, EDSS, and relapses.

Results: Preliminary results show that the CD4:CD8 ratio is higher in MS than in age/sex matched HC and this difference is accentuated upon aging in untreated MS. TNF levels show a more important positive correlation with age than disease duration in MS subjects. IL-18 levels increase with aging in HC but even more so in MS subjects. Leptin levels are higher in women than men and in MS than HC, at all ages. BDNF levels decrease upon aging in active/progressive MS patients but not in benign MS. Globally, results from MS subjects treated with first-line injectables suggest an immune profile closer to HC donors than to untreated patients.

Conclusion: Alterations of the peripheral immune profile associated with aging are more pronounced in MS than in HC donors.

P005

Measurement of Insulin-like Growth Factor (IGF)-1 and IGF-Binding Protein 3 in Pediatric Multiple Sclerosis Patients

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Background: Obesity is a risk factor for pediatric-onset MS (POMS). Adipose tissue secrete and regulate hormones, including leptin and adiponectin, that have pro-inflammatory or anti-inflammatory properties. Adipose tissue is affected by the growth

hormone signaling axis, including insulin-like growth factor (IGF1), the primary mediator of growth hormone, and IGF binding protein 3 (IGFBP3). IGFBP3 mediates cell signaling through direct binding and inhibition of IGF1 in a 1:1 fashion, but can also act independently of IGF1, including inhibition of adipocyte maturation. Moreover, 1,25-dihydroxyvitamin D upregulates IGFBP3. In adults with MS, increased IGFBP3 and decreased IGF1/IGFBP3 ratio has been shown in MS compared to healthy controls and increased IGFBP3 has been correlated with increased disability in primary progressive MS. However, another study reports decreased IGFBP3 levels in adult MS patients.

Objectives: Here we assess IGF1 and IGFBP3 levels in pediatric MS patients and healthy controls.

Methods: Serum was obtained from both male and female patients and healthy controls enrolled in a biomarker study at the Partners Pediatric MS Center at Massachusetts General Hospital. Pediatric MS patients are defined by the criteria as defined by the International Pediatric MS Study Group. Levels of IGF1, IGFBP3, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, leptin and adiponectin were measured using ELISA kits. Linear regression was used.

Results: 41 MS patients (29 female, 12 male) and 58 healthy controls (45 female, 13 male) were analyzed. Age range was from 6-18 years old. There was no statistical significance in the levels of IGF1 or IGFBP3 between the two groups including when controlling for age, BMI, vitamin D, leptin, and adiponectin.

Conclusion: This is the first study of IGF1 and IGFBP3 in pediatric MS. Further studies are required in assessing the significance of IGF1 and IGFBP3 and relationship to MS.

P006

CNS Penetration of Dimethyl Fumarate and Its Effect on CSF Biomarkers in Secondary Progressive Multiple Sclerosis: A Pharmacokinetic/Biomarker Study

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Background: The mechanism of action of dimethyl fumarate (DMF), an approved treatment for relapsing multiple sclerosis (MS), appears to be mediated through activation of the nuclear factor (erythroid derived 2)-related factor 2 (Nrf2) and hydroxycarboxylic acid receptor 2 (HCAR2). Nonclinical studies have shown DMF to have both cytoprotective and anti-inflammatory effects. Cerebrospinal fluid (CSF) levels of DMF or its active metabolite, monomethyl fumarate (MMF), in humans have not been evaluated and no data are available on the effect of DMF treatment on neuronal and glial CSF biomarkers in humans.

Objectives: To investigate the pharmacokinetics of MMF in plasma and CSF, and to explore the effect of DMF on neuronal and glial biomarkers in subjects with secondary progressive MS (SPMS).

Methods: Sixteen SPMS patients were treated with oral DMF 120 mg BID for 4 weeks, followed by 240 mg BID for 24 weeks. During Week 6 (the second week on DMF 240 mg), plasma samples were collected before the morning dose and then at 2, 3, 5, 6, 7, 8 and 10 hours post morning dose. In addition, CSF samples were collected at 3, 5, or 7 hours post-dose (4 patients at each time point), or at 10 hours post-dose (3 patients). MMF concentrations in plasma and CSF samples were determined by liquid chromatography and mass spectrometry. CSF levels of neurofilament light (NfL), tau, glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) were measured by the Single Molecule Array (SIMOA) assay at baseline, week 6 and week 28.

Results: At baseline, patients had a mean EDSS of 4.4, a disease duration of 22.5 years, and no Gd+ lesions. The mean maximum plasma concentrations (Cmax) was 1750 ng/mL, and the mean time to maximum concentration (Tmax) was 4.6 hours. The highest CSF level of MMF was at 7 hours post-dose, with maximal concentration of 39–79 ng/mL. The mean CSF-to-plasma ratio for MMF was ~11%. Baseline CSF NfL levels in SPMS patients were 572±296 pg/mL. Mean EDSS decreased to 3.4, reflecting clinical improvement in 9 of 13 patients. NfL remained stable over the course of DMF treatment to week 28 (569±316 pg/mL), except for an increase in one patient with disease exacerbation at week 18.

Conclusion: MMF readily penetrates the CNS as measured by CSF levels. CSF NfL was stable except for an increase in one patient upon disease exacerbation, consistent with the proposed value of NfL as a marker of MS disease activity and treatment monitoring.

P007

Identifying a Role for Factor VIII and Vwf in Multiple Sclerosis and EAE Relapses

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Background: The pathogenic basis for what initiates and propagates an acute relapse in multiple sclerosis (MS) and its animal model experimental allergic encephalomyelitis (EAE)has been well-studied but remains incompletely understood. Theimmune system and the coagulation system can interact with each other in multiple conditions, including multiple sclerosis. Anecdotal clinical observations suggested that some MS patients have transiently elevated von Willebrand factor (vWf) levels and Factor VIII activity levels during an acute relapse.

Objectives: In this series of experiments, based on clinical observations, the levels of vWF, Factor VIII as well as Factor VIII activity were measured systematically for the first time in two EAE models and correlated with disease course.

Methods: Deidentified patient data was evaluated over individual MS relapse courses and clinical scenarios. Based on these findings, large scale EAE experiments were conducted with two models of EAE, and EAE clinical score was correlated with blood levels of vWF, Factor VIII activity, and Factor VIII antigen levels using spectrophotometric methods.

Results: EAE studies confirmed clinical observations and show a characteristic and transient rise in vWf, Factor VIII antigen, and Factor VIII activity blood levels coincident with relapse onset and peak disease. Additionally, the plasma FVIII level was directly associated with the disease severity of mice in both models. Steroid treatment at disease onset does not immediately impact these values.

Conclusion: Our observations and experiments identify potential measurable blood test biomarkers to characterize MS and EAE relapses. The functional roles of vWF and Factor VIII in MS remain to be determined, but lends further support to the growing involvement of the coagulation cascade in the pathogenesis of multiple sclerosis.

P008

Investigating Immune Phenotype Biomarker Changes in Patients with Relapsing MS Treated with Fingolimod 0.5 Mg/Day: The Fluent Study

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Background: Lymphopenia and rare instances of progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by JC virus (JCV), have been reported in patients with relapsing MS (RMS) on long-term therapies such as fingolimod. Relationships between fingolimod and immune cell profile changes, and the significance of anti-JCV antibody levels associated with PML risk are currently unknown.

Objectives: FLUENT, a 12 month, prospective, multicenter, non-randomized, open-label study in adult patients with RMS receiving fingolimod 0.5 mg/day, will investigate changes in immune phenotype biomarkers in patients who are fingolimod-naïve (Cohort 1) or previously treated with fingolimod continuously for ≥2 years (Cohort 2).

Methods: Two hundred patients will be enrolled into each cohort to receive fingolimod for 12 months after a 4 week screening period. Inclusion and exclusion criteria are reflective of routine clinical practice. Primary variables are: change from baseline to Month 6 in CD4+ and CD8+ naïve, central and effector memory T cells; CD4+ T helper (Th)1, Th2 and Th17 cells; CD19+ naïve, memory and regulatory B cells; CD14+ monocytes; CD16+ neutrophils; and CD56+ natural killer cells. Secondary variables include change from baseline to Months 3 and 12 in immune cell subtypes, patients' anti-JCV antibody status, and change from baseline in the anti-JCV antibody index at Months 3, 6 and 12. Change in serum neurofilament levels from baseline to Months 3, 6 and 12 is an exploratory variable. Descriptive statistics will be provided with 95% confidence intervals calculated for mean values. Two hundred patients in Cohort 1 will detect a 0.30 effect size with 89% power at 0.05 significance. For both cohorts, this effect size will yield estimates within 0.14 of the standard deviation of the variables. In addition, the frequency of adverse events will be assessed.

Results: A planned interim analysis will be performed when 50% of the patients in Cohort 2 have reached 6-month follow-up. Primary analysis will be conducted when all patients in each cohort have reached their 6-month follow-up.

Conclusion: FLUENT will be the first study to investigate temporal changes in immune cell subtypes, as well as the relationship between the risk of PML development and anti-JCV antibody changes in patients receiving short- and long-term therapy with fingolimod 0.5 mg/day. Screening for these immune phenotype biomarkers may become common practice in patients with RMS. Study sponsored by Novartis.

P009

Therapeutic Targets: Mirnas Possibly Contributing to Cognitive Impairment in Multiple Sclerosis

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Background: Cognitive impairment (CI) is a frequent complication affecting people with multiple sclerosis (MS). Besides MRI measures, few other biomarkers exist to help predict the development of CI and understand its biology. MiRNAs are relatively stable non-coding RNA molecules about 22 nucleotides in length that have been widely used as biomarkers and possible therapeutic targets.

Objectives: 1) identify miRNAs that are abnormally expressed in dementias that overlap with dysregulated miRNAs in MS, 2) Annotate the proteins and pathways targeted by the identified dysregulated miRNAs.

Methods: 1) From prior MS studies, we identified dysregulated miRNAs, 2) From prior subcortical and cortical dementia studies, we identified dysregulated miRNAs that overlap with dysregulated miRNAs in MS.

Results: From our literature review, we identified several shared miRNAs between MS and dementias. **MiRNAs that possibly preserve cognition**: *miR-23a, miR-214, miR-219 and miR-22.* These miRNAs increase expression of neuroprotective proteins such as Sirtuin-1 (SIRT 1) which participate in neurogenesis, neuronal repair, and proteins involved in memory such as (tailless) TLX receptors. They also decrease expression of pro-apoptotic proteins and those responsible for mitochondrial fragmentation. **MiRNAs that possibly accelerate cognitive impairment**: *miR-15, miR-128, miR-572, miR-181, miR-155, miR-138, miR-142, let-7 and miR-21.* These miRNAs decrease proteins involved in re-myelination, synaptic plasticity, and those involved in memory such as cAMP response element-binding protein (creb). They also increase the expression of proteins that promote glutamate toxicity, astrocyte excitotoxicity and amyloid

formation. Eight miRNAs, namely *miR-124, miR-29, miR-223, miR-146a, miR-34a, miR-9, miR-191 and miR-132* have mixed roles, coding for both neuroprotective and neurodegenerative proteins.
Conclusion: The dysregulated miRNAs identified in MS that overlap with those in dementias are involved in pathways related to apoptosis, neuroinflammation, glutamate toxicity, astrocyte activation, microglial burst activity, synaptic dysfunction, remyelination delay and amyloid formation, mechanisms of action that could be relevant to cognitive impairment in MS. With emerging therapies influencing miRNA expression, miRNAs can prove as pharmaceutical targets when determining treatment for MS patients with cognitive impairment.

P010
Biomarkes for Diagnosis and Prognosis in Multiple Sclerosis
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Background: Multiple Sclerosis clinical course varies greatly, reflecting complexity in pathophysiology. Different mechanisms combine together in various degrees to create a unique clinical result for each patient. Distinguishing reliable biomarkers for every independent MS pathogenic factor is of primary importance.
Objectives: To evaluate the possible correlation of the presence in the serum and/or CSF of Tau protein, CXCL13 and Neurofilaments, with the risk of developing Clinically Definite MS, following an initial clinically isolated syndrome CIS
Methods: 29 patients with CIS from our MS Centre were included in a prospective study in addition to 23 controls and followed up for 1-5 years. The primary end point of the study was the conversion from CIS to CDMS. We compared the percentage of patients who were positive for 1 or more of the suggested biomarkers in their sera/CSF who developed CDMS after 1-5 years of follow up, with the percentage of those who were negative for the same biomarkers. A secondary end point was to establish a quantitative correlation between the levels of the biomarkers in the serum and/or CSF and the probability of conversion to CDMS.
Results: During the follow up period, 20 patients were finally diagnosed with CDMS and 9 patients remained as CIS with similar gender distribution between the two groups. A significant difference between the values of CXCL13 and neurofilaments in the sera of patients who converted to CDMS as compared to patients who remained CIS throughout the study period. 75% of patients and 70% of patients who were diagnosed as CDMS tested positive for CXCL13 or NFL in their serum vs only 1 out of 9 (for either CXCL13 or NFL) who remained as CIS. Double positivity was found to have a strong negative predictive value as zero percent of the CIS patients were double positive, and 10 out of 20 CDMS patients (50%) were found to be positive for both CXCL13 and NFL. The values in the CSF were insignificant which could be attributed to the long period of preservation of the CSF or could signify the need of more sensitive methods for their measurement. Tau levels were not significant neither in the CSF nor in the sera of the tested population
Conclusion: CXCL13 and neurofilaments in the serum of patients with CIS, may represent significant predictive biomarkers for conversion to CDMS.

P011
Ethnics and Nutritional Effect on MS
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Background: Multiple sclerosis (MS) is multifactorial disease of the central nervous system in young adults. MS etiology is unknown; however, it probably results from an interplay between unidentified genetic and environmental factors. Nutrition might be a modifiable environmental factor involved in the course of MS, however, the role of nutrition in MS pathology remains unclear. Epidemiologic studies have demonstrated variation in MS susceptibility between different populations. Therefore, ethnicity may affect MS frequency among people living in the same area.
Objectives: We hypothesize that there is a connection between nutrition, oxidative stress, and the clinical state of MS patients. The aim of this work was, therefore, to study the relationship between nutrition, oxidative stress, and the clinical status in both Jewish and Arab MS patients. Comparison between the study groups may provide a laboratory basis for nutritional intervention.
Methods: We examined 100 Israeli Jewish and Arab volunteers. After signing an informed consent and filling the dietary questionnaire, blood was taken from all volunteers and was separated to serum, RBC, platelets, and lymphocytes. We conducted some tests to measure antioxidant capacity and quantification of the percent of intracellular reactive oxygen species. Additionally, we quantified an array of fatty acids from RBCs, and compared nutritional values obtained from blood tests.
Results: We found differences in nutritional parameters and habits between ethnic groups (Jews vs. Arabs), between MS and healthy groups, and between mild and severe MS patients. Low levels of total antioxidant capacity and higher ROS percentage was measured in severe MS patients versus healthy controls and mild MS patients. The questionnaire data indicated a significant difference between the groups on their average daily consumption of 18 different compounds.
Conclusion: We found a variety of nutritional factors related to MS severity, and ethnicity. Perhaps, a larger study group is needed to test yield more intense results, however the initial findings here point to specific directions to be considered for future research.

P012
Interleukin 1 Receptor Antagonist and 2'-5'-Oligoadenylate Synthetase-like Molecules As Novel Biomarkers for Multiple Sclerosis Patients in Bahrain
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Background: Multiple sclerosis (MS) is a multi-factorial disease of the Central Nervous System (CNS) affecting young adults leading to significant disabilities over time. MS is now believed to be prevalent in Arabian Gulf area with high incidence due to environmental factors and unknown genetic variations.
Objectives: The objectives of this study was to detect up-regulated potential genes that might be involved in neuroinflammatory process in MS patients in Bahrain and to measure the protein levels of the expressed genes.

Methods: A microarray was used to investigate mRNA expression from 12 MS patients and 12 control subjects in Bahrain where the mRNA came from peripheral blood leukocytes. Also, 80 MS patients and 80 control subjects were analyzed to measure serum protein levels of the expressed genes by ELISA.
Results: The data showed 15,480 genes expressed from over 47,000 transcripts and variants. Only 5 genes were significantly up-regulated in MS patients vs control subjects; namely TNF-AIP6, IL-1RA, OASL, CLC and DOCK4 ($p<0.05$). Conversely, KIAA0125 gene was significantly down-regulated ($p<0.0003$). Analysis of the effector molecules of the up-regulated genes revealed that 83 MS patients had positive serum level of OASL, 87 MS patients had positive serum levels of IL-1RA, and none of the 88 MS patients showed detectable serum levels of TNF-AIP6, CLC or DOCK4.
Conclusion: OASL and IL-1RA genes were strongly expressed in MS patients and that their effector molecules may be considered as biomarkers associated with the inflammatory process of the disease and possibly treatment response.

P013

Primary Progressive Multiple Sclerosis with Negative Oligoclonal Bands: Case Report

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Background: Multiple sclerosis (MS) is a chronic inflammatory disease ofthe CNS that leads to focal plaques of primary demyelination and diff use neurodegeneration in the grey and white matter of the brain and spinal cord. Patients with primary progressive disease (PPMS) miss the relapsing and remitting stage and start with uninterrupted progression from disease onset. PPMS affects only 10–15% of the MS population and is associated with a rapid disease progression. Cerebrospinal fluid (CSF) electrophoresis of people with MS contains oligoclonal bands (OCB), suggesting a polyclonal IgG response to a limited range of epitopes.
Objectives: Report case of primary progressive multiple sclerosis naive with 8 years of evolution with OCB-negative.
Methods: Male 63 years old attended in Caribbean Neurology and Rehabilitation Unit (UNyR-C), Cartagena, Colombia with a clinical history of 8 years of evolution who started with a decrease in muscle strength in the lower limbs, progressing to paraparesis, received ambulatory management for cervical myelopathy. For 1 year the clinic has been accompanied by dysarthria, dysphagia to solids, urinary incontinence. Patient conscious, alert, dysarthria, "scanning speech", MMSE: 24/30, with alteration of episodic and working memory, and calculus, amblyopia, without alterations of eye movements, muscle strength M1 in lower limbs, with spasticity and patellar and aquilian hyperreflexia bilateral, babinski bilateral, dysmetria and left adiadochokinesia. EDSS: 7,5.
Results: Isoelectricfocusing OCB-negative in 2 controls, with negative; complete autoimmunity panel. Magnetic resonance imaging of the brain and spinal cord with MS lesions
Conclusion: Detection of oligoclonal immunoglobulin G bands in the CSF is one of the most sensitive biomarkers for diagnosing MS. Up to 95% of Caucasian MS patients harbor OCB in CSF. OCB-negative patients, known to differ genetically from OCB-positives, are characterized by less global and regional brain atrophy.

Clinical Outcome Measures

P014

Effect of Ocrelizumab on Visual Outcomes in Patients with Baseline Visual Impairment in the OPERA Studies in Relapsing Multiple Sclerosis

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Background: Visual impairment is a common clinical manifestation of multiple sclerosis (MS). Measures of low-contrast letter acuity (LCLA) can detect reduced visual function even in the absence of a clinically evident episode of optic neuritis. Ocrelizumab (OCR) increased the cumulative probability of confirmed improvement in LCLA in the intention-to-treat population in the pooled OPERA trials in relapsing MS (RMS).
Objectives: To determine the impact of OCR on LCLA in the pooled OPERA I and II studies in a subgroup of patients with visual impairment at baseline (BL).
Methods: Binocular LCLA testing (1.25% and 2.5% contrast, Sloan charts) was conducted at BL and every 12 weeks until Week 96. The subgroup of patients with visual impairment (defined as visual Functional System Score ≥1) at BL was evaluated. Change from BL in the number of letters identified correctly on LCLA testing was assessed using a mixed-effect model of repeated measures. Improvement was defined as a ≥5-, ≥7- or ≥10-letter increase on the Sloan LCL chart confirmed after 12 weeks; a 7-letter change is considered the minimal clinically important difference for this test. The cumulative probability of confirmed improvement was estimated by Kaplan-Meier analysis; the hazard ratio (HR) was calculated using a Cox proportional hazard regression model.
Results: We identified 375 patients randomized to OCR and 373 to interferon (IFN) β-1a with visual impairment at BL. At BL, the mean (SD) number of letters identified correctly on LCLA testing at 2.5% contrast was 35.2 (16.0) for the OCR group and 35.1 (15.4) for the IFN β-1a group; after 96 weeks, the mean change from BL was significantly improved with OCR vs IFN β-1a (3.440 vs -0.470 letters; $p<0.001$). The relative increases in cumulative probability of ≥5-, ≥7- and ≥10-letter improvements at 2.5% contrast, confirmed after 12 weeks, with OCR vs IFN β-1a were 46% (46.5% vs 34.8%; HR=1.464; $p=0.003$), 54% (36.3% vs 25.5%; HR=1.538; $p=0.003$) and 39% (26.4% vs 19.8%; HR=1.393; $p=0.048$). Additional analyses will include change from BL in the number of letters identified correctly, by confirmed improvement status, and the proportion of patients with 12-week

confirmed visual improvement at ≥5 of 7 visits. Results of LCLA testing at 1.25% contrast will also be presented.
Conclusion: Ocrelizumab was associated with significant improvement in visual outcomes, assessed by LCLA testing, in patients with RMS with visual impairment at BL.

P015

Evaluation of No Evidence of Progression or Active Disease (NEPAD) in Patients with Relapsing Multiple Sclerosis in the OPERA I and OPERA II Trials

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Background: No evidence of disease activity (NEDA) is a composite measure to assess the absence of relapses, confirmed disability progression as measured by the Expanded Disability Status Scale (EDSS), and MRI disease activity. Previous studies suggest that maintenance of NEDA at 2 years has a high positive predictive value for no disability progression, assessed by EDSS, at 7 years. Incorporation of hand/arm function and walking assessments, as proposed for the novel endpoint 'no evidence of progression or active disease' (NEPAD), increases the sensitivity for clinical disability worsening/progression compared with current definitions of NEDA.
Objectives: To assess the effect of ocrelizumab vs interferon beta-1a (IFN β-1a) on the proportion of patients with NEPAD up to Week 96 in a post-hoc exploratory analysis of pooled data from the OPERA studies.
Methods: Patients in the OPERA studies received intravenous infusions of ocrelizumab 600 mg every 24 weeks or subcutaneous IFN β-1a 44 μg three times weekly for 96 weeks. NEPAD was defined as having NEDA (no protocol-defined relapse; no 12-week confirmed progression of ≥1/≥0.5 points on the EDSS if the baseline score was ≤5.5/>5.5 points, respectively; and no brain MRI activity [no new/enlarging T2 lesions and no T1 gadolinium-enhancing lesions]) and no 12-week confirmed progression of ≥20% on the timed 25-foot walk test (T25FW) or the 9-hole peg test (9HPT). Brain MRI assessments were conducted at baseline and Weeks 24, 48 and 96.
Results: This analysis included patients from the OPERA studies who received ocrelizumab (n=740) or IFN β-1a (n=753) and were evaluable for NEPAD at baseline. Ocrelizumab increased the proportion of patients with NEPAD at Week 96 by 82% compared with IFN β-1a (39.3% vs 21.5%; risk ratio [95% CI]: 1.82 [1.55, 2.14]; p<0.0001). Ocrelizumab also showed consistent trends in the proportion of patients with pairwise components of NEPAD vs IFN β-1a, including NEDA and no T25FW confirmed progression (40.4% vs 22.2%), NEDA and no 9HPT confirmed progression (44.3% vs 25.1%) and no T25FW or 9HPT confirmed progression (83.1% vs 77.4%).
Conclusion: Compared with IFN β-1a, ocrelizumab increased the proportion of patients with NEPAD, a clinically expanded version of the NEDA outcome that incorporates hand/arm function and walking assessments.

P016

Leveraging Real-World Evidence for Comparative Effectiveness: Delayed-Release Dimethyl Fumarate Vs. Fingolimod and Glatiramer Acetate in RRMS

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Background: Real-world evidence (RWE) is increasingly utilized as a novel means to contribute to the totality of evidence needed to assess the effectiveness of therapies in multiple sclerosis (MS). Delayed-release dimethyl fumarate (DMF), fingolimod (FTY), and glatiramer acetate (GA) are widely used therapies approved for the treatment of relapsing-remitting MS (RRMS). In light of the expanding set of therapies approved for the treatment of RRMS and the lack of direct comparison studies, RWE can provide much needed comparative effectiveness data to guide patients and healthcare providers in treatment decision-making.
Objectives: To utilize RWE to compare DMF with FTY and GA in patients with RRMS.
Methods: EFFECT (NCT02776072) is a multicenter, international, retrospective, single-time-point medical record review study comparing the effectiveness of DMF vs other DMTs including FTY and GA. Endpoints included the Kaplan-Meier (KM) estimated proportion of patients relapsed at 12 months and annualized relapse rate (ARR). Baseline covariates were used in estimating propensity scores (PS). The data were divided into 4 strata using quartiles of PS (trimmed analysis set, TAS). After assessing for balance in baseline covariates between the treatment groups, KM estimates of relapse and estimates of treatment effects were pooled across the 4 strata.
Results: The full analysis set included 816 DMF, 781 FTY, and 1042 GA patients; treatment groups were well balanced after PS stratification. In the TAS, the estimated proportion of DMF patients (n=668) that relapsed at 12 months after treatment initiation was 12% vs. 13% for FTY patients (n=664) (hazard ratio

[HR] [95%, CI] 1.07 [0.78, 1.46]; p=0.6926); the adjusted ARR ratio (95% CI) was 1.09 (0.80, 1.49; p=0.5754). In the DMF vs GA TAS, the estimated proportion of DMF patients (n=711) that relapsed at 12 months was 12% vs. 21% for GA patients (n=1008) (HR [95% CI] 0.71 [0.54, 0.95]), representing a significant decrease of 29% (DMF vs GA; P=0.0195). The adjusted ARR (95% CI) ratio was 0.66 (0.50, 0.87), representing a significant decrease of 34% (p=0.0033).

Conclusion: This study leveraged RWE to assess the comparative effectiveness of DMF vs FTY and GA. Over 12 months, no significant difference was observed between the DMF and FTY groups in the proportion of patients who had relapsed; however, DMF exhibited a statistically significant higher proportion of relapse-free patients and lower ARR vs GA.

P017

Neurex: App-Based Documentation of Neurological Exam Eliminates Noise in Current Disability Scales and Provides a New Scale with Enhanced Sensitivity

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Background: Current scales of disability in Multiple Sclerosis (MS) research, the Expanded Disability Status Scale (EDSS), Scripps Neurological Rating Scale (SNRS) Ambulation Index (AI), and IPEC scale, condense selected elements of neurological examination into a single number that correlates with neurological disability, although it remains uncertain if the feature selection, or their translation into the scale is optimal. Furthermore, because the translation of the neurological examination has not been unambiguously defined, different raters may assign different scale value to identical patient, generating noise that lowers the utility of the scales.

Objectives: To eliminate noise and enhance sensitivity and specificity of clinical scales by developing a neurological examination app available on mobile platforms that would allow clinicians to rapidly and efficiently document a standardized set of features automatically translated into the most common MS disability scales.

Methods: The Filemaker Pro-based NeurEx app is divided into 17 sections – each of them addressing a specific neurological system. The default normal grading for each feature can be changed by simple finger gesture. The app automatically transforms the neurological exam into standard MS scales (EDSS, SNRS, AI, and IPEC) using pre-defined algorithms, including the calculation of functional systems as a combination of clinician-defined spatial information and severity grade.

Results: We tested the performance of the NeurEx app by retrospective translation of 722 documented neurological exams of MS patients. The inter-clinician differences in grading were comparable to differences between clinician-based and App-calculated scores with r>0.93 and p<2.9e-173. Using longitudinal cohort of 197 patients we identified almost 100-fold higher dynamic range of NeurEx compared to EDSS (average progression 0.15 EDSS units/year versus 10.77 NeurEx units/year). NeurEx also explained the highest proportion of variance (R^2=0.86) among all tested neurological scales in calculated progression slopes of individual patients.

Conclusion: We have developed a Filemaker Pro-based app that allows clinicians to electronically document a neurological exam in a rapid and standardized manner. The app provides calculation of standard MS disability score, effectively reducing the noise in disability scales and increasing the dynamic range for detection of disability progression almost 100-times compared to EDSS.

P018

Wearable Multi-Sensor Device Captures Limb Dysfunction and MS Progression

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Background: Gold standard MS outcome metrics are often insensitive to disability changes over the short-term and are prone to inter-rater variability. Application of technology developed in the gaming and computer control industry offers the opportunity to create new metrics with greater sensitivity and reproducibility.

Objectives: To determine if a small multi-sensor, easy to use wearable device can capture limb dysfunction and subtle MS progression.

Methods: Consecutive clinic patients who met published MS criteria and healthy controls were offered enrollment. Subjects completed finger and foot taps wearing the device with 3 sensors: accelerometer, gyroscope and surface electromyogram. Raw signals were processed to reduce noise and artifacts. Intraclass correlation coefficients (ICC) assessed inter-test reproducibility. Time and waveform-based textural features were extracted from sensor data. We compared case vs. control differences with logistic regression, adjusting for age and sex. Handedness was addressed in all analyses. Extracted features were compared to disability metrics with Spearman correlation coefficients and multivariable regression methods. Patient-specific models of change over time were generated for participants returning for follow-up.

Results: Baseline data for 88 participants with MS (EDSS 0-7.0) and 23 healthy controls were analyzed. ICC's for temporal signal features ranged from 0.81-0.84 for all limbs. These features distinguished cases from controls even for those with EDSS<2.0 (OR 2.0 per sec, 95%CI 1.2, 3.3 p=0.01). The most informative combination of waveform textural features from all 3 sensors strongly correlated with EDSS (r^2=0.77-0.82). In longitudinal analyses (n=56), a composite metric of irregularity in the waveforms of all sensor signals over time distinguished progressive from relapsing participants over the 1-year observation period (sensitivity 87.5%, specificity 76.9%). In one participant, a relapse event was detected by the composite metric prior to clinical detection of the event.

Conclusion: Time and texture-based extracted features from this multi-sensor device demonstrated inter-test reliability, distinguished cases from controls, and demonstrated strong correlations with disability outcomes. Ideal for future generalizability in the clinic, the assessments were brief (a few minutes) and wearing of the small device was non-disruptive to a standard MS physical exam.

P019

Satisfaction and Efficacy Outcomes When Switching from Injectable Disease-Modifying Therapies to Fingolimod in PREFERMS: Effect of Previous Treatment

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Background: PREFER*MS* was a 12-month, phase 4, active-controlled, open-label, multicenter study that compared treatment retention on fingolimod and on injectable disease-modifying therapies (iDMTs) in patients with relapsing multiple sclerosis. In the iDMT group, 58.1% of patients switched to fingolimod, leading to improved outcomes in this group by the end of study (EoS) compared with the end of randomized treatment (EoRT).

Objectives: To assess the impact of previous treatment status (naïve or previously treated) on the effects of switching from iDMTs to fingolimod by comparing treatment-satisfaction, annualized relapse rate (ARR) and exposure-adjusted percentage brain volume loss (BVL) before and after switching.

Methods: At enrolment, patients were either treatment-naïve (n=471, 53.8%) or were treated with one class of iDMTs (n=404, 46.2%; interferon or glatiramer acetate). Patients were randomized (1:1) to fingolimod 0.5 mg/day or a pre-selected iDMT. One treatment switch was allowed for any reason after ≥3 months, or before for efficacy or safety. Treatment satisfaction (measured using the Medication Satisfaction Questionnaire [MSQ]), ARR and BVL were compared at EoRT and EoS for the subgroup of patients randomized to iDMT who later switched to fingolimod (n=254). Data were also analyzed according to treatment status before enrolment (treatment-naïve [n=99] or previously treated [n=155]). These *post hoc* analyses and *p* values were for hypothesis generation only.

Results: For patients who switched from iDMT to fingolimod, outcomes improved at EoS compared with EoRT, including patient satisfaction (% of patients with MSQ score ≥5; odds ratio [95% confidence interval (CI)], 5.65 [3.38–9.45], $p<0.0001$), relapses (ARR ratio, 0.53 [95% CI, 0.32–0.89], $p=0.0158$) and BVL (% [CI]; EoRT, 0.874% [0.56–1.19]; EoS, 0.463% [0.32–0.61]). Similar trends were observed regardless of previous treatment status for MSQ (ratio [95% CI]; treatment-naïve, 2.50 [1.26–4.96], $p=0.0088$; treated, 10.09 [4.67–21.80], $p<0.0001$), ARR (ratio [95% CI]; treatment-naïve, 0.41 [0.19–0.89], $p=0.0242$; treated; 0.65 [0.32–1.31], $p=0.2257$) and BVL (% [CI]; treatment naïve, EoRT, 0.84% [0.40–1.27]; EoS, 0.54% [0.33–0.74]; treated, EoRT, 0.90% [0.44–1.36]; EoS, 0.42% [0.21–0.62]).

Conclusion: In PREFER*MS*, many of the switches from iDMT to fingolimod tended to be associated with improvements in MSQ, ARR and BVL. The benefit of these switches was observed regardless of previous treatment status.

P020

Mobile Universal Lexicon Evaluation System (MULES) in MS: Evaluation of a New Visual Test of Rapid Picture Naming

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Background: Vision-based measures of rapid number naming (King-Devick [K-D]) have improved the sensitivity of sports-related concussion screening and also demonstrate slower testing times in patients with multiple sclerosis (MS). K-D requires saccades and vergence, measuring aspects of frontal, parietal and brainstem centers. We developed the Mobile Universal Lexicon Evaluation System (MULES) to capture a more extensive vision network, integrating saccades, color perception, and object identification.

Objectives: This study introduces the MULES, a new vision-based test of rapid picture naming, to the visual assessment of patients with MS.

Methods: We administered the MULES and K-D tests in addition to binocular measures of low-contrast letter acuity (LCLA) and high-contrast visual acuity (VA) in an MS cohort and in a group of disease-free controls.

Results: Among 22 patients with MS (median age 37 years, range 20-72) and 22 disease-free controls (median age 34 years, range 19-59), MULES test times were greater (worse) among the patients (59.6 vs. 40.0 seconds). Accounting for age, MS vs. control status was a predictor of MULES test times ($P=0.03$, logistic regression). Faster testing times were noted among patients with MS who had greater (better) scores for binocular LCLA at 2.5% contrast ($P<0.001$, linear regression, accounting for age), binocular high-contrast VA ($P<0.001$), and K-D test times ($P<0.001$). Both groups demonstrated 8-10-second improvements in MULES test times between trials 1 and 2 ($P<0.0002$, paired t-tests).

Conclusion: A complex task, the MULES test of rapid picture naming involves a more extensive visual network than the K-D test, capturing color perception and object characterization, in addition to saccades. Color recognition occurs early in object processing and requires area V4 and the inferior temporal projections. MULES scores reflect performance of LCLA, a widely-used measure of visual function in MS clinical trials. These results provide evidence that the MULES test can add visual information to the assessment of patients with MS.

P021

Longitudinal OCT in SPMS

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Background: Limited prospective information exists regarding spectral-domain optical coherence tomography (SD-OCT) in secondary progressive multiple sclerosis (SPMS).

Objectives: Document cross-sectional and longitudinal retinal nerve fiber layer (RNFL) and ganglion cell plus inner plexiform layer (GCIPL) features of an SPMS clinical trial cohort.

Methods: Prospective, observational study using a 2-year randomized placebo-controlled SPMS trial cohort with yearly SD-OCT testing. Post-hoc analysis determined influences of optic neuritis (ON), disease duration, and baseline SD-OCT on annualized atrophy and the correlation between OCT and whole brain atrophy.
Results: Mean RNFL and GCIPL values of patients (n=47, mean age 59, mean disease duration 30 years) were significantly lower among eyes with prior ON than those without (NON). Annualized RNFL (-0.31 μm/year) and GCIPL (-0.29 μm/year) atrophy rates did not differ between ON and NON eyes. Baseline RNFL thickness >75 microns was associated with greater annualized RNFL atrophy (-0.85 μm/year). Neither RNFL nor GCIPL atrophy correlated with whole brain atrophy. A sample size calculation using these atrophy results with a similar effect size (atrophy rate of -0.31μm/year, SE 0.38 μm, Cohen's d=0.129) determined that 4513 subjects would be needed per arm of a treatment study to observe a 30% difference in RNFL atrophy.
Conclusion: This study suggests that eyes with and without ON history may be pooled for atrophy analysis in SPMS clinical trials utilizing SD-OCT. Low baseline RNFL, small retinal atrophy rates, and lack of correlation with whole brain atrophy in this population are important trial design considerations.

P022

Long-Term Outcomes in Patients with Progressive Forms of Relapsing MS Treated with Teriflunomide: Real-World Evidence

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Background: Despite recent reports of positive outcomes in clinical trials, a significant unmet need exists in the treatment of patients with progressive forms of MS. The TEMSO (NCT00134563) and TOWER (NCT00751881) trials of teriflunomide in patients with relapsing forms of MS (RMS) included a small proportion of patients (n=122; 5.4%) classified at the time as having secondary progressive MS (SPMS) or progressive relapsing MS (PRMS). Post hoc analysis of data from these patients with progressive forms of RMS demonstrated that treatment with high-dose teriflunomide (14 mg) could be associated with long-term stabilization of Expanded Disability Status Scale (EDSS) score. Experience of the use of teriflunomide in this patient population from real-world clinical practice complements evidence obtained from randomized, placebo-controlled clinical studies.
Objectives: To present updated long-term disability data, as measured by EDSS, in patients with progressive forms of RMS treated with teriflunomide in the real-world setting.
Methods: Clinical and MRI outcomes were collected retrospectively for 20 patients with progressive forms of RMS treated with teriflunomide in 2 large MS centers in the USA.
Results: Nineteen of the 20 patients had a diagnosis of SPMS; the 1 remaining patient had PRMS. The mean age was 57 years and 75% of the patients were female. Disease duration since initial diagnosis of MS ranged from 7 to 37 years. Patients were treated with teriflunomide for 3 to 5 years; 1 patient received teriflunomide 7 mg, the remainder with the 14-mg dose. All patients had received prior disease-modifying therapy (DMT), the majority with an injectable DMT (interferon, glatiramer acetate). EDSS scores at the last visit ranged from 2 to 7.5. In 17 (85%) patients, EDSS scores remained stable vs their score at initiation of teriflunomide. Scores for 3 patients worsened (6.0 to 6.5; 6.5 to 7.0; 6.5 to 7.5); in these cases, disability worsening corresponded with worsening based on MRI. Two of the patients who had an increased EDSS score had interrupted teriflunomide treatment.
Conclusion: These real-world observational outcomes provide supportive evidence that treatment with teriflunomide 14 mg is associated with long-term stable disability in patients with progressive forms of RMS. These results are in accordance with those from the teriflunomide clinical trial program

Clinical Trials

P023

Ozanimod Demonstrates Efficacy and Safety in a Phase 3 Trial of Relapsing Multiple Sclerosis (SUNBEAM)

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Background: Ozanimod is an oral, once-daily immunomodulator that selectively targets sphingosine 1-phosphate 1 and 5 receptors.
Objectives: Report results from SUNBEAM (NCT02294058), one of two phase 3 studies comparing once-daily ozanimod with 30 μg weekly intramuscular interferon β-1a (IFN) in relapsing multiple sclerosis (RMS).
Methods: This multicenter, randomized, double-blind, double-dummy, active-controlled study evaluated once-daily oral ozanimod HCl 1 mg or 0.5 mg (7-day dose escalation) for ≥12 months (m) vs IFN. The primary endpoint was annualized relapse rate (ARR). Secondary MRI endpoints included new/enlarging T2 lesions through 12 m, gadolinium enhancing (GdE) T1 lesions at 12 m, and brain volume loss (BVL) baseline to 12 m.
Results: 1346 RMS patients were enrolled. Baseline characteristics, including MRI parameters, were similar across arms. Ozanimod 1 mg (0.181; p<0.0001) and 0.5 mg (0.241; p=0.0013) reduced adjusted ARR vs IFN (0.350). Adjusted mean number of

new/enlarging T2 lesions per scan was reduced by 48% for ozanimod 1 mg (1.465; p<0.0001) and 25% for 0.5 mg (2.139; p=0.0032) vs IFN (2.836). Adjusted mean number of GdE lesions was reduced by 63% for ozanimod 1 mg (0.160; p<0.0001) and 34% for 0.5 mg (0.287; p=0.0182) vs IFN (0.433). Ozanimod 1 mg significantly slowed normalized whole BVL vs IFN (32.5%, p<0.0001) with a more modest slowing for ozanimod 0.5 mg (12.3%, p=0.0615). Both ozanimod doses significantly slowed cortical gray matter loss (1 mg, 83.8%; 0.5 mg, 61.4%; p<0.0001 for each), and thalamic BVL (1 mg, 38.5% [p<0.0001]; 0.5 mg, 34.3% [p=0.0001]). Overall, a consistent dose response was observed across efficacy endpoints. Treatment-emergent adverse events (TEAEs) were mostly mild, with similar incidence across treatment arms. Serious TEAE incidence was low (ozanimod 1 mg, 2.9%; 0.5 mg, 3.5%; IFN, 2.5%). Discontinuation rates due to TEAEs were low and similar across treatment arms (ozanimod 1 mg, 2.9%; 0.5 mg, 1.5%; IFN, 3.6%). No first-dose, clinically significant reduction in heart rate or second degree or higher atrioventricular block were reported.

Conclusion: In this phase 3 study, both ozanimod doses demonstrated superior efficacy vs IFN on relapse and MRI endpoints, including BVL. These efficacy, safety, and tolerability results demonstrate that ozanimod is a novel oral therapy with a favorable benefit-risk profile for patients with RMS.

P024

Meta-Analysis of the Age-Dependent Efficacy of Multiple Sclerosis Treatments

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Background: As new multiple sclerosis (MS) drugs gain FDA-approval, clinicians are able to develop treatment plans better tailored to a patient's disease course. However, it has become difficult to select the most efficacious therapy, as this selection would require a comparative analysis of the drugs across different age groups.

Objectives: To perform a meta-analysis of randomized, blinded, clinical trials in MS to investigate whether advancing age strongly modifies the efficacy of immunomodulatory disease-modifying therapies (DMTs), and, if so, determine the best model(s) for this dependency.

Methods: We performed a comprehensive literature review and screened relevant studies using PRISMA guidelines to obtain 38 clinical trials that used EDSS outcomes to determine the effects of therapeutic efficacy on disability progression. We computed the mean of the weighted residuals for FDA-approved drugs in approved indications and used the sign of this mean to dichotomize drugs into low and high efficacy categories. To examine the hypothesis that age strongly modulates therapeutic efficacy, we employed a step-down procedure to fit a weighted linear regression, with interaction between age and efficacy, to data from all trials. Inclusion of baseline EDSS as a term in the model did not significantly improve the model fit.

Results: The meta-analysis included over 28,000 patients in 38 trials involving 13 categories of immunomodulatory DMTs. As patients age, therapeutic efficacy rapidly declines ($R^2 = 0.6757$, p = 6.39e-09) until age 53 years, when the model suggests that there is no predicted benefit to receiving disease-modifying therapy. Furthermore, we determined that there was a statistically significant difference between high and low efficacy therapy prior to age 40.5 years, after which point there was no observable difference between the two treatment categorizations.

Conclusion: The results of the meta-analysis demonstrate that the efficacy of immunomodulatory DMTs on disability accumulation significantly declines with advancing age. The model suggests that MS patients derive the most benefit from high efficacy therapy during early stages of the disease, and, after age 53, there is no observable benefit on disability progression to prescribing current DMTs to the average MS patient.

P025

The Paradigms Study: A Randomized Double-Blind Trial of Fingolimod Versus Interferon β-1a in Patients with Multiple Sclerosis Aged 10 to < 18 Years

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Background: Multiple sclerosis (MS) symptoms typically manifest in adulthood. In approximately 3–5% of cases, onset occurs before 18 years of age. Younger patients invariably have a relapsing–remitting form of MS (RRMS), with a 2–3-fold higher relapse rate than patients with adult-onset MS. The PARADIGMS trial is the first international controlled study to examine the efficacy and safety of fingolimod (FTY) in pediatric/adolescent patients.

Objectives: To investigate the efficacy and safety of FTY up to 0.5 mg/day versus interferon β-1a (IFN β-1a) 30 µg intramuscularly (IM) in pediatric/adolescent patients with RRMS.

Methods: PARADIGMS was a randomized, double-blind, active-controlled, parallel-group trial of up to 2-year duration, followed by a 5-year open-label extension period in patients with MS aged 10 to < 18 years at randomization. Eligible patients must have had an Expanded Disability Status Scale (EDSS) score of 0 to 5.5,

inclusive and ≥ 1 relapse in the past year, or 2 relapses in the previous 2 years, or have evidence of ≥ 1 gadolinium-enhancing (Gd+) lesion on magnetic resonance imaging (MRI) in the 6 months preceding randomization. Patients were randomized (1:1) to receive oral FTY up to a dose of 0.5 mg/day (dose adjusted for body weight) or IFN-β1a 30 μg IM once a week. The primary endpoint was annualized relapse rate. Key secondary endpoints included MRI- and relapse-related outcomes. Safety and tolerability were also assessed.

Results: In total, 215 patients were randomized. Most patients were female (62%, n = 134) and Caucasian (92%, n = 197). Mean age at randomization for the FTY and IFN-β1a groups was 15.2 and 15.4 years, respectively (median, 16.0; range, 10–17 and median, 16.0, range 11–18*, respectively). Mean disease duration since first symptom was 1.9 years for the FTY group and 2.4 years for the IFN-β1a group. The mean number of relapses in the past year was 1.5 for both groups and the median EDSS score was 1.5 for both groups. Primary efficacy results, MRI outcomes and safety and tolerability data will be presented at the meeting.

Conclusion: PARADIGMS is the first randomized clinical trial in pediatric/adolescent patients with MS. Results will determine whether FTY is beneficial in this young patient population that has active disease, typically of a shorter clinical duration than patients with adult-onset MS.

*Actual age < 18 years. Local law only allows reporting of birth year and age; 18 years based on the imputed date.

P026

Durable Improvements in Relapse and Disability Outcomes over 7 Years with Alemtuzumab in CARE-MS II Patients: Results from the TOPAZ Study

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Background: In CARE-MS II (NCT00548405), 2 courses of alemtuzumab demonstrated significantly greater improvements on clinical outcomes vs SC IFNB-1a over 2 years (y) in patients (pts) with active RRMS and inadequate response to prior therapy. Alemtuzumab pts who were followed for a further 4 y in an extension study (NCT0090553) showed durable efficacy, even though most received no additional alemtuzumab or other disease-modifying therapy (DMT). In CARE-MS II, pts received 2 courses of alemtuzumab 12 mg/day (baseline: 5 days; 12 months [mo] later: 3 days); in the extension, pts could receive as-needed alemtuzumab retreatment (12 mg/day on 3 consecutive days; ≥12 mo after previous course for relapse or MRI activity) or another DMT (per investigator discretion). Pts completing the extension could enroll in the 5-y TOPAZ study (NCT02255656) for further long-term evaluation.

Objectives: Evaluate efficacy and safety of alemtuzumab in CARE-MS II pts over 7 y.

Methods: In TOPAZ, pts can receive alemtuzumab retreatment ≥12 mo after previous course or another DMT at any time (both per investigator discretion); MRI scans are done annually. Assessments included: annualized relapse rate (ARR); proportions of relapse-free pts; 6-mo confirmed disability worsening (CDW); 6-mo confirmed disability improvement (CDI); no evidence of disease activity (NEDA); adverse events (AEs).

Results: 338/393 (86%) CARE-MS II alemtuzumab-treated pts who entered the extension remained on study until end of Y6. 336 then entered TOPAZ; 317 (94%) remained on study through Y7. Low ARR was maintained (0.14 at Y7). 87% of pts were relapse-free in Y7. Proportion of pts with stable or improved EDSS remained high (Y7: 73%). Through 7 y, 69% of pts were free of 6-mo CDW, 44% experienced 6-mo CDI, and the majority achieved NEDA in each year. These effects were achieved with 47% of pts receiving no further treatment (alemtuzumab or another DMT) after their initial 2 alemtuzumab courses. Incidences of most AEs, infusion-associated reactions, and infections decreased over time and were reduced vs the 2-y core study. Thyroid AE incidence peaked at Y3, then declined through Y7.

Conclusion: Clinical efficacy of alemtuzumab was durable for 7 y in pts who had inadequate response to prior therapy, despite 47% receiving no further treatment since the initial 2 alemtuzumab courses. The majority of pts maintained low ARR, were relapse-free, showed stabilized or improved disability, and achieved NEDA in each year.

P027

Phase 1 Trial of Intrathecal Rituximab in Progressive MS Patients with Evidence of Leptomeningeal Contrast Enhancement

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Background: Leptomeningeal inflammation is associated with increased cortical demyelination, neuronal damage and worse clinical outcomes, suggesting it may play a role in MS disease progression. Contrast-enhanced FLAIR imaging can detect areas of leptomeningeal contrast-enhancement (LME) corresponding to meningeal inflammation. Since B cells contribute to meningeal

inflammation in MS, we hypothesized that targeting them using intrathecal (IT) rituximab could potentially impact LME.
Objectives: To assess the safety of IT rituximab in progressive MS (PMS). Also, to assess effects of IT rituximab on the persistence of LME detected by MRI, and on cerebrospinal fluid (CSF) biomarkers.
Methods: PMS patients had a screening MRI to detect areas of LME. Those with LME who satisfied other eligibility criteria underwent repeat scanning to confirm presence of LME, followed by two IT administrations of 25 mg rituximab 2 weeks apart. Follow up lumbar puncture and MRI were performed at 8 and 24 weeks following the first treatment. We performed clinical evaluations and safety labs at baseline and at weeks 2, 8, 24 and 48. We measured levels of CXCL13, CCL19, CCL21, BAFF, sCD14 in the CSF collected before and after IT rituximab. We then assessed changes in LME lesions and CSF biomarker levels over 24 weeks.
Results: We screened 36 PMS patients and identified 15 with LME. Eleven consented, and 8 fulfilled eligibility criteria and received study treatment. Median age was 55.5 years (IQR: 9.0), 5 were female, and number of LME lesions ranged from 1 - 3. No serious adverse effects (AE) occurred. Two participants had worsening of their EDSS over 48 weeks of follow up.
We noted a profound reduction in peripheral blood B cells from baseline (median: 18.55%, IQR:7.2) to week 2 (0.1%, IQR: 1.2) and 8 (0.1%, IQR: 0.8) with some return at 24 weeks (3.6%, IQR: 9.0). However, we noted no change in the number of LME following IT rituximab over the 24-week MRI follow up. We observed transient reductions in CSF B cells (p=0.018) and CXCL-13 levels (p=0.045) with an increase in BAFF levels (p=0.17) with treatment.
Conclusion: LME incidence in our PMS cohort was similar to previous reports. IT rituximab was well tolerated in PMS patients and resulted in profound peripheral B cell depletion. IT rituximab had transient effects on CSF biomarkers of inflammation but did not change LME detected on imaging. IT rituximab was insufficient to completely resolve meningeal inflammation in this small PMS cohort.

P028

6 Month Results of a Phase 2a Multicenter Study of Ublituximab, a Novel Glycoengineered Anti-CD20 Monoclonal Antibody, in Relapsing Multiple Sclerosis

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Background: Ublituximab (UTX) is a novel monoclonal antibody 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 (RTX). 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.
Objectives: To assess the safety, B cell depletion dynamics, and clinical efficacy of UTX in patients with Relapsing MS (RMS)
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. 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.
Conclusion: 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.

P029

Sprint-MS/NN 102 Phase II Trial of Ibudilast in Progressive MS: Top-Line Results

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Background: Treatment options for progressive MS are limited. Ibudilast, a phosphodiesterase- and macrophage inhibitory factor-inhibitor, was suggested to have a neuroprotective effect in relapsing-remitting MS. We conducted a phase II clinical trial of ibudilast in primary and secondary progressive MS.
Objectives: Report top-line safety, tolerability, and efficacy of ibudilast in progressive MS.
Methods: 255 subjects with primary or secondary progressive MS, with evidence for disability progression in prior two years, were randomized to receive either ibudilast up to 100 mg/d or matching placebo, and followed over 96 weeks. Clinical and imaging outcomes were assessed every 24 weeks. Primary outcome was change in brain atrophy as measured by brain parenchymal fraction (BPF) over 96 weeks. Secondary outcomes included magnetization transfer ratio, diffusion tensor imaging, and optical coherence tomography. Analysis was based on a modified ITT (mITT) approach: subjects who received ≥1 dose of study medication and had ≥1 BPF efficacy assessment after baseline. Linear mixed effects modeling was used to estimate the rate of change within imaging measures for each treatment group. The difference in the estimated rates between groups was used to assess efficacy.
Results: Last follow-up visit was completed on 11May2017. Out of 255 randomized subjects, 244 were included in the mITT population for efficacy analyses. Of these 244 subjects, 220 (90.2%) completed 96-week follow-up, with 184 subjects (83.6%) remaining on assigned study medication for the full 96-week treatment period. Primary outcome, several secondary outcomes, and safety data will be presented.
Conclusion: The NN102/SPRINT-MS study will evaluate the activity, safety, and tolerability of ibudilast in progressive MS.

P030

Safety of Ozanimod Versus Interferon β-1a in Phase 3 Studies in Relapsing Multiple Sclerosis (SUNBEAM and RADIANCE Part B)

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Background: Ozanimod, an oral, once-daily immunomodulator that selectively targets sphingosine 1-phosphate 1 and 5 receptors, is in clinical development for treating relapsing multiple sclerosis (RMS). We report safety results from two similarly designed phase 3 RMS studies, SUNBEAM (NCT02294058) and RADIANCE Part B (NCT02047734).
Objectives: Compare the safety of ozanimod versus 30 μg, once-weekly, intramuscular interferon β-1a (IFN) in RMS patients.
Methods: SUNBEAM and RADIANCE Part B were multicenter, randomized, double-blind, parallel-group, active-controlled, double-dummy studies evaluating once-daily oral ozanimod HCl 1 mg or 0.5 mg (initiated with a 7-day dose escalation) versus IFN. The primary endpoint in both studies was annualized relapse rate. Here we report safety over ≥12 months in SUNBEAM and 24 months in RADIANCE.
Results: In both studies, a greater percentage of IFN-treated than ozanimod-treated patients experienced treatment-emergent adverse events (TEAEs) (SUNBEAM: ozanimod 1 mg, 60%; 0.5 mg, 57%; IFN, 76%; RADIANCE: ozanimod 1 mg, 75%; 0.5 mg, 74%; IFN, 83%). Most TEAEs were mild; the most common AE was nasopharyngitis (SUNBEAM: ozanimod 1 mg, 6.7%; 0.5 mg, 9.7%; IFN, 8.1%; RADIANCE: ozanimod 1 mg, 15.7%; 0.5 mg, 13.4%; IFN, 10.9%). The overall incidences of serious TEAEs were low and balanced across treatment arms (SUNBEAM: ozanimod 1 mg, 2.9%; 0.5 mg, 3.5%; IFN, 2.5%; RADIANCE: ozanimod 1 mg, 6.5%; 0.5 mg, 7.1%; IFN, 6.4%). Infection rates were

similar across treatment arms in both studies; serious infection rates were low and similar across treatment arms, with no disseminated or serious opportunistic infections. More IFN-treated than ozanimod-treated patients discontinued study drug due to TEAEs (SUNBEAM: ozanimod 1 mg, 2.9%; 0.5 mg, 1.5%; IFN, 3.6%; RADIANCE: ozanimod 1 mg, 3.0%; 0.5 mg, 3.2%; IFN, 4.1%). First-dose monitoring demonstrated no second degree or higher atrioventricular blocks. There was one death in RADIANCE, due to drowning considered unrelated to study drug.

Conclusion: This favorable tolerability and AE profile, coupled with efficacy results, demonstrates that ozanimod is a novel oral agent with a favorable benefit-risk profile for RMS patients.

P031

Crisp: Clozapine and Risperidone for the Treatment of Progressive Multiple Sclerosis

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Background: Previous research has shown that the atypical antipsychotics, clozapine and risperidone, can readily pass through an intact blood brain barrier and reduce neuroinflammation in humans and mice.

Objectives: Given the urgent need for therapeutics that target the central nervous system-compartmentalized inflammation in progressive multiple sclerosis (MS), the CRISP trial was designed to determine if clozapine and risperidone were suitable for use in patients with progressive MS.

Methods: The CRISP trial (ACTRN12616000178448) is a blinded, randomized, placebo-controlled trial with three parallel arms (n = 12/arm). Participants with progressive MS and an expanded disability status scale (EDSS) between 3.5 and 7.0 are randomly allocated to clozapine (100 mg/day for 3 months followed by 150 mg/day for 3 months), risperidone (2 mg/day for 3 months followed by 3.5 mg/day for 3 months), or placebo (6 months). Clinical parameters are collected at baseline, 3 months, and 6 months, and included measures of MS (EDSS, MS functional composite, and fatigue severity scale), treatment acceptability (treatment satisfaction questionnaire for medicines-9; TSQM-9), and immunological parameters (full blood counts and immune phenotype profile). The primary outcome measures are safety (AE/SAE) and acceptability (TSQM-9).

Results: After completion of the first block of participants, recruitment was halted to allow a formal interim analysis to be performed. The results of this interim analysis will be presented.

Conclusion: The CRISP trial will determine the suitability of two atypical antipsychotics, clozapine and risperidone, for people with progressive MS, and the results will guide the design of future trials to assess clinical efficacy.

P032

Peginterferon Beta-1a Demonstrated Better Clinical Outcomes Than Teriflunomide in Newly Diagnosed RMS Patients: A Matching-Adjusted Comparison

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Background: Peginterferon beta-1a and teriflunomide are both first-line disease-modifying therapies (DMTs) for relapsing multiple sclerosis (RMS), but no head-to-head trials have directly compared their clinical efficacy. A matching-adjusted indirect comparison of weighted individual patient data with aggregate Phase 3 trial data can provide relevant comparative efficacy data to clinicians.

Objectives: Determine indirect comparative clinical efficacy of peginterferon beta-1a and teriflunomide both in RMS patients and in a subgroup of newly diagnosed, DMT-naive RMS patients.

Methods: Individual patient data from the Phase 3 studies of subcutaneous (SC) peginterferon beta-1a 125 mcg every 2 weeks (ADVANCE/ATTAIN) and pooled summary data of patients from two Phase 3 studies of oral teriflunomide 14 mg once daily (TEMSO and TOWER) were used. The study designs and patient populations of TEMSO and TOWER were sufficiently similar to allow pooling of data. A matching-adjusted indirect comparison of efficacy outcomes was conducted by weighting individual peginterferon beta-1a–treated patients to match multiple key aggregate baseline characteristics of teriflunomide-treated patients. The newly diagnosed patient subgroup was diagnosed with RMS ≤1 year prior to study enrolment and had no prior DMT use. 24-week–confirmed disability worsening (CDW) and annualized relapse rate (ARR) were analyzed.

Results: After matching, baseline characteristics were well-balanced across groups. In the overall RMS patient population at 108 weeks, peginterferon beta-1a (effective n=382) had a significantly lower proportion of patients with 24-week CDW compared with teriflunomide (n=728) (8.4% vs 12.6%; P=0.032). The ARR was numerically lower in patients receiving peginterferon beta-1a vs teriflunomide (0.257 vs 0.354; P=0.051). Similarly, in newly diagnosed RMS patients, the ARR was numerically lower in patients treated with peginterferon beta-1a (effective n=163) vs teriflunomide (n=183) at 108 weeks (0.201 vs 0.270; P=0.384) and at 5 years (0.142 vs 0.196; P value not analyzed).

Conclusion: In this matching-adjusted indirect comparison of Phase 3 trials, the proportion of patients with 24-week CDW was significantly lower with peginterferon beta-1a compared with teriflunomide. For both the overall population and the newly diagnosed subgroups, ARR was numerically lower in the peginterferon beta-1a–treated group than in the teriflunomide-treated group.

P033

The Influence of Alcohol Coingestion on the Pharmacokinetics of Alks 8700 in Healthy Adults

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Background: ALKS 8700 is a prodrug of monomethyl fumarate (MMF), the active metabolite of dimethyl fumarate (DMF), which is approved for relapsing forms of multiple sclerosis (RMS). ALKS 8700 has physiochemical properties that are distinct from DMF and thus is designed to effectively treat RMS with the same active metabolite as DMF but with the potential for improved gastrointestinal tolerability.
Objectives: To evaluate the effect of alcohol coingestion on the pharmacokinetics (PK) of ALKS 8700 in healthy adults.
Methods: This was a phase 1, single-center, open-label, randomized, 3-period, 6-sequence, crossover study. Potential participants underwent a tolerability test to ensure tolerance to high alcohol doses. In each treatment period, participants received a single oral dose of ALKS 8700 (462 mg) administered with distilled water (W), 5% v/v ethanol–distilled water solution (5%ETOH), or 40%ETOH. Blood samples were taken within 1 h predose and at varying intervals from 0.25-72 h postdose. Treatment-emergent adverse events (TEAEs) were monitored for the study duration.
Results: Of 31 randomized participants, 30 completed the study. Mean age was 42.4 yrs (standard deviation [SD], 9.40); 81% were male; 61% White and 32% Black or African American; and mean body mass index was 26.2 (SD, 2.62) kg/m^2. Mean maximum observed concentration (Cmax) for MMF was 1.36 (SD, 0.598), 1.27 (SD, 0.555), and 1.13 (SD, 0.547) μg/mL with ALKS 8700+W, ALKS 8700+5%ETOH, and ALKS 8700+40%ETOH, respectively. Mean area under the concentration-time curve (AUC) from time zero to infinity was 3.06 (SD, 0.925), 3.26 (SD, 0.938), and 2.92 (SD, 0.762) h•μg/mL. AUC from time zero to the last quantifiable time interval was 2.68 (SD, 0.915), 2.74 (SD, 1.002), and 2.68 (SD, 0.956) h•μg/mL. Maximum plasma MMF concentrations were observed 2.5–3.0 h postdose with all treatments. Mean plasma MMF concentrations were comparable for ALKS 8700+W and ALKS 8700+5%ETOH and slightly lower for ALKS 8700+40%ETOH. Incidence of TEAEs was 63%, 61%, and 83% with ALKS 8700+W, ALKS 8700+5%ETOH, and ALKS 8700+40%ETOH, respectively. Flushing (37%, 35%, 37%) and feeling hot (23%, 26%, 30%) were the most common TEAEs. One participant discontinued the study due to TEAEs. There were no deaths or serious AEs.
Conclusion: ETOH coingestion had no significant effects on the PK of ALKS 8700 in healthy participants. No evidence of dose dumping of ALKS 8700 was observed with ETOH coingestion.

P034

Week 24 Results: GNbAC1 in RRMS (GNC-003, CHANGE-MS; Clinical trial assessing the HERV-W Env antagonist GNbAC1 for Efficacy in MS)

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Background: Human endogenous retroviruses (HERVs) result from ancestral, germline, retroviral DNA insertions, representing 8% of the human genome. A pathogenic member of the HERV-W family [pHERV-W; formally, the multiple sclerosis-associated retrovirus (MSRV)] may be tansactivated by environmental factors such as Epstein-Barr Virus (EBV) to generate pathogenic viral products, including the envelope protein [(pHERV-W Env); a potent agonist of Toll-like Receptor 4 (TLR4)]. The humanized IgG4-κ monoclonal antibody (mAb) GNbAC1 targets pHERV-W Env, inhibiting TLR4-mediated pathogenicity, including;

- activation of macrophages and microglia into pro-inflammatory phenotypes and;
- direct inhibition of remyelination via TLR4, expressed on oligodendroglial precursor cells (OPCs) during maturation.

To date, GNBAC1 has been studied in 3 completed Phase 1 and 2a clinical trials, in 54 healthy subjects and 10 MS patients.
Objectives: To evaluate a novel mAb, neutralizing a pathogenic, HERV-generated envelope protein in relapsing-remitting multiple sclerosis (RRMS).
Methods: This international (12 European countries), placebo-controlled, Phase IIb study randomized 270 RRMS patients 1:1:1:1 to GNbAC1 (6, 12 or 18 mg/kg) or placebo, via monthly, IV infusion, for 24 weeks (Period 1). At week 24, placebo patients were re-randomized 1:1:1, in a dose-blind manner, to active GNbAC1 for an additional 24 weeks (Period 2). The Week 24 primary endpoint: cumulative number of gadolinium enhancing (Gd+) lesions seen on 4-weekly brain magnetic resonance imaging (MRI) scans from weeks 12 – 24. Secondary efficacy endpoints include annualized relapse rate and change in magnetization transfer ratio (MTR) in pre-defined, periventricular (PV) bands of normal-appearing white matter (NAWM), cerebral cortex and regions of interest (ROIs) defined by Gd+ T1 lesions.
Results: Week 24 results of primary efficacy, secondary efficacy and safety analyses, will be provided. Additional exploratory analyses may also be provided.
Conclusion: Week 24 efficacy and safety results from the GNC-003 (CHANGE-MS) Phase IIb study will be provided. GNbAC1, a novel therapeutic approach for the treatment of multiple sclerosis (MS); blocking a potential causal agent, without directly affecting normal immunity, as well as promoting remyelination via disinhibition of OPC maturation blockade, will be discussed.

P035

Efficacy of Alemtuzumab Retreatment in Patients Who Experienced Disease Activity after the Initial Two Courses: Results from the CARE-MS II Extension

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Background: In the CARE-MS II trial (NCT00548405), alemtuzumab (administered as 2 courses of 12 mg/day at baseline [5 days] and 12 months later [3 days]) demonstrated significantly greater improvements on clinical and MRI outcomes vs SC IFNB-1a over 2 years in patients with active RRMS who had inadequate response to prior therapy. In an extension trial (NCT0090553), alemtuzumab-treated patients could receive as-needed alemtuzumab retreatment for relapse and/or MRI activity (12 mg/day on 3 consecutive days; ≥12 months after previous course) or another disease-modifying therapy (DMT; per investigator discretion). These patients continued to show durable efficacy over an additional 4 years, even though most did not receive additional alemtuzumab or other DMT.
Objectives: To evaluate the efficacy of alemtuzumab retreatment in CARE-MS II patients who received ≥1 additional course of alemtuzumab due to relapse and/or MRI activity.
Methods: Efficacy outcomes in patients who were re-treated with ≥1 additional alemtuzumab course in the extension were compared during the 12 months prior to Course 3 (C3) vs up to 3 years after C3: annualized relapse rate (ARR), improved/stable EDSS (vs core study baseline), and 6-month confirmed disability improvement (CDI). Patients who received a different DMT in the extension were not included in this analysis. Additional analyses evaluated patients who were re-treated due to relapse only.
Results: Through Year 6, 344/393 (88%) CARE-MS II patients entering the extension remained on study. 178/393 (45%) patients received ≥1 additional course of alemtuzumab without receiving another DMT. ARR significantly decreased following alemtuzumab retreatment, from 0.85 (12 months prior to C3) to 0.20 (12 months after C3; rate ratio [95% CI], 0.24 [0.17–0.34]; $P<0.0001$), and remained low (0.27) up to 3 years later. 68% of patients maintained stable/improved EDSS after the time of C3 administration. The percentage of patients with CDI increased 12 months after C3 vs 12 months prior to C3 (14.4% vs 4.4%). Findings were similar in patients who were re-treated due to relapse only.
Conclusion: These data support that in the CARE MS II extension, patients who experienced MRI activity or relapse after Course 2 benefitted from retreatment with a third alemtuzumab course, which can reduce relapses and improve disability.

P036

Rationale and Design of the Traditional Versus Early Aggressive Therapy for Multiple Sclerosis (TREAT-MS) Trial

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Background: FDA-approved multiple sclerosis (MS) disease-modifying therapies target the relapsing phase of MS but have minimal impact once the progressive phase begins. It is unclear if, in the relapsing phase, there is an advantage of early aggressive therapy with respect to preventing long-term disability. The infectious risks and other complications associated with higher-efficacy treatments highlight the need to quantify their effectiveness in preventing disability.
Objectives: To describe a clinical trial that will evaluate treatment strategies in early MS.
Methods: The TREAT-MS trial (TRaditional versus Early Aggressive Therapy for MS) is a pragmatic, randomized controlled trial with two primary aims: 1) to evaluate, jointly and independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, vs. starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy vs. a new first-line therapy have different intermediate-term risk of disability.
Results: TREAT-MS is funded by the Patient-Centered Outcomes Research Institute. The final protocol was adjudicated by a Study Advisory Committee that includes patients, stakeholders, expert clinicians, and statisticians. 900 participants are categorized as at lower vs. higher risk of longer-term disability and then are randomized, stratified by this risk, to higher-efficacy vs. first-line therapies. We will evaluate if there is an intermediate-term benefit, with respect to disability, of higher-efficacy therapy and if that benefit differs based on baseline disability risk. We will also explore, in those deemed at low risk of long-term disability at onset, if switching to another first-line therapy vs. escalation to a more aggressive medication has an impact on subsequent disability measures as well. Additional outcomes will include validated patient-reported outcomes and imaging obtained as standard of care.
Conclusion: There is a great unmet need to identify the most appropriate treatment strategy for people with MS, especially early in the disease course when it may be possible to maximize an individual's chance for preventing long-term disability. TREAT-MS will address this critical gap, laying the foundation for a meaningful evidence base for people with MS.

P037

No Evidence of Disease Activity in Natalizumab-Treated Patients with Early Relapsing-Remitting Multiple Sclerosis: A 2-Year Analysis of STRIVE

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Background: Treatment with natalizumab early in the relapsing-remitting multiple sclerosis (RRMS) disease course may improve

clinical outcomes. STRIVE was designed to determine the proportion of anti–JC virus antibody-negative RRMS patients initiating natalizumab early in their disease course who demonstrated no evidence of disease activity (NEDA).

Objectives: To determine the proportion of natalizumab-treated early RRMS patients who achieve NEDA at year 2.

Methods: STRIVE is a multicenter, observational, open-label, single-arm study in which NEDA was defined as no Expanded Disability Status Scale (EDSS) progression (24-week–confirmed), no relapses, no gadolinium-enhancing (Gd+) lesions, and no new or enlarging T2-hyperintense lesions. Clinical NEDA was defined as no EDSS progression and no relapses. Continuous variables were analyzed with summary statistics. Categorical variables were analyzed with frequency distributions. *P* values and odds ratios (ORs) were obtained from logistic regression models adjusted for baseline EDSS score (≤2 vs >2), age group (<40 vs ≥40 years), number of relapses 1 year prior to natalizumab infusion, baseline T2 lesion volume, baseline Gd+ lesions, and multiple sclerosis (MS) disease duration, as applicable. A Kaplan-Meier analysis was used to evaluate time to disability worsening and time to disability improvement.

Results: The intent-to-treat population (N=222) had early MS with mean (standard deviation [SD]) time since MS diagnosis of 1.6 (0.8) years and a mean (SD) EDSS score of 2.0 (1.1). Half (50%) of the patients had not received prior disease-modifying therapies. At year 2, 76 of 171 patients (44.4%) had achieved NEDA (95% confidence interval [CI]: 37.0%–51.9%), and 131 of 181 patients (72.4%) had achieved clinical NEDA (95% CI: 65.9%–78.9%). A higher proportion of patients without than with baseline Gd+ lesions (54.7% vs 31.9%) achieved NEDA at year 2 (OR: 2.89; 95% CI: 1.35–6.18; *P*=0.006). At year 2, patients with baseline EDSS score ≤2 had a significantly higher chance of achieving NEDA than those with baseline EDSS score >2 (OR: 2.33; 95% CI: 1.08–5.04; *P*=0.032). At year 2, a higher proportion of patients experienced 24-week–confirmed EDSS improvement than worsening (28.4% vs 14.1%). The serious adverse event profile up to year 2 was consistent with natalizumab's well-established safety profile.

Conclusion: These 2-year results support the effectiveness of natalizumab in maintaining NEDA in early RRMS patients.

P038

Comparative Effectiveness of Teriflunomide and Dimethyl Fumarate in Patients with Relapsing-Remitting MS in the Real-World Teri-RADAR Study

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Background: Teriflunomide and dimethyl fumarate (DMF) are 2 of the oral disease-modifying therapies (DMTs) approved for relapsing-remitting MS (RRMS). There are currently no head-to-head trials of oral DMTs for RRMS.

Objectives: To compare the effectiveness of teriflunomide and DMF in patients with relapsing forms of MS (RMS) based on real-world data collected retrospectively in the phase 4 Teri-RADAR study.

Methods: Teri-RADAR is a retrospective, longitudinal cohort study of real-world data from 5 US MS centers in patients with RMS initiating treatment with teriflunomide (n=50) or DMF (n=50). Patients were age-matched between groups at treatment initiation. Logistic regression was used to compare the proportion of patients with new/enlarging T2 or Gd-enhancing (Gd+) T1 lesions, the primary study endpoint. Secondary endpoints included additional volumetric MRI and clinical outcomes, and safety and tolerability. Data were collected for the following periods: 6–18 mo before treatment initiation, treatment start, and follow-up (9–30 mo after treatment start [9–24 mo for MRI data]).

Results: At treatment initiation, cohorts were similar for age and Expanded Disability Status Scale score. However, the proportion of patients with relapse in the previous 18 mo was higher in the teriflunomide cohort (22%) vs the DMF cohort (10%); annualized relapse rate (ARR): 0.274 vs 0.083. At follow-up, mean treatment exposure was 15.2 and 15.7 mo for the teriflunomide and DMF cohorts, respectively; 30% of teriflunomide-treated patients had new/enlarging T2 or Gd+ T1 lesions vs DMF-treated patients (40.0%, odds ratio [95% CI]: 0.62 [0.26, 1.47]; *P*=0.28). Annualized percent whole brain volume change (PBVC) was lower for teriflunomide vs DMF (-0.2% vs -0.5%, respectively, *P*=0.02), and fewer teriflunomide-treated patients developed brain atrophy above the annualized pathological PBVC cut-off of -0.4% (25.9% vs 58.6%, respectively, *P*=0.01). Compared with the pre-treatment period, ARR decreased by 24% in the teriflunomide cohort (from 0.274 to 0.209) but increased by 43% in the DMF cohort (0.083 to 0.119). Treatment-related adverse events were reported for 24% and 28% of teriflunomide- and DMF-treated patients, respectively.

Conclusion: Results from this retrospective study indicate that, in a real-world clinical setting, teriflunomide had superior effectiveness to DMF on a number of MRI endpoints. These results reinforce the established real-world effectiveness of teriflunomide 14 mg for the treatment of RRMS.

P039

Safety and Efficacy of Intravenous Cladribine in Multiple Sclerosis Patients

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Background: Cladribine is an adenosine analog prodrug which is FDA approved for hairy cell leukemia. Oral and intravenous forms of Cladribine have also been studied in randomized, placebo controlled trials for both progressive Multiple Sclerosis and relapsing remitting MS (RRMS). Recent results of these studies have shown robust clinical and radiological improvement with relatively mild side effects. Cladribine is not yet FDA approved for multiple sclerosis.

Objectives: To evaluate safety and efficacy of IV Cladribine in a small cohort of relapsing remitting and progressive MS patients who have failed first or second line disease modifying therapy (DMT).

Methods: We conducted a retrospective cohort chart review of 28 patients with Multiple Sclerosis who received IV Cladribine between 1/1/1990 to 12/31/2016 at the University Hospital, RUTGERS, in Newark USA. Disease course of MS, number of clinical attacks before and after Cladribine, MRI variables (new T2 lesions and T1 gadolinium enhancing lesions before and after, walking status, total lymphocyte count and any side effects were reported.
Results: Of 28 patients with MS who received IV Cladribine, 64 % were female and 86% were diagnosed with MS at age of 19 to 40. The median age at diagnosis was 26 years old, and the median age to receive the first dose of Cladribine was 36.5. The mean duration of MS prior to receiving Cladribine was 10.3 years. 60% of our patients had RRMS and 30% had SPMS. 93% of Patients tried at least 2 DMT before starting Cladribine. The annual relapsing rate for patients whom received >1 Cladribine cycle was 0.38 while before Cladribine the annual relapsing rate was 0.6 (P= 0.0024). The mean number of clinical relapses within one year for patients who received Cladribine was 0.095 while before cladribine the mean number of clinical relapse was 0.9 (P= 0.0004). The number of enhancing lesions on the MRI brain within a year post Cladribine dose was less by 40% (2.46 before cladribine, 1.46 after). 93% (26 of 28 patients) had no significant side effects. Two patients had complications, one had a recurrent UTI and the second one has ophthalmic zoster, without evidence of visual problems.
Conclusion: While our study is a pre and post therapy, non-randomized and non-blinded study, it showed that intravenous Cladribine was both effective and relatively safe. There is statistically significant reduction in the annual relapsing rate and the mean number of clinical relapses after receiving Cladribine. The side effects were relatively safe.

P040
Ory-2001 in Multiple Sclerosis: First Clinical Trial of a Dual Lsd-1/MAO-B Inhibitor
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Background: There is increasing evidence for the role of epigenetics in central nervous system (CNS) disorders. Multiple sclerosis (MS) is a chronic immune disorder associated with irreversible progression of disability. Phase I studies of ORY-2001 are complete in human volunteers; showing the drug to be safe, well tolerated and engaging target at a low dose range. Preclinical work shows upregulation of genes involved in neuroprotection and reduction of neuro-inflammation, with improved clinical scores on the experimental autoimmune encephalomyelitis (EAE) mouse model with greatly reduced infiltration of inflammatory cells in histopathological analysis. While new compounds have been approved for MS in recent years, ORY-2001 is an oral small molecule, with a very clean pharmacology and safety profile in humans and preclinical data suggesting neuroprotective activity, an aspect still undermanaged with current treatments. Thus ORY-2001 is an ideal compound to test in MS.
Objectives: To test the safety and tolerability of ORY-2001 over 36-weeks in a phase IIa double-blind study of 24 patients with either relapsing-remitting (RRMS) or secondary progressive (SPMS) and seeking signals of efficacy using recognized research measures.
Methods: Patients from four Spanish centers will be randomized to two doses of ORY-2001 and placebo (9/9/6). The primary outcome will be safety and tolerability, the secondary outcome, differences in inflammatory magnetic resonance imaging (MRI) measures compared to placebo. Exploratory measures will be MRI measures of focal/diffuse lesions, optical coherence tomography (OCT) of diffuse lesions, clinical scales and serum neurofilaments.
Results: Will be reported at study end. Primary endpoints will be frequency and severity of adverse events. The secondary endpoint will be the cumulative number of combined unique active lesions and exploratory outcomes include number of T1 Gd-enhancing lesions, change in brain volume, changes in retinal nerve layer thickness, number of relapses and serum neurofilament light chain level.
Conclusion: ORY-2001 will start its first study in patients with RRMS and SPMS in the fourth quarter of 2017. Preclinical and in vivo studies suggest the combined reduction in inflammation and neuroprotection, along with the safe and effective profile from phase I offer the possibility of ORY-2001 to be the first epigenetic compound to be a therapeutic option that manages several of the pathological components in MS.

P041
Limited Impact of Long-term Teriflunomide Treatment on Lymphocyte Counts and Infection Rates in the Pooled TEMSO and TOWER Core and Extension Trials
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Background: In TEMSO (NCT00134563) and TOWER (NCT00751881) core trials, teriflunomide was associated with lymphocyte count reductions within the first 3 months, yet mean counts remained within normal range. In the long-term extensions (TEMSO: NCT00803049), low-grade lymphopenia was uncommon and not associated with increased risk of infection.
Objectives: To describe lymphocyte counts and infection rates in teriflunomide-treated patients in TEMSO and TOWER core and extension trials.
Methods: Data from pooled core trials are reported for placebo- or teriflunomide 14 mg-treated patients. In the extensions, placebo-treated patients were re-randomized to teriflunomide; results from pooled core and extension trials are reported for the teriflunomide 14-mg group. Lymphocyte counts were obtained every 2 weeks up to Week 24, then every 6 weeks until study end. Lymphopenia (2 consecutive lymphocyte counts below lower limit of normal) was graded by Common Terminology Criteria for AEs.
Results: Cumulative exposure to teriflunomide 14 mg in pooled core and extension trials (n=1354) was 4449 patient-years. In the core trials, placebo- (n=745) or teriflunomide- (n=729) treated

patients experienced Grade 1 (0.7%/2.1%) and 2 (0.5%/1.4%) lymphopenia infrequently. Infections occurred in 40.0% and 75.0% of placebo- and 73.3% and 20.0% of teriflunomide-treated patients with Grade 1 and 2 lymphopenia, respectively. No patients with Grade 1 and 1 placebo-treated patient with Grade 2 lymphopenia had a serious infection. In combined core and extension trials, few teriflunomide-treated patients experienced Grade 1 (3.0%) or 2 (2.5%) lymphopenia; infections were reported in 62.5% and 55.9% of these patients, respectively, vs 56.1% of patients without lymphopenia. Serious infections occurred in patients without lymphopenia (3.7%) and those with Grade 1 (2.5%) or 2 (8.8%) lymphopenia. No Grade 3 or 4 lymphopenia was reported. At baseline, mean lymphocyte counts were 1.94, 1.26, and 1.21 x 10^9/L in patients without lymphopenia, or with Grade 1 or 2 lymphopenia, respectively. At study end, counts were 1.72, 1.01, and 0.91 x 10^9/L (mean change from baseline: -0.22, -0.24, and -0.31 x 10^9/L), respectively.

Conclusion: In long-term TEMSO and TOWER trials, low-grade lymphopenia was uncommon, with no reports of high-grade lymphopenia. Infection rates were similar in patients with or without lymphopenia, consistent with an immunomodulatory mechanism of action of teriflunomide with limited impact on protective immunity.

Study supported by Sanofi.

P042

Efficacy and Safety of Daclizumab Beta Vs Intramuscular Interferon Beta-1a in Patients Previously Treated with Glatiramer Acetate in the Decide Study

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Background: In phase 3 DECIDE, daclizumab beta (DAC BETA) 150mg demonstrated greater efficacy vs intramuscular (IM) interferon (IFN) beta-1a 30mcg on several clinical, radiographic and patient-centered outcomes in patients with relapsing-remitting multiple sclerosis (RRMS).

Objectives: To examine efficacy and safety of DAC BETA vs IM IFN beta-1a in the subgroup of RRMS patients treated with glatiramer acetate (GA) as their only previous disease-modifying therapy (DMT) before entering DECIDE.

Methods: In DECIDE, 1841 RRMS patients (age 18–55y, baseline Expanded Disability Status Scale score 0–5.0) were randomized (1:1) to receive DAC BETA 150mg subcutaneous every 4 weeks (n=919) or IFN beta-1a 30mcg IM weekly (n=922) for 96–144 weeks. Efficacy endpoints and safety outcomes were examined post hoc in patients with MS who had received GA as their only DMT before enrollment in DECIDE (n=92). Study protocol required that such patients were not to be exposed to GA within 30 days prior to baseline. Missing data for MRI were imputed using multiple imputation.

Results: 42/922 (5%) IM IFN beta-1a and 50/919 (5%) DAC BETA patients had received treatment with GA only prior to DECIDE. Baseline characteristics were balanced between treatment groups, including duration of prior treatment with GA, reasons for discontinuing GA and time between GA discontinuation and start of treatment in DECIDE. The annualized relapse rate was 42% lower in patients treated with DAC BETA vs IM IFN beta-1a (Rate ratio [95%CI], 0.58 [0.29, 1.14]). DAC BETA also reduced risk of relapse by 53% (Hazard ratio [95%CI], 0.47 [0.23, 0.99]; p=0.048) and the mean number of new/newly enlarging T2-hyperintense lesions at Week 96 by 58% (lesion mean ratio, 0.42 [95%CI: 0.20, 0.87]; p=0.021) vs IM IFN beta-1a. In patients treated with GA only before DECIDE, 98% of IM IFN beta-1a patients and 94% of DAC BETA patients reported any adverse event (AE), 2% of IM IFN beta-1a and 16% of DAC BETA patients had a serious AE (excluding MS relapse; n=1 for each SAE reported in either treatment group), and 10% of IM IFN beta-1a and 12% of DAC BETA patients discontinued treatment due to an AE (excluding MS relapse). Incidence of elevations of ALT or AST ≥3x ULN (>5x ULN) was 10% (0%) in the IM IFN beta-1a group and 8% (4%) in the DAC BETA group.

Conclusion: Results of this post hoc analysis are consistent with those observed in the DECIDE general population and support the clinical utility of DAC BETA in patients previously exposed to GA.

P043

Flex-201: A Multicenter, Randomized, Blinded Study to Evaluate the Utility of FLX-787 in Treating MS Spasticity

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Background: α-Motor neurons are considered the 'final common pathway' for all motor commands. Diseases, such as ALS, CMT and MS can alter the degree of motoneuron excitability and cause aberrant α-motor neuron output that leads to a breakdown in motor control resulting in spasticity, muscle cramps and/or spasms. FLX-787 is a TRPA1/TRPV1 ion channel co-activator that is efficacious in decreasing the intensity of electrically-induced muscle cramps or the frequency of nocturnal leg cramps. Activation of TRP ion channels by FLX-787 causes excitatory sensory input which stimulates brainstem nuclei, and which is believed to subsequently activate descending spinal tracts that inhibit motoneuron hyperexcitability, reducing muscle cramps. To understand how inhibition of α-motor neuron hyperexcitability might impact spasticity, the exploratory study, Flex-201, was initiated in MS patients to evaluate the safety and efficacy of FLX-787 in an indication where spasticity is prevalent.

Objectives: Assess the efficacy of FLX-787 as measured by: 1.) cramp/spasm frequency; 2.) Modified Ashworth Scale; 3.) Tardieu Scale; 4.) Numerical Rating Scale; 5.) Barthel Activities of Daily Living; 6.) Timed 25-Foot Walk; 7.) Clinical Global Impression; 8.) Quality of Life questionnaires (SF-36 and MSSS-88); and 9.) the Insomnia Severity Index Sleep Survey.

Methods: Flex-201 is a multicenter, randomized, blinded, cross-over study in subjects with MS and symptoms of spasticity,

spasms and cramps (n~45-55 subjects). After a 2-week Run-in period to establish baseline spasticity and cramp/spasm frequency, subjects were dosed with either FLX-787 or control for 14-days followed by a 7-to-14 day wash-out period and then crossed-over for an additional 14-days on the other treatment.
Results: In this exploratory study, FLX-787 will be assessed on both the initial parallel portion of the study and crossover period. An interim analysis of the run-in portion of the study revealed that pain experienced by subjects was correlated with both cramps/spasms as well as self-reported stiffness.
Conclusion: Results in human studies suggest that repeat dosing of FLX-787 increases inhibitory tone in spinal circuits, thereby limiting muscle cramps, and may have the potential to improve spasticity and associated pain.

P044

Real-World Experience with Ocrelizumab

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Background: The efficacy and safety of ocrelizumab were demonstrated in three phase 3 randomized controlled trials. This study evaluates the generalizability of those findings to a real-world setting.
Objectives: To evaluate the effectiveness, safety and tolerability of ocrelizumab in clinical practice at a large referral center for MS.
Methods: This study is a prospective longitudinal cohort study. Subjects were identified by chart review and data was abstracted from the electronic medical record. For inclusion, participants had to be adults age 18-75, start ocrelizumab after the regulatory approval date, be followed clinically for at least 6 months prior to starting ocrelizumab, and have a confirmed diagnosis of MS. Demographic data, disease course, disease duration, prior disease modifying therapies, baseline and monitoring MRIs, screening and monitoring laboratory assessments, infusion-related reactions (IRRs), on-treatment side effects, and quantitative neuro-performance and patient reported outcomes were collected.
Results: To date, we have reviewed the records of 63 patients and anticipate the inclusion of over 150 patients in this study. Of the patients analyzed, 56% (n=22) had relapsing-remitting MS (RRMS), 26% (n=10) had secondary progressive MS (SPMS), and 18% (n=7) had primary progressive MS (PPMS). Demographic data was similar to the clinical trial populations with 64.1% women and a median age of 44. Median disease duration was 10 years for PPMS, 8 years for RRMS, and 18.5 years for SPMS. In the 6 months prior to starting ocrelizumab, 10.3% of patients had a clinical relapse. There were new or enhancing MRI lesions for 33.3% of PPMS patients, 40.9% of RRMS patients, and 20% of SPMS. 50% of PPMS and 70% of SPMS patients started ocrelizumab because of disability progression, whereas 40.9% of RRMS patients started ocrelizumab because of new or enhancing MRI lesions and another 40.9% because of their JC virus status. 12.9% of patients had a mild IRR during one of the first two infusions (itching, rash, throat irritation, and vomiting).
Conclusion: Patients started on ocrelizumab at our center were similar to the clinical trial populations, but disease duration was longer for PPMS and RRMS patients. 12.9% of patients had an IRR during one of the first two infusions. This was lower than the numbers reported for clinical trials (34.3% and 39.9%), but patients were followed for a shorter period of time.

P045

Annual Relapse Rates (ARR) in Patients with Spinal Progressive Multiple Sclerosis Treated with MD1003 (High-Dose Pharmaceutical Biotin)

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Background: MS-SPI was a 12-month (M), double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of MD1003 (high-dose pharmaceutical biotin) in patients with non-active progressive multiple sclerosis (PMS), followed by an open-label extension phase where all patients received MD1003.
Objectives: To evaluate in patients from the MS-SPI study the annual MS relapse rate (ARR) in relation to the phase of the study and to the type of PMS. The ARR is a commonly reported outcome for MS.
Methods: The ARR were first evaluated separately and compared for the 12-month double-masked phase (M0 to M12; n=154) and the 24-month extension phase (M12 to M36; n=133). The ARR were then evaluated per PMS history (secondary PMS [SPMS] and primary PMS [PPMS]) for both study phases.
Results: The ARR were similar in the 12-month double-masked phase in the MD1003 group (0.085; n=103) and placebo group (0.089; n=51), and to those in the 24-month extension phase in the MD1003 group (0.093; n=91) and the placebo group (0.070; n=42). The ARR in placebo groups during the 12-month double masked phase was similar between SPMS (0.123; n=38) and PPMS subgroups (0.093; n=13), which highlights the homogeneity of the PMS population, regardless of the disease history. In patients with SPMS, there was a slight ARR increase between the double-masked phase and extension phase in patients continuing MD1003 (0.076 [n=61] to 0.111 [n=50]), and a slight ARR decrease in patients who switched from placebo to MD1003 (0.0123 [n=38] to 0.075 [n=32]). In patients with PPMS, there was a slight ARR decrease between the two phases in both patients continuing MD1003 (0.098 [n=42] to 0.068 [n=41]) and those who switched from placebo to MD1003 (0.093 [n=13] to 0.054 [n=10]). ARR values were within normal range.
Conclusion: In patients with PMS from the MS-SPI study, the annual MS relapse rate is not influenced by exposure to MD1003 or by MS history (SPMS or PPMS).

P046

MD1003 (High-Dose Pharmaceutical Biotin) for the Treatment of Progressive Multiple Sclerosis: Baseline Data and Results from an Early Access Program

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Background: MD1003 (high-dose pharmaceutical biotin) was granted an early access program called Qizenday® cohort Authorization for Temporary Use (ATUc) in July 2016, following a named patient use called nominative ATU (ATUn) granted in 2015 by the French National Agency for Medicines and Health Products Safety, for treatment of adult patients with primary or secondary progressive multiple sclerosis (PPMS or SPMS) relapse free for 1 year.
Objectives: To assess ATUc baseline characteristics; changes in Expanded Disability Status Scale (EDSS) score, walking distance (WD) and Clinical Global Impression (CGI) scale; and safety results between July 13, 2016 and July 12, 2017.
Methods: MD1003 100 mg three times a day was prescribed to PPMS and SPMS patients. There was no interventional control in this registry database. The ATUc included 5,483 patients (61% female) between July 13, 2016 and January 12, 2017 (SPMS: 3,079 [56%]; PPMS: 1,524 [28%]; PMS type not reported: 880 [16%]); 2,781 patients (51%) already received MD1003 as an ATUn. Further patients are currently included in the ATUc. To date, mean baseline values were age: 57 years; time from diagnosis: 18 years (SPMS: 21 years; PPMS: 13 years); Expanded Disability Status Scale (EDSS) score: 6.1 (SPMS: 6.2; PPMS: 5.9) and walking distance (WD): 218.1m. Here, we report follow-up changes in EDSS, WD and CGI over a period of 1 year. Further results covering the period until July 13, 2017, with additional patients and a longer observation period, will be presented.
Results: To date, efficacy data (mean change EDSS, WD and CGI) suggest a stabilization for the majority of patients over 1 year, while a small proportion of patients show an improvement or an aggravation. Safety data were consistent with the MD1003 summary of product characteristics.
Conclusion: In this large cohort of patients, the efficacy and safety of MD1003 are consistent with those of the MS-SPI trial results.

P047

Analysis of 6-Month Confirmed Disability Progression in RRMS Patients Treated with Subcutaneous Interferon Beta-1a

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Background: Confirmed disability progression (CDP) is a measure of sustained increase in disability in patients with multiple sclerosis (MS). The Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis Study (PRISMS-2) examined 3-month confirmed disability progression (CDP) in patients treated with subcutaneous interferon beta-1a (scIFNβ-1a) and placebo. As CDP is more robust when assessed over 6 months, we examined 6-month CDP (6MCDP) at 96 weeks using data from PRISMS-2.
Objectives: To assess 6-month confirmed disability progression in relapsing remitting MS patients treated with scIFNβ-1a.
Methods: Post-hoc analysis of patients from the PRISMS-2 intention-to-treat population randomized to scIFNβ-1a 44 μg (n=184) and placebo (n=187) three times weekly (tiw) for 2 years. 6MCDP was defined as an increase in Expanded Disability Status Scale (EDSS) score of ≥1.5 or ≥1.0 points if baseline EDSS was 0 or ≥0.5, respectively, sustained over two consecutive visits for ≥6 months (≥166 days). EDSS values obtained from both unscheduled and scheduled visits were considered. Patients were categorized into one of three groups at 96 weeks, those with: no EDSS progression; ≥1 confirmed EDSS progression; or unknown progression (patients with no progression but who withdrew from the study before 83 weeks). The number and percentage of patients in each category at Week 96 are presented descriptively. Kaplan Meier survival estimates at the last event were calculated for each treatment arm, and were analysed using a Cox proportional hazard model with fixed effects for treatment. Hazard ratios (HR) for the time to 6-month sustained change in EDSS score and 95% confidence intervals (CI) were calculated.
Results: A greater proportion of patients treated with scIFNβ-1a 44 μg tiw were free from 6MCDP at 96 weeks than placebo: 100 (54.3%) vs 68 (36.4%), respectively. Four (2.2%) and seven (3.7%) patients had unknown progression in the scIFNβ-1a 44 μg tiw and placebo groups, respectively. At Week 96, there were fewer cumulative events of 6MCDP with scIFNβ-1a 44 μg tiw (80/184, 0.43; 95% CI 0.36–0.51) than with placebo (112/187, 0.60; 95% CI 0.53–0.67). scIFNβ-1a 44 μg tiw led to a 33% reduction in the risk of 6MCDP compared with placebo: HR 0.67; 95% CI 0.50–0.90; p=0.0068.
Conclusion: In the PRISMS-2 study population, subcutaneous interferon beta-1a 44 μg tiw was efficacious in delaying 6-month confirmed disability progression versus placebo.

P048

Effect of MD1003 (High-Dose Pharmaceutical Biotin) for the Treatment of Progressive MS: 36-Month Follow-up Data

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Background: MS-SPI was a 12-month (M), double-blind study where patients (pts) with non-active progressive multiple sclerosis (PMS) were randomized to MD1003 or placebo. In the open-label extension phase, all pts received MD1003.
Objectives: To assess the efficacy and safety of MD1003 over 36 Ms (MD1003>MD1003 [MM] vs placebo>MD1003 [PM]).

Methods: 154 pts were included from M0–M9 (MD1003: 103; placebo: 51) and 133 pts were included from M12–M36 (MM: 91; PM: 42). At M12, M24, and M36, we analyzed confirmed Expanded Disability Status Scale (EDSS) score or timed 25-foot walk (TW25) improvement; mean EDSS change from baseline (mEDSS); TW25 evolution; and Clinician and Subject Global Impression (CGI and SGI) scales.

Results: EDSS or TW25 improvement was significantly higher for MM vs PM pts at M9 (13% vs 0%, $P<0.05$; confirmed at 3 Ms); the trend was similar at M18 (13% vs 7%) and M30 (10% vs 2%; both confirmed after 6 Ms).

mEDSS slightly decreased in MM and worsened in PM pts at M12 (−0.03 vs 0.13, $P=0.01$). When all pts 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 pts in Year 3, but increased again in PM pts in Year 3 (M36: 13% vs 30%).

CGI and SGI results were significantly better in favor 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; 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% of MM pts vs 79% of PM pts.

Conclusion: 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 36 Ms.

P049

Effect of MD1003 (High-Dose Pharmaceutical Biotin) in Spinal Progressive Multiple Sclerosis (MS-SPI): Subgroup Analyses

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Background: MS-SPI was a 12-month (M), double-blind, randomized, placebo-controlled study evaluating the effect of MD1003 on patients with non-active progressive multiple sclerosis (PMS; 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 group compared with the placebo group, using the Expanded Disability Status Scale (EDSS) score.

Objectives: Subgroup analyses were performed in the main phase of the study to determine if only certain subgroups of patients benefit from MD1003 treatment.

Methods: The global population (n=154) was split into the following subgroups of interest: EDSS score, low (4.5–5.5; n=35) or high (6–7; n=119); concomitant use of fampridine (n=72) or not (n=82); primary progressive MS (PPMS; n=55) or secondary PMS (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 / PMS 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 favored MD1003 over placebo. Although the relatively small numbers of patients in some of the subgroups precluded statistical significance, the same trends were observed among all different subgroups.

Conclusion: There is no evidence that a specific subgroup did not benefit from MD1003 treatment in patients included in the MS-SPI trial.

P050

Effect of Ocrelizumab on Severe Progression of Upper Extremity Impairment in Patients with Primary Progressive Multiple Sclerosis in ORATORIO

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Background: Upper extremity (UE) functional impairment is prevalent in primary progressive multiple sclerosis (PPMS) and alters patients' quality of life. The nine-hole peg test (9HPT) is a validated quantitative assessment of UE function in MS. Ocrelizumab (OCR) reduced the risk of ≥15%, ≥20% and ≥25% confirmed progression (CP) of UE disability, assessed by 9HPT, relative to placebo in the ORATORIO PPMS study.

Objectives: To further evaluate the effect of OCR on UE function in patients with PPMS in the ORATORIO study using higher thresholds of UE disability progression.

Methods: The 9HPT was administered at baseline (BL) and every 12 weeks until the end of the study. The average BL 9HPT times from two trials of the dominant and nondominant hands were compared; the hand with the lower time was termed "better hand (BH)," and the hand with the higher time was termed "worse hand (WH)." The average BL 9HPT times were further combined and termed "both hands (2H)." Time to CP in UE function, defined as ≥30% or ≥35% increase in 9HPT time from BL, confirmed for 12 and 24 weeks, was assessed in the intention-to-treat (ITT) population (placebo [PBO]: n=244; OCR: n=488) and the subgroups of patients with BL Expanded Disability Status Scale (EDSS) scores of <6.0 (PBO: n=163; OCR: n=348) and ≥6.0 (PBO: n=81; OCR: n=139).

Results: Compared with PBO, OCR reduced the risk of 12- and 24-week CP of ≥35% increase on 9HPT time by 49% (HR: 0.512; p=0.002) and 41% (HR: 0.592; p=0.027) for 2H, 26% (HR: 0.736; p=0.16) and 40% (HR: 0.604; p=0.033) for BH and 50% (HR: 0.496; p<0.001) and 48% (HR: 0.519; p=0.002) for WH in the ITT population. In patients with BL EDSS <6.0, the reduction in risk of CP with OCR was 49% (HR: 0.515; p=0.039) and 35% (HR: 0.655; p=0.26) for 2H, 23% (HR: 0.771; p=0.40) and 42% (HR: 0.576; p=0.11) for BH and 49% (HR: 0.506; p=0.020) and 50% (HR: 0.502; p=0.025) for WH. In patients with BL EDSS ≥6.0, the reduction in risk of CP with OCR was 41% (HR: 0.587; p=0.069) and 35% (HR: 0.650; p=0.16) for 2H, 19% (HR: 0.811; p=0.50) and 26% (HR: 0.735; p=0.35) for BH and 42% (HR: 0.575; p=0.044) and 38% (HR: 0.617; p=0.096) for WH. Similar trends were observed in analyses of 12- and 24-week CP on 9HPT of ≥30% increase.

Conclusion: In this post hoc set of analyses, OCR treatment appeared to lower the risk of progression of more severe UE disability on 9HPT compared with PBO in patients with PPMS for both hands, better hand and worse hand.

P051

Effect of MD1003 (High-Dose Pharmaceutical Biotin) in Spinal Progressive Multiple Sclerosis (MS-SPI): EDSS Sub-Scores

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Background: The MS-SPI study is a double-blind, randomized, placebo-controlled trial of MD1003 in patients (pts) with progressive, not clinically active multiple sclerosis and evidence of spastic paraparesis. It showed a reversal of Expanded Disability Status Scale (EDSS) score and/or timed 25-foot walk (TW25) in 12.6% of MD1003 pts vs 0 placebo pts (*P*=0.005) at 12 months (M).

Objectives: To measure EDSS sub-scores for each of the pts included in the main phase of MS-SPI.

Methods: In each of the 154 pts included in the study, EDSS sub-scores were recorded for each of the following functional systems (FSs): pyramidal (P), sensory (S), cerebellar (C11), visual (V), brainstem (BS), bowel and bladder (BB), and cerebral (Cb). Change in sub-score from baseline at each visit was used to define pts as responders (improved) or worsened, depending on whether the score was lower or higher than baseline.

Results: Disability was well balanced in each arm, and only a small proportion had major disability (score ≥3), other than for the P FS. The most common baseline sub-scores (percentage of pts) were P: 3–4 (~90%); S: 2–3 (~70%); C11: 2–3 (~70%); V: 0–2 (~60%); BS: 0–2 (~50%); BB: 1–2 (~70%); and Cb: 0–2 (~50%).

P scores were ≥4 in 36% of MD1003 pts at baseline and 35% at M12, and in 43% of placebo pts at baseline and 53% at M12. Between M9 and M12, 10% of MD1003 pts and 2% of placebo pts were responders, while 6% of MD1003 pts and 13% of placebo pts worsened.

S scores were ≥4 in 3% of MD1003 pts at baseline and 2% at M12, and in 4% of placebo pts at baseline and 11% at M12. Between M9 and M12, 18% of MD1003 pts and 16% of placebo pts were responders, while 9% of MD1003 pts and 31% of placebo pts worsened.

For other FSs, the percentage of pts defined as responders/worsened was similar in each arm. For Cb, BS, and V, the majority of pts had no impairment or had mild to moderate disability. For C11 and BB, the majority of pts had symptoms but only mild to moderate impairment. However, BB scores between M9 and M12 showed that 10% of MD1003 pts and 13% of placebo pts were responders and 18% of MD1003 pts vs 27% of placebo pts worsened.

Conclusion: For P and S scores, these results show improvement in the MD1003 group and worsening in the placebo group. Improvement in the active arm fits with the positive effect on EDSS scores and TW25. Pts included in the study exhibited high baseline P and S scores, while those of other FSs were mild to moderate and, thus, had less scope to improve.

Diagnostic Criteria and Differential Diagnosis

P052

Mc Ardle Sign: A Specific Sign of Multiple Sclerosis

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

Objectives: 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 ($r=0.41$, $p=0.002$) 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.

P053

Erdheim Chester Disease Involves Inflammatory CNS Demyelination and Atrophy with Macrophage Infiltration

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Background: Histiocytoses are characterized by proliferation and infiltration of myeloid cells (histiocytes or macrophages) into multiple organs, including the brain. These histiocytes exhibit both neoplastic and inflammatory characteristics, leading to the classification of Erdheim-Chester Disease as an inflammatory neoplasm. When the CNS is prominently affected, the clinical picture can mimic progressive MS, neuro-sarcoid or glioma. Here, we describe the clinical, radiologic and pathologic features of Erdheim-Chester Disease, a treatable histiocytic disorder.
Objectives: To characterize the spectrum of neurologic involvement in Erdheim-Chester Disease
Methods: 61 patients were prospectively enrolled in a natural history study, and clinical, imaging, laboratory, neurophysiologic, CSF and pathologic data were collected.
Results: 92% of patients had neurologic signs or symptoms, and 15% of the cohort presented with neurologic complaints. The most common findings were cognitive impairment, peripheral neuropathy, cranial neuropathies and cerebellar ataxia. Imaging revealed the presence of focal lesions, atrophy and demyelination (confirmed with diffusion tractography). Lesions were located throughout the nervous system, including the dura and extra-axial structures, rarely enhanced, and were variably demarcated. Pathology revealed lesions containing lipid-laden histiocytes characteristic of ECD. CSF analysis was consistent with macrophage-driven inflammation.
Conclusion: Erdheim-Chester Disease frequently causes neurologic morbidity and is in the differential of white matter inflammatory or neoplastic disorders. Given that diagnosis took a median of 4.2 years, neurologists play a central role in identifying Erdheim-Chester Disease and thereby enable timely treatment of this disease.

P054

From Balo's Concentric Sclerosis to Multiple Sclerosis: A Series of 7 Patients

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Background: Balo's disease is characterized by alternating lamellae (≥1 bands) on MRI and has been mainly described in case reports and small series. Although association with several disorders has been reported, the main issue is its relationship with multiple sclerosis (MS) since it can occur at the onset or during the evolution of classical MS.
Objectives: To describe clinical (including follow-up), MRI and biological findings in a single centre (CHUM-Hopital Notre-Dame, MS Clinic) series of 7 patients with new onset neurological symptoms and an MRI compatible with Balo's disease.
Methods: We retrospectively recorded clinical findings and radiological data including T1 (with and without gadolinium), T2, FLAIR, DWI images. Four patients had spectroscopic analysis and 2 had perfusion imaging.
Results: Seven patients (6 female/1 male) with a mean age at onset of 25 years old (18-54) were included. Main symptoms at onset were hemiparesis and/or hemihypoesthesia in 6/7 and were multifocal in 1/7. On brain MRI performed 30 days (2-68) after onset, 3/7 patients had an isolated lesion, whereas 4/7 patients presented with additional MS-like lesions (median number = 2) including 2 with multiple concentric Balo's lesions. Five patients had concentric rings and 2 had a more complex pattern, made of parallel lamellae. Alternating bands were more visible on DWI sequences and corresponding ADC maps, whereas gadolinium enhancement was seen in 5/7 patients. Spectroscopic analyses disclosed an elevated choline/creatine ratio in the 4/4 patients and

perfusion imaging disclosed low CBV values at the outer layers. One patient with susceptibility imaging had central hypointensity within the main lesions. Most of the patients had multiple MRI during initial screening; it disclosed a progression over more than 2 months in 2/7 patients. CSF analysis disclosed oligoclonal bands and elevated IgG index in 5/6 patients. Six out of 7 patients were initially treated (IV steroids in 6 and plasmapheresis in 5/7 and 4/7 patients had prolonged immunomodulatory/immunosuppressive treatment. At the end of the follow-up (7 years: 2-10), 6/7 patients had a diagnosis of MS. Overall disability was mild (mean EDSS 1.75; 0-4) and mean annualized relapse rate was low (0.12).
Conclusion: Our series of 7 patients with thorough MRI evaluation allows a precise description of imaging findings in Balo's lesions including a systematic DWI analysis. Moreover, the extended follow-up data give a new insight into the relationship between MS and Balo's disease.

Disease Modifying Therapies-Mechanism of Action

P055

Global Effect of Dimethyl Fumarate on DNA Methylation in MS

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Background: Dimethyl fumarate (DMF) is an effective first line treatment in RRMS. However, its mechanism of action is unclear.
Objectives: To investigate the molecular mechanisms underlying the effect of DMF using whole-genome DNA methylation data.
Methods: CD4+ T cells were purified from blood from 183 RRMS patients (70% female, age: mean ±SD= 40±7) receiving DMF (n=101) or glatiramer acetate (GA) (n=82). DNA methylation was measured using Illumina EPIC array. After quality control, data was normalized using Noob+BMIQ algorithms. Logistic regression analysis was performed to assess the association between DNA methylation and treatment using beta values from 481,279 CpG sites with variability>0.01, accounting for the effects of age and sex.
Results: 52 CpGs passed Bonferroni correction (p<1e-7), 14,264 CpGs passed suggestive level of significance (p<5e-5), and 158,831 CpGs had FDR-corrected p<0.05; 91%, 96%, and 91% of those, respectively, were hypermethylated in patients receiving DMF. As the data suggested a global hypermethylation pattern in DMF-treated patients in comparison to GA, we calculated a measure of global methylation for each individual by averaging the beta values from all CpGs. Mean methylation was significantly higher in the DMF group (p=5e-7). We further performed a GWAS on a subset of samples that had available genotyping data (n=120) to search for potential genetic modifiers of the effect of treatment on mean methylation. In patients receiving DMF, rs7572183_G dosage was associated with higher mean methylation, while this effect was reverse in the GA group (interaction-p=1.6e-8; MAF=0.5).
Conclusion: We suggest global DNA hypermethylation as an important mechanism underlying the effect of DMF. Our results are consistent with findings from a previous study with smaller sample size that demonstrated hypermethylation in a large number of CpGs in DMF-treated compared to GA-treated and untreated MS patients (Zhu et al, ACTRIMS 2017). Our results are further supported by evidence from: 1) tumor cells with intracellular fumarate accumulation as a result of mutation in the fumarate hydratase gene that show increased global DNA methylation; 2) experiments demonstrating a dose-related increase in global DNA methylation in cancer cell cultures exposed to different concentrations of fumarate. Further studies are required to assess whether the change in mean methylation is associated with response to treatment or DMF side effects, and whether rs7572183 (in the ARHGAP25 gene) can predict those effects.

P056

New Insights into Dimethyl Fumarate Mechanism of Action: Modulating Immunity By Targeting GAPDH and Aerobic Glycolysis

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Background: Although the mechanism of action of dimethyl fumarate (DMF, a derivative of the Krebs cycle metabolite fumarate) remains uncertain, it has been shown to covalently modify cysteine residues - a process termed succination. Endogenous fumarate attacks cysteines in a similar manner and has been shown to inactivate the glycolytic enzyme GAPDH by succination of an active-site cysteine. We hypothesized that DMF similarly targets GAPDH. Because activated myeloid cells and pathogenic T-cell subsets undergo a requisite metabolic switch to aerobic glycolysis, we further hypothesized that inhibition of glycolysis via GAPDH inactivation mediates the immunologic actions of DMF.
Objectives: 1) To determine whether DMF and its metabolite monomethyl fumarate (MMF) succinate/inactivate GAPDH; 2) To examine the downstream effects on aerobic glycolysis in activated macrophages/lymphocytes; 3) To determine whether the effects on GAPDH and glycolysis mediate DMF immunologic actions.
Methods: Mass spectrometry was used to study modification of GAPDH by DMF/MMF, with enzyme assays and metabolomics to evaluate effects on GAPDH activity. Glycolysis was measured using a Seahorse XF analyzer. In vitro analysis of macrophage/lymphocyte activation/polarization was combined with experimental autoimmune encephalomyelitis (EAE) to evaluate the effect of GAPDH inactivation on immunologic actions of DMF.
Results: DMF succinates GAPDH at its catalytic cysteine, both *in vitro* and after oral treatment in mice and human MS patients. Succination of GAPDH markedly diminishes catalytic activity and down-regulates aerobic glycolysis, with blockade at GAPDH confirmed by metabolomics. The actions on GAPDH and aerobic glycolysis mediate the immunologic effects of DMF, as these are sensitive to glucose concentration and reversed by over-expressing GAPDH. Finally, selective GAPDH inhibition is sufficient to inhibit macrophage activation and attenuate EAE.

Conclusion: We describe a novel mechanism for DMF that 1) appears to exploit a physiologic feedback function of endogenous fumarate and 2) may underlie the differential effects of DMF on lymphocyte populations in patients, as cells depleted by DMF (Teff cells) require aerobic glycolysis, while those spared by DMF (naïve and Treg cells) use oxidative phosphorylation. The data also provide proof-of-principle for metabolism as a viable target in autoimmunity, suggesting that other strategies aimed at decreasing glucose utilization (including dietary measures) may have a role in therapy.

P057

Cellular Adhesion Molecules Are Differentially Regulated on MS Patient's Treg during Disease Modifying Therapy and Disease Progression

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Background: Effector T cells (Teff) cells have been widely implicated in multiple sclerosis (MS) pathology, entering the CNS using cellular adhesion molecules (CAMs), leading to blood-brain barrier (BBB) and blood-meningeal barrier (BMB) breakdown and inducing lesion formation. Regulatory T cells (Treg) are one of the key components of immune tolerance, protecting against autoimmune disease. Previous work demonstrated that Treg are present in a subset of MS patients and are capable of producing anti-inflammatory IL-10, thus leaving open the possibility Treg might be functional. Currently, relatively little is known about how Treg enter the CNS or how they function within the CNS.

Objectives: To unravel the mechanisms by which Treg migrate across the blood brain barrier (BBB) or the blood meningeal barrier (BMB) and investigate whether Treg possibly regulate entry of pathogenic cells through interaction with the BBB, thereby limiting damage. The secondary objective is to investigate whether either type of MS (CIS, RRMS, SPMS, PPMS) or disease modifying treatments (DMT) commonly prescribed to RRMS patients have an effect on Treg migratory signature.

Methods: Using FACS, the expression of cellular adhesion molecules ICAM-1, VCAM-1, ALCAM, CD6, MadCAM and MCAM has been studied on BMB-EC and BBB-EC of human origin, treated with various pro- or anti-inflammatory cytokines. Their presence on the BBB *in situ* has been confirmed using confocal microscopy on MS lesions. The expression of their respective counter-ligands (LFA-1, VLA-4, ALCAM, CD6, MadCAM and MCAM) and Treg functional markers ST2L, PSGL-1 and CD147 were assessed on Treg in peripheral blood and CSF of MS patients using FACS as well.

Results: Pro-inflammatory cytokines induce expression of ICAM-1, VCAM-1, ALCAM and MCAM on BBB and BMB-EC, whereas anti-inflammatory cytokines have the opposite effect. VLA-4 and MCAM are differentially regulated on Treg during various DMT in MS patients compared to healthy control individuals. VLA-4, MCAM and CD6 are upregulated on Treg in SPMS and untreated RRMS compared to HC. In contrary, Treg functional markers ST2L and CD147 are downregulated in these patients compared to HC. In untreated RRMS MCAM, ALCAM and VLA-4 are higher expressed on Treg in the CSF compared to the peripheral blood.

Conclusion: Although Treg function seems decreased, a compensatory mechanism of upregulating CAMs to aid migration into the CNS might be at play, even more so since these CAMs are more upregulated in the CSF compared to peripheral blood.

P058

Dimethyl Fumarate Treatment Alters NK Cell Function in MS

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Background: Dimethyl fumarate (DMF) is commonly used to treat multiple sclerosis (MS). We and others have demonstrated effects of DMF on the adaptive immune system. However, the longitudinal effects on natural killer (NK) cells have not been well studied.

Objectives: To assess the effects of DMF on the NK cell compartment in MS and to determine the direct effects of DMF and MMF on NK cells.

Methods: We enrolled patients with RRMS initiating DMF and obtained PBMCs at baseline and 6-months post-treatment initiation. We performed multiparametric flow cytometry to identify immune cell subsets – NK cells, $CD56^{bright}$ NK cells, CD4+ and CD8+ T cells. We also examined T cell memory and cytokine production. We compared pre- and post-treatment immune cell subset proportions. We then examined correlation between changes in $CD56^{bright}$ NK cells and other immune cell populations.

To understand the effects of DMF and MMF on NK cells we isolated NK cells from healthy donors by negative selection and treated them in vitro with DMF or MMF and measured changes in CD107a expression to measure degranulation. We also performed NK + T cell co-culture following treatment of NK cells with various doses of DMF or MMF and assessed NK cell CD107a expression to determine cytotoxicity.

We also used polyclonally activated T cells from healthy donors to assess CD155 expression – a T cell surface molecule that potentiates NK cell cytotoxicity.

Results: We noted no alteration in the percentage of NK cells but found a 44.5% relative increase in the proportion of $CD56^{bright}$ NK cells following DMF treatment ($p=0.008$). We noted reductions in CD8+ > CD4+ T cells and within each of these populations, noted reductions in memory > naïve populations. Reductions in memory CD8+ T cells ($r=-0.56$, $p=0.01$) and pro-inflammatory cytokine producing (IFN-γ, TNF-α) T cells significantly correlated with increase in $CD56^{bright}$ NK cells.

We noted increases in NK cell degranulation and cytotoxicity (assessed by CD107a expression) with both MMF (100 μM) and DMF (1 & 10 μM), in NK + T cell co-culture. We also noted higher expression of CD155 on activated CD8+ as compared to CD4+ T cells ($p < 0.01$) and memory as compared to naïve cells ($p<0.01$), which is consistent with the pattern of selective depletion noted with DMF treatment.

Conclusion: These results identify novel effects of DMF on the NK cell compartment and suggest that direct modulation of NK cell function may help mediate the immunological effects of DMF.

P059

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: In ORACLE-MS, the cladribine tablets group (3.5 mg/kg) demonstrated a 67.3% reduction in risk of conversion to clinically defined multiple sclerosis versus placebo. Evaluation of lymphocyte subtypes from patients treated with cladribine tablets 3.5-mg/kg showed a transient ~82% median reduction in CD19+ B-cell count by Week 13, with reconstitution from Week 24 to 48. CD4+ and CD8+ T cells were also reduced (median reductions between ~40% and ~55%). The influence on cells with regulatory immune function is also of interest.

Objectives: 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 ORACLE-MS.

Methods: Peripheral blood T lymphocytes were immunophenotyped at baseline and Weeks 5, 13, 24, and 48 in patients treated with cladribine tablets at Weeks 1 and 5 in ORACLE-MS (3.5-mg/kg group; n=41) using T lymphocyte surface markers. Absolute numbers and proportions of central memory (CD4+ CD45RO+CCR7+), effector memory (CD4+CD45RO+CCR7-), T-helper (Th)1-type cells (CD4+CXCR3+), and nTregs (CD4+ CD25+CD127-), including naïve-like nTregs (CD4+CD25+ CD127-CD45RA[HI]+) and memory-like nTregs (CD4+CD25+ CD127-CD45RA-), 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 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. Proportions of nTregs and naïve-like nTregs in total CD4+ cells were not changed. Memory-like nTregs slightly increased up to Week 48 after treatment with cladribine tablets (median increase from baseline in 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 proportions. Further investigation is ongoing to explore the implications for the mechanism of action of cladribine tablets and the effects of treatment initiation at Year 2.

P060

Selective, Discontinuous Reduction of B and T Lymphocytes and NK Cells in Patients with Early, Relapsing MS after administration

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Background: In CLARITY, cladribine tablets 3.5 mg/kg demonstrated lower annualized relapse rates versus placebo (0.14 vs 0.33; p<0.001) at 96 weeks in patients with relapsing-remitting multiple sclerosis (MS). In ORACLE-MS, cladribine tablets 3.5 mg/kg demonstrated a 50% risk reduction in time to conversion to McDonald MS versus placebo (hazard ratio 0.50; 95% CI 0.39-0.63; p<0.001) at 96 weeks in patients with early MS.

Objectives: 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 EXT 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 3.5-mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo switched to active treatment groups (CLARITY EXT). Lymphocytes were immunophenotyped at baseline and at 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 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 81%, 84%, and 82% median reductions for patients in CLARITY (N=97), CLARITY EXT (N=136), and ORACLE-MS (N=41). Reconstitution of CD19+ B cells from Week 24 to 48. CD4+ and CD8+ T cells were also markedly reduced, but to a lesser degree than CD19+ B cells (55% at Week 13 for CD4+ cells; 48% attained at Week 13, then plateauing through Week 48 for CD8+ cells 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).

Conclusion: Cladribine tablets reduced approximately 75% of peripheral blood B cells by Week 5, with recovery to normal limits and a moderate and discontinuous reduction in T-cell counts. Treatment with cladribine tablets is associated with early decreases in NK cells followed by recovery to normal limits.

P061

Neutrophil and Monocyte Cell Numbers Remained Within Normal Limits in Patients with RRMS Treated with Cladribine Tablets 3.5 Mg/Kg (CLARITY/CLARITY EXT.)

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Background: In CLARITY and CLARITY Extension (EXT), lymphopenia was the most common adverse event, which is consistent with the proposed mechanism of action of cladribine tablets (CT). Absolute lymphocyte counts (ALCs) were shown to recover toward the normal range over time in these studies.
Objectives: To evaluate the effect of CT on innate immune cell counts.
Methods: Data from patients randomized to CT 3.5 mg/kg (CT 3.5; cumulative dose over 2 years) in CLARITY or CLARITY EXT (N=685) were pooled to provide long-term follow-up data. Data from patients randomized to placebo in CLARITY and followed up in PREMIERE are also reported (N=435). Neutropenia was graded by Common Terminology Criteria for Adverse Events v3.0.
Results: At baseline (start of CLARITY or CLARITY EXT), median neutrophil counts were 4.19×10^9/L for CT 3.5 and 4.20×10^9/L for placebo. At the end of Year 1 (48 weeks), median neutrophil counts were 3.80×10^9/L and 4.24×10^9/L for CT 3.5 and placebo, respectively. At the end of Year 2 (96 weeks), median neutrophil counts were 3.71×10^9/L (2.90–4.70) and 4.30×10^9/L (3.32–5.46) in CT 3.5 and placebo patients, respectively. At the end of Years 3 and 4 (144 and 192 weeks), median neutrophils in the CT 3.5 group (with no further treatment) plateaued at 3.60×10^9/L. In the placebo group, median neutrophils were 4.28×10^9/L (3.30–5.25) and 3.46×10^9/L (2.49–5.80) at the end of Years 3 and 4, respectively. Following CT 3.5 treatment, median neutrophil counts remained within normal values (>2.03x10^9/L) over the 2 treatment years and beyond, and ≤6 (<2%) patients treated with CT 3.5 reported Grade 3 or 4 neutropenia at any single time point. Baseline median (Q1–Q3) monocyte counts were 0.40×10^9/L (0.30–0.50) for CT 3.5 and 0.42×10^9/L (0.31–0.53) for placebo. At the end of Year 1 (48 weeks), the monocyte count was 0.36×10^9/L (0.27–0.45) for CT 3.5 and 0.42×10^9/L (0.34–0.53) for placebo. At the end of Years 2, 3, and 4, monocyte counts in the CT 3.5 group were 0.34×10^9/L (0.28–0.45), 0.36×10^9/L (0.28–0.48), and 0.36×10^9/L (0.26–0.44), respectively. In the placebo group, monocyte counts were 0.41×10^9/L (0.30–0.51), 0.40×10^9/L (0.32–0.50), and 0.42×10^9/L (0.32–0.55) at the end of Years 2, 3, and 4, respectively.
Conclusion: These data, together with the previously reported data on ALCs, support the concept that CT selectivity reduces adaptive immune cell counts, and that the impact on the innate immune system is relatively minor.

P062

Favourable S1P1R/5R Selectivity Profile of Ozanimod Confers Safety Benefit Relating to S1P3R-Mediated Pro-Fibrotic Changes in Fibroblasts

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Background: Ozanimod (RPC-1063) has shown therapeutic benefit in clinical trials for relapsing multiple sclerosis (RMS) and confers selectivity for $S1P_{1R}$ and $S1P_{5R}$ avoiding potential safety concerns around activation of $S1P_{2R,3R,4R}$. Fingolimod is approved to treat RMS; however, it has activity on four of the five S1P receptors ($S1P_{1R,3R,4R,5R}$).
Objectives: To understand the potential safety risks associated with $S1P_{3R}$ signaling, the dynamics of $S1P_{3R}$ receptor down-modulation and the role of chronic effects on $S1P_{3R}$ in promoting myofibroblast differentiation and pulmonary fibrosis were evaluated.
Methods: HEK293T cells expressing human $S1P_{3R}$ were used to monitor receptor down-regulation *in vitro* by flow cytometry and ERK1/2 phosphorylation. To assess myofibroblast differentiation, α-smooth muscle actin (α-SMA) and fibronectin upregulation was measured in ozanimod and fingolimod treated human lung fibroblasts by Western blot. To assess the role of $S1P_{3R}$ in fibrosis *in vivo*, an $S1P_{3R}$ antagonist was administered daily in the 14-day bleomycin-induced mouse model of pulmonary fibrosis.
Results: Ozanimod is not active on $S1P_{3R}$ but fingolimod results in robust $S1P_{3R}$-mediated signaling. In contrast to $S1P_{1R}$, activation of $S1P_{3R}$ does not result in receptor down-modulation; receptors remain on the cell surface and may undergo repeat activation. The functional consequence of $S1P_{3R}$ activation was assessed in primary human lung fibroblasts where fingolimod treatment was found to enhance differentiation and upregulation of α-SMA and fibronectin (31% and 85% over vehicle, respectively). Upregulation of α-SMA and fibronectin by fingolimod was blocked by an $S1P_{3R}$ antagonist. Ozanimod is not active on $S1P_{3R}$ and does not promote differentiation of lung fibroblasts *in vitro*. Furthermore, $S1P_{3R}$ activation promoted fibrosis *in vivo* as treatment with an $S1P_{3R}$ antagonist reduces pulmonary fibrosis, lung weight and lavage fluid collagen.
Conclusion: Activation of $S1P_{3R}$ does not lead to receptor down-regulation or desensitization, resulting in chronic $S1P_{3R}$ stimulation by non-selective agonists. This study confirms that ozanimod is a selective $S1P_{1R/5R}$ modulator that does not activate $S1P_{3R}$ and does not promote myofibroblast differentiation, avoiding risks inherent in the chronic activation of $S1P_{3R}$.

P063

Ory-2001 Reduces Inflammatory Cell Infiltration in the Theiler's Murine Encephalomyelitis Virus Model and Highlights the Epigenetic Axis in MS

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Background: ORY-2001 is a clinical stage Lysine Specific Demethylase 1 (LSD1) and Monoamine Oxidase B (MAO-B) inhibitor in development for treatment of neurodegenerative disease. LSD1 demethylates H3K4me1/2 and together with HDAC1/2, forms part of co-repressor complexes recruited by ZNF factors to control transcription. We have previously reported that ORY-2001 greatly reduced the clinical score in a mouse model of Experimental Autoimmune Encephalomyelitis (EAE), supported by reduction of a severity of the pathology, lymphocyte egress and infiltration of immune cells in the spinal cord, preventing demyelination. Here we provide data on the characterization of the mode of action (MoA) of ORY-2001 in mice infected with the Theiler's murine encephalomyelitis virus (TMEV).
Objectives: The aim of this study is to evaluate the efficacy of ORY-2001 following an oral daily gavage administration in the TMEV mice model.
Methods: 6 weeks old mice were infected in the cerebral parenchyma following a standard protocol with $2x10^6$ plaque forming units of the Daniel's strain of TMEV and treated orally with 0.3 and 1.0 mg/kg of ORY-2001 during two weeks following onset of symptoms, at day 72 after induction. Body weight, clinical score, motor function and finally histopathological analysis were evaluated.
Results: Data showed that ORY-2001 a) did not produce any body weight changes b) significantly reduced the clinical score c) improved the motor activity, reflected by significant changes in the horizontal activity d) significantly reduced the inflammatory $CD4^+$ and $CD8^+$ cell infiltration as revealed by histopathological analysis and provided a tendency to reduce microglia and astroglia activation.
Conclusion: ORY-2001, a novel epigenetic drug that has recently finalized a Phase I clinical trial, has demonstrated proof of concept in the EAE and Theiler models in mouse. The compound will be tested in a Phase IIa clinical trial in patients with relapsing-remitting (RRMS) or secondary progressive multiple sclerosis (SPMS).

P064

A Possible Role for a Diabetes-Related Pancreatic Secretion in Multiple Sclerosis

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Background: In type 1 diabetes, the pancreatic β-cells are destroyed, resulting in little to no production of insulin, the peptide secretion that stimulates trafficking of the GLUT4 glucose transporter from the cytosol to the membrane of GLUT4-containing cells. Though less understood, C-peptide is a 31 amino acid peptide that is co-secreted in equimolar amounts with insulin from the same pancreatic β-cell granules. Recently, we reported that C-peptide and Zn^{2+} display specific binding behavior to such cells as red blood cells (RBCs), but only when delivered in combination with each other and the blood protein albumin. In continuance, we measured C-peptide binding to RBCs in a study involving 200 subjects. The average C-peptide bound to RBCs in MS samples was significantly higher than non-MS subjects and healthy controls. Here we report findings involving C-peptide delivery to RBCs that may have direct implications on MS onset.
Objectives: To demonstrate increased zinc binding to MS RBCs and a resultant increase in trafficking of GLUT1 to RBC membranes, as well as to demonstrate the inhibitory effect of IFN-β on RBCs on these pathways.
Methods: Whole blood was obtained from consenting donors and RBCs were isolated by centrifugation and washed in buffer prior to use. 20 picomoles of radioisotopic ^{65}Zn, mixed with albumin and C-peptide, was added to the RBCs. Scintillation counting was used to determine ^{65}Zn binding to RBCs. To measure GLUT1 in the RBC membranes, RBC ghosts were prepared by removing the cytosolic contents of the RBC, and keeping the membrane intact using lysis buffer. RBC ghosts were subjected to SDS-PAGE and sequential western blot analysis. Image J software was used to quantify color density, and GLUT1 bands were normalized to the spectrin bands of each sample.
Results: Basal levels of GLUT1 in MS RBCs are 23.3% higher than basal levels in control RBCs, and the levels decrease with the addition of IFN-β to MS RBCs.
Conclusion: MS RBCs bind elevated amounts of C-peptide, which also correlates to increased specific deposition of zinc on the RBC membrane. When added in combination, this albumin/C-peptide/Zn^{2+} ensemble results in GLUT1 translocation. When treated with IFN-β, both the RBC zinc binding and GLUT1 concentrations decrease. Basal levels of GLUT1 in MS RBC membranes is significantly increased; therefore, we propose that IFN-β may be working by removing zinc from the bloodstream, leading to a decreased amount of both zinc binding to RBCs and RBC membrane GLUT1, affecting cell metabolism.

P065

Teriflunomide May Modulate Viral Replication Via Its Impact on Host Pyrimidine Metabolism

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Background: The etiology of MS is poorly understood but likely to result from a combination of genetic and environmental factors, among which viral exposure may play an important role. Exploring potential effects of DMTs on viral replication may inform treatment choice and treatment sequencing so as to optimize patient outcomes in MS.
Teriflunomide, a once-daily oral DMT approved for relapsing-remitting MS, has a well-characterized safety profile, and does not significantly diminish protective immunity, as demonstrated in immunization studies. Teriflunomide reduces proliferation of activated B and T lymphocytes by selective, reversible inhibition of dihydroorotate dehydrogenase (a key enzyme in de novo pyrimidine synthesis). As viral replication requires host cell machinery, reducing de novo pyrimidine synthesis may, in turn, impede viral replication.
Objectives: To review the effects of teriflunomide and leflunomide on viral replication, and the potential role these effects may have in MS therapy.
Methods: Literature review of studies investigating effects of teriflunomide and/or its precursor, leflunomide, against a range of viruses in order to understand how inhibiting de novo pyrimidine synthesis impacts the viral life cycle.

Results: Preclinical and clinical studies have reported evidence that teriflunomide/leflunomide impacts the replication of a broad range of viruses. This includes demonstrable effects (reduced viral loads, clearance of infection) against members of herpesvirus and polyomavirus families. Moreover, in a study of teriflunomide-treated patients with RMS, anti-EBV viral capsid antigen and nuclear antigen-1 titers were reduced vs healthy controls. Disruption of virus assembly and effects on host cell cycle have been proposed as a mechanism for teriflunomide-/leflunomide-related modulation of viral replication. Furthermore, an in vitro study of inhibition of viral replication by a small-molecular-weight compound demonstrated that replication of a range of viruses could be restored in the presence of excess uridine, suggesting that reduced viral replication is linked to depletion of pyrimidine pools.
Conclusion: Given the effects of teriflunomide on viral replication, and the possible role of viruses in MS etiology, studies are ongoing to assess the susceptibility of viruses, including EBV and JCV, to teriflunomide.

P066

Alemtuzumab and Cladribine: A Comparison of Pharmacodynamics and Mechanism of Action

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Background: MS therapies targeting T and B lymphocytes vary in efficacy and safety. Both alemtuzumab and cladribine deplete T and B cells, but a need exists to differentiate their mechanism of action (MoA) and pharmacodynamics (PD) to inform clinical decision making.
Objectives: To understand differences in alemtuzumab and cladribine MoA and PD.
Methods: Literature review of alemtuzumab and cladribine MoA and PD.
Results: Alemtuzumab, a humanized monoclonal antibody, selectively depletes CD52-expressing T and B cells by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Following depletion, a relative increase in regulatory T cells (Treg) and decrease in proinflammatory cytokines occurs, potentially leading to rebalancing of the immune system. B cells return to baseline levels within 6 months; T-cell levels generally reach lower limit of normal by 12 months. The distinct pattern and time course of lymphocyte repopulation are consistent across treatment courses. Alemtuzumab restores Treg function by promoting long-term increase in Treg suppressive activity against myelin basic protein-specific Th1 and Th17 cells. Cladribine, a synthetic purine analogue, enters cells and is incorporated into DNA, leading to cellular apoptosis and/or autophagy. Cladribine is selective for lymphocytes due to their relatively high levels of drug-activating deoxycytidine kinase and low levels of drug-inactivating 5′-nucleotidase. After cladribine treatment, lymphocytes reach a nadir by 9 weeks (wk). In a clinical trial, slight lymphocyte recovery occurred before re-dosing at Wk 48. Reduced median lymphocyte counts persisted to Wk 96. Cladribine caused greater suppression of T than B cells in both the short and long terms, with modest decreases in neutrophils at Wk 96. Cladribine PD may include regulation of cell cycle, signalling, and proliferation genes; cladribine may also modulate pro-inflammatory cytokine profiles.
Conclusion: Durable effects of alemtuzumab, an approved high-efficacy MS therapy, may be due to its selective depletion and distinct pattern of repopulation of circulating T and B cells thought to play a role in MS pathogenesis. Cladribine (approved in the European Union for the treatment of highly active relapsing MS) induces T-and B-cell apoptosis, in part by suppressing DNA synthesis and repair. These distinctions in MoA and PD may underlie differences in short- and long-term efficacy, safety, and the potential need for retreatment.

P067

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 eventually 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 activation of the nuclear factor (erythroid derived 2)-related factor 2 (Nrf2) and hydroxycarboxylic acid receptor 2 (HCAR2). Nonclinical studies have shown DMF to have both cytoprotective and anti-inflammatory effects. We have developed a progressive MS mouse model consisting of three cycles of cuprizone-treatment and spontaneous recovery and resulting in a significant loss of axons in the corpus callosum and progressive neurological decline between 62-77 weeks.
Objectives: 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® (NC) platform; white matter myelin was evaluated using a myelin-loss sensitive magnetization transfer ratio (MTR) via MRI.
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).
Conclusion: DMF treatment immediately following insult demonstrated 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.

Disease Modifying Therapies- Risk Management

P068

Patterns and Safety of Newer Disease-Modifying Therapy Use in Pediatric Multiple Sclerosis in the US

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Background: Treatment of pediatric multiple sclerosis (MS) is challenging given high relapse rates and the lack of safety and efficacy data for disease-modifying therapies (DMTs) in children. Conventional first-line injectable agents may be poorly tolerated and may not adequately control the disease, requiring escalation to more potent newer agents.
Objectives: We aim to characterize the use and safety of newer DMTs in children with MS and clinically isolated syndrome (CIS) treated under 18 years of age.
Methods: This is a retrospective cohort study of prospectively collected data including children with a last available diagnosis of MS or CIS followed at 12 clinics participating in the US Network of Pediatric MS Centers. Patients are typically seen at least every 6 months with documentation of demographic and clinical features including DMT use. Start and stop dates, indication, side effects, and reason for discontinuation are recorded for each DMT. We examine patterns of newer DMT use, including demographic and clinical features, and timing of DMTs used. We examine side effects documented in patients receiving newer DMTs.
Results: As of January 2017, 1,114 pediatric patients with MS (n=846) or CIS (n=268) had been entered in the database (66% female, mean onset age 13.2+/-3.9 years, mean follow up duration 3.3+/-3.0 years), with 77% with MS and 8% with CIS ever receiving a DMT. Most patients ever on DMT had been exposed to at least 1 injectable agent (any beta-interferon n=376; glatiramer acetate n=328). Newer DMTs used included natalizumab (n=136), dimethyl fumarate (n=105), fingolimod (n=78), rituximab (n=73), daclizumab (n=6), and teriflunomide (n=2). The first agent was a newer DMT in 13% (32 dimethyl fumarate, 22 natalizumab, 20 rituximab, 9 fingolimod, 1 teriflunomide), while 87% began treatment with an injectable (307 any beta-interferon, 243 glatiramer acetate). Analyses of changes in treatment patterns over the last 10 years are in progress. The overall side effect profiles of newer DMTs were not different than reported in adults.
Conclusion: Newer DMTs are often used in individuals with pediatric MS, and appear to have similar short-term side effect profiles to use in adults. Further studies of efficacy and long-term side effects are required. These findings may be helpful in guiding pediatric MS management.

P069

Alemtuzumab Induces Unexplored Cardiac Effects in Multiple Sclerosis Patients

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Background: Alemtuzumab is a highly effective monoclonal antibody approved for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). Its use is associated with several and potentially life-threatening side effects, with no relevant cardiac safety concerns emerging from clinical trials. Recently isolated cases of severe bradycardia have been reported.
Objectives: to explore the cardiac safety profile of Alemtuzumab.
Methods: 34 consecutive RRMS patients prescribed with Alemtuzumab since November 2016 in 2 MS centers were followed up during their first treatment course. Vital parameters, including heart rate (HR), were collected before the infusion and every 30 minutes thereafter until discharge. The same evaluation was performed in a cohort of MS patients treated with steroids for relapse as control group. Continuous electrocardiogram (EKG) monitoring was performed for 5 days in a subgroup of 5 Alemtuzumab-treated patients.
Results: A significant increase in HR was recorded during the first two days of treatment (mean largest increase 21.3±11.5 bpm; $p < 0.0001$) compared with baseline values (Day 1, before premedication, after 30 min rest). Conversely, a statistically significant reduction in the HR compared with baseline starting from day 3, peaking at day 4 (mean largest reduction 15.5±8.1 bpm, $p < 0.0001$) and still unrecovered at day 5 ($p=0.04$) was observed. Forty one percent of patients experienced asymptomatic sinus bradycardia (HR< 50 bpm), and HR dropped below 40 bpm in 17% of subjects. A single patient experienced

symptomatic severe bradycardia (30 bpm) on day 3 leading to treatment discontinuation. Continuous EKG monitoring confirmed a progressive decrease of HR starting from day 3; moreover, sinus blocks and pauses (max 3.6 seconds) were recorded during the night starting from day 3 in 3/5 subjects. A slight reduction of HR was also seen in the control group but only 11% (3/27) of patients experienced HR <50 bpm and none below 40 bpm. Improvement of HR at day 5 in the Alemtuzumab group was more prompt in patients pre-treated with steroid only for the first 3 days compared with those exposed to steroids for 5 days, suggesting a possible add-on effect of steroids on HR reduction.

Conclusion: Reduction of HR with remarkable bradycardia can occur and represents a potentially clinically relevant adverse event related to Alemtuzumab infusion. EKG monitoring during Alemtuzumab courses should be considered in case our preliminary results will be confirmed in larger studies.

P070

Integrated Safety Analysis of Infections during Periods of Grade 3 or 4 Lymphopenia in Patients Taking Cladribine Tablets 3.5 Mg/Kg

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Background: In CLARITY, the cladribine tablets 3.5-mg/kg group demonstrated lower annualized relapse rates versus placebo (0.14 vs 0.33; $p<0.001$) at 96 weeks. The most common adverse event (AE) was lymphopenia, reflecting the proposed mode of action of cladribine. An integrated analysis of safety showed that the overall incidence of infections was not higher in patients receiving cladribine tablets 3.5 mg/kg than in patients receiving placebo, except for herpes zoster.

Objectives: This *post hoc* analysis examined the infectious AEs occurring during exact periods of Grade (G) 3 or 4 lymphopenia in patients treated with cladribine tablets 3.5 mg/kg; previous analyses used recovery to G1 or better.

Methods: A monotherapy oral cohort was derived from CLARITY, CLARITY Extension, ORACLE-MS, and the PREMIERE registry, with 923 patients receiving cladribine tablets 3.5 mg/kg. The AE profile for cladribine tablets 3.5 mg/kg during the exact periods of G3 or G4 lymphopenia (defined as time from onset of G3 or G4 lymphopenia to first G2 or lower plus 2 weeks). Adjusted AE incidences per 100 patient years (Adj-AE per 100PY) were calculated.

Results: Adj-AE per 100PY for any infections and infestations during periods of G3 or G4 lymphopenia (with G3/4) was 57.53 versus 24.50 outside these periods (without G3/4). Types of infectious AEs were similar between the two periods. More than half of cases occurring with G3/4 were treatable infections of the upper respiratory tract (Adj-AE per 100PY: nasopharyngitis, 13.48 vs 5.24 without G3/4; upper respiratory tract infection, 9.67 vs 3.41 without G3/4; pharyngitis, 4.51 vs 0.73 without G3/4). Herpes zoster was reported in 4 patients with G3/4 (Adj AE per 100PY: 4.50 vs 0.73 without G3/4); cases were dermatomal and mild to moderate in severity. Single occurrences were reported for most infectious AEs. Opportunistic infections were single occurrences of 'urinary tract infection fungal' and 'fungal infection' (preferred terms) and neither were severe or serious.

Conclusion: Severe lymphopenia was associated with an increased frequency of infections but not with a differential effect on types of infectious AEs in patients treated with cladribine tablets 3.5 mg/kg monotherapy. The profile of herpes zoster was uncomplicated, consistent with the findings of previous safety analyses.

P071

Choosing Disease-Modifying Therapy in Multiple Sclerosis (MS) Patients with Progressive Multifocal Leukoencephalopathy (PML): Now What?

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Background: PML has been reported with natalizumab, fingolimod, and dimethyl fumarate. Choosing disease-modifying therapy (DMT) for MS patients who survive PML is complex and challenging given concerns about the risks of additional immunosuppression. There are no clear guidelines for such decision-making. A retrospective review of post-natalizumab PML patients suggested that glatiramer acetate, interferon beta, dimethyl fumarate and fingolimod can be safely administered.

Objectives: We aim to report our center's experience with such challenging cases.

Methods: We performed retrospective chart review of four patients with PML diagnosed and followed at our center. We collected data including disease activity and functional status pre and post diagnosis of PML.

Results: We follow four patients who survived PML occurring in the setting of iatrogenic immunosuppression due to MS medications. Three of them were due to natalizumab and one due to fingolimod. Two out of four patients were on prior immunosuppression. All patients on natalizumab tested positive for JC virus antibody with high index (>0.9). The most common clinical presentation was cognitive decline. DMT for MS was started in all the patients 4-6 months after PML diagnosis. Two patients had active brain MRI scans with enhancing MS lesions prior to starting DMT. Two patients were started on glatiramer acetate and the other two on interferon beta 1B. One patient was switched to teriflunomide 2 years after taking interferon beta 1B due to a new enhancing lesion. The other 3 patients have had no evidence of clinical or MRI activity with 1-4 years of follow up. None showed any indication of PML progression or relapse.

Conclusion: Choosing MS DMT in post-PML patients is challenging. According to our experience to date, DMT's not associated with PML seem safe and may be effective to prevent further MS lesions. Clearly, ongoing monitoring, particularly with regular brain MRI's is needed. As even large MS centers are likely to have limited experience with these issues, assessment of a much larger sample size using one or more patient registries would be welcome.

P072

Tuberculosis Screening in the Setting of Multiple Sclerosis Disease Modifying Therapies

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Background: Disease modifying therapies (DMTs) for multiple sclerosis (MS) have diverse effects on the immune system, and several can affect the risk for certain infections such as tuberculosis (TB). Screening for TB is recommended prior to initiation of certain DMTs, but TB testing generally occurs in the setting of ongoing DMT use. Results of the serum Interferon Gamma Release Assay (IGRA) for TB screening may be affected by use of certain DMTs, but this has not been described.
Objectives: To determine the effects of different MS DMTs on serum-based TB screening via IGRA, and to evaluate whether an indeterminate test result is related to lymphopenia.
Methods: We identified patients with MS who underwent TB testing via IGRA in preparation for transition to ocrelizumab beginning in March 2017. We recorded the IGRA results, current DMT, and absolute lymphocyte count. The proportion of patients with indeterminate TB test results were compared across DMTs via Chi-squared testing. Logistic regression was used to determine whether the odds of indeterminate testing are increased in the setting of lymphopenia.
Results: To date, we have reviewed the records of 63 patients transitioning to ocrelizumab, and anticipate inclusion of over 150 patients in this study. Of the patients analyzed, 40 underwent TB screening via IGRA. 92.5% (n = 37) tested negative, 2.5% (n = 1) tested positive, and 5.0% (n = 2) had indeterminate results. DMTs administered at the time of testing included dimethyl fumarate, fingolimod, natalizumab, intravenous methylprednisolone, oral prednisone, interferon beta, and glatiramer acetate. One patient with an indeterminate result was taking fingolimod and had an absolute lymphocyte count (ALC) of 0.41 k/uL; the second was taking dimethyl fumarate and oral prednisone, with an ALC of 1.38 k/uL. At this time, we do not have a dataset sufficiently large enough to further examine the association of certain DMTs or lymphopenia with an indeterminate IGRA result.
Conclusion: Certain DMTs may affect the results and interpretation of serum TB testing via IGRA. Our small database thus far does not demonstrate consistent patterns of indeterminate results within certain DMTs or lymphocyte counts, likely due to its small size. However, based on clinical observation of this phenomenon, we anticipate more informative data as we continue to include more patients in the study. Ongoing analysis will examine the effects of lymphopenia in more detail.

P073

A Risk Aversion Calculator for Augmenting the Disease Modifier Selection Process

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Background: Settling into the use of a multiple sclerosis disease modifier can seem like taking an exam consisting of a single multiple-choice question with 16 equally appropriate responses, having months or even years to second-guess your choice, and then getting a grade but never being told the correct answer. Choosing between these options can be overwhelming, leaving patients feeling both disempowered and depersonalized in the decision-making process.
Objectives: In order to augment the decision-making process, we introduce a side effect aversion calculator, that takes a patient's individual side effect aversion profile into consideration and evaluate if it has any impact on patient self-efficacy.
Methods: Multiple sclerosis patients who have a provider-identified need for disease modifier initiation or switch were recruited and then randomized into one of four arms. Those randomized to "calculator arms" were reminded that the purpose of the calculator is to facilitate the medication choice discussion, NOT make the decision. Subjects were asked to rate their level of concern over the most common adverse events (AEs) across all treatments. The calculator multiplies subject responses by the prevalence of that AE reported within available prescribing information. The sum of these weighted scores reveals a disease modifier's Total Aversion score and medication ranking by patient's specific side effect aversion profile, therefore framing discussion between subject and provider. Enrollment visits concluded with surveys designed to collect MS clinical history, enduring MS symptoms, medication history, and finally questions pertaining to medication adherence and self-efficacy. This same survey was conducted prior to the subsequent three clinic visits.
Results: Preliminary analysis from the first three months of study recruitment demonstrates the efficacy of this calculator within the Duke Multiple Sclerosis Clinic.
Conclusion: Providing a tool such as a personalized risk aversion calculator can have substantial benefits in the confusing decision-making process surrounding disease modifiers.

P074

Review of Clinical Experience with Dimethyl Fumarate Use at an Academic Medical Center

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Background: Dimethyl fumarate (DMF) is an oral medication for relapsing remitting multiple sclerosis (MS). While the exact mechanism of action of DMF in MS is unknown, it does activate the nuclear factor-like 2 pathway, which results in decreased lymphocyte proliferation. In the phase 3 studies, grade 3 lymphopenia was reported at 5%. Lymphopenia in DMF has led to a number of opportunistic infections including 5 cases of progressive multifocal leukoencephalopathy. Recent studies have shown lymphopenia is more common than previously thought in DMF use, with grade 2-3 at 17%.
Objectives: Our goal was to do a retrospective study in our patient population on DMF to evaluate risk of lymphopenia. Secondary outcomes looked at the rate of discontinuing DMF due to lymphopenia versus other side effects. We also assessed infection rates in patients on DMF with or without lymphopenia.
Methods: Retrospective analysis of patients identified using the Healthcare Enterprise Repository for Ontological Narration (HERON) from 1/2013-3/2016. Patients were identified by a

primary diagnosis of MS and DMF use. A thorough chart review was done on the 205 identified patients.
Results: The HERON search resulted in 205 patients. Of these, 6 never took DMF. We excluded 1 based on age less than 18, and 66 who had no available labs. Of the 132 remaining patients, age ranged from 18-78 years; 73% were female. 25% of patients had grade 2-3 lymphopenia. Grade 3 lymphopenia was present in 9%, grade 2 in 16%, and grade 1 in 8%. Subgroup analysis of those over the age of 55 revealed 24% grade 3 lymphopenia, compared to 5% in those 18-55. Infections reported to the treating neurologist were 6%, with 50% of those having grade 3 lymphopenia. DMF was discontinued by 41 patients (31%); 13 for side effects, 9 continued disease activity, 8 fear of serious side effects, 7 lymphopenia, 3 unknown, and 1 lack of insurance coverage.
Conclusion: DMF in the treatment of MS is associated with increased risk of lymphopenia particularly over the age of 55. Lymphopenia associated with DMF use is higher in clinical practice compared to phase 3 studies. One reason may be the age limit of 55 years in both clinical trials. Age should be considered when using DMF in the treatment of MS.

P075

Pseudo-Hyperthyroidism in a Multiple Sclerosis Patient Taking High-Dose Biotin

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Background: Biotin is an important co-enzyme for carboxylases involved in energy metabolism and fatty acid synthesis with a potential role in re-myelination. Recently, it has been used increasingly for progressive forms of Multiple Sclerosis (MS) after a pilot non-blinded study demonstrated a promising impact of high-dose biotin (300mg/day) on disease progression and permanent disability[1]. Further interest ensued after a randomized, double-blind, placebo-controlled study showed sustained reversal of MS-related disability in progressive MS patients taking high-dose biotin[2]. While generally safe and well-tolerated, biotin has been associated with cases of apparent hyperthyroidism, and investigations indicate that this is likely due to interference with thyroid assays.
Objectives: To increase awareness in the MS community that high-dose biotin can cause laboratory changes that mimic thyrotoxicosis.
Methods: We report a case of a 55-year-old woman with MS without medical history of thyroid disease who developed laboratory abnormalities suggestive of thyrotoxicosis on routine testing. Thyroid Stimulating Hormone (TSH) 0.032 uIU/ml [Reference Interval (RI) 0.45-4.5 uIU/ml]; Thyroxine T4, Free-Direct (T4-Free) >7.77 ng/dL [RI 0.82-1.77ng/dL]. At time of testing, she expressed no complaints of mood irritability, sleep difficulty, tachycardia, heat intolerance, diarrhea, or weight loss. Her daily medications included: dimethyl fumarate 240mg twice daily, low-dose naltrexone 4.5mg, baclofen 30mg, escitalopram 10mg, biotin 300mg, vitamin D-3 5000IU, and vitamin B-complex.
Results: The mismatch between our patient's clinical symptoms and her laboratory results suggested the possibility of pseudo-hyperthyroidism. Prior to any further endocrine work up in our patient, biotin was held for three days and repeat testing showed normalized thyroid lab values: TSH 2.46 uIU/mL; T4-free 1.1 ng/dL. As confirmation, the patient re-challenged with biotin. This again resulted in low TSH and high T4-free that normalized after holding biotin.
Conclusion: High-dose biotin is associated with inaccurate laboratory measurements that mimic thyroid disease; various cases, published in endocrine or medicine journals, describe excess biotin displacing antigen-antibody complexes used in biochemical assays resulting in false decrease in analyte measurements[3,4,5,6]. MS specialists should be aware of this phenomenon and should know how to differentiate pseudo-hyperthyroidism from true endocrine disease to avoid unnecessary testing or treatment.

P076

How Much Testing Is Enough? Evaluating the Stability of Serial JCV Antibody Tests in Natalizumab Patients

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Background: John Cunningham virus (JCV) can cause a highly prevalent infection which most often goes undetected. This virus can opportunistically spread in immunosuppressed patients and cause a debilitating brain infection called Progressive Multifocal Leukoencephalopathy (PML). The management of Multiple Sclerosis (MS) with disease modifying therapies (DMTs), such as natalizumab, carries the risk of PML. Testing antibody titers against JCV is the only available biomarker which allows clinicians to gauge a patient's risk of developing PML and, as such, influences treatment decisions. Higher antibody index values are thought to signify higher risk. However, the fluctuations in a patient's antibody titer over time are still not fully understood and pose uncertainty around interpreting PML risk from JCV index values.
Objectives: It has been suggested that patients receiving natalizumab treatment have higher rates of JCV seroconversion compared to individuals who are not receiving DMTs. In this retrospective analysis of JCV index values from MS patients treated with natalizumab, we explore the variability of the JCV test by assessing seroconversion rates on sequential tests and ask how often you have to test to be confident in the patient's serostatus.
Methods: We analyzed JCV antibody index values from over 150 MS patients treated with natalizumab at Penn Medicine's Multiple Sclerosis Center. All patients in this study had multiple JCV index values. The average follow-up period for which JCV tests are presented is over two years.
Results: Of the over 150 MS patients treated with natalizumab, 133 tested negative on their initial JCV test. Around 90% of these patients went on to remain seronegative on their second test while we saw around 13% of patients who were negative seroconverting on their third JCV test. Seroconversion rates among those who continued testing were up to 19% on a fourth JCV test and over 25% by time of a fifth test and beyond. The majority of initially seronegative patients stayed negative for the entirety of our two-year study period but significant numbers of patients converted.
Conclusion: The majority of natalizumab patients who tested negative for JCV on their first test remained JCV seronegative on

all subsequent tests. However, the more often patients were tested for JCV antibodies, the more seroconversions we detected. Over 20% of seroconversions could have been missed if patients were tested only twice as supposed to four or five times over our 24-month follow-up.

P077

Ocrelizumab Safety in Patients with Multiple Sclerosis: Updated Analyses with a Focus on Infusion-Related Reactions

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Background: Ocrelizumab (OCR) safety/efficacy data from Phase III studies in relapsing (RMS; OPERA I/II [NCT01247324 and NCT01412333]), primary progressive multiple sclerosis (PPMS; ORATORIO [NCT01194570]) and open-label extension (OLE) periods (including Phase II data in relapsing remitting multiple sclerosis [NCT00676715]) are reported to further understand its long-term benefit–risk profile.
Objectives: To report ongoing safety evaluations from OCR clinical trials.
Methods: OCR recipients received 600 mg doses intravenously (IV) every 24 weeks in OPERA I/II (96 weeks; first dose as 2×300 mg infusions split by 14 days) and ORATORIO (≥120 weeks; all doses split). Patients in the Phase II study received 600 or 2000 mg infusions through Week 24 (both doses split); treatment through Week 96 was OCR 600 mg (patients starting on 600 mg dose and those receiving placebo or interferon beta-1a 30 μg) or 1000 mg (those starting on OCR 2000 mg). Comparators were placebo (ORATORIO and Phase II) and interferon beta-1a (44 μg subcutaneous/three times [OPERA] or 30 μg intramuscular weekly [Phase II]). Infusion-related reaction (IRR) prophylaxis was methylprednisolone (100 mg IV per-protocol) and antihistamines and analgesics/antipyretics (recommended). Patients completing controlled-treatment periods could enroll in OLE with OCR 600 mg/24 weeks. Data presented are from OCR recipients (including those switching from comparators) and include serious infection, malignancy (first event) and common adverse event (AE) data.
Results: IRRs were the most common overall AE in OCR recipients during the controlled-treatment periods of the OPERA (≥1 IRR, 283/825 patients [34.3%]; pooled analyses) and ORATORIO studies (≥1 IRR, 194/486 patients [39.9%]), most often seen during the first infusion, generally mild-to-moderate in severity and manageable. As of February 17, 2017, 2,301 patients with multiple sclerosis (MS) received OCR, resulting in 7,748 patient-years of exposure and mean (SD) number of doses received per patient of 7.3 (3.3). Reported rates per 100 patient-years (95% confidence interval) were as follows: AEs, 226 (222–229); serious AEs, 7.18 (6.59–7.80); infections, 71.3 (69.5–73.2); serious infections, 1.86 (1.57–2.19) and malignancy, 0.454 (0.316–0.632).
Conclusion: 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.

P078

Rapid Evolution of Natalizumab-Associated Brainstem PML–IRIS: Lessons Learned in Diagnosis and Management

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Background: It is challenging to diagnosis and manage natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML). Earlier diagnosis and rapid restoration of immune surveillance of the brain are necessary. Management includes plasma exchange (PLEX) or immunoadsorption (IA). However, immune reconstitution inflammatory syndrome (IRIS) can develop within days and may lead to detrimental clinical changes or death. Proper identification of IRIS followed by administering steroids may help stabilize the patient. Additional measures may include mirtazapine, maraviroc, and mefloquine
Objectives: To present a challenging case of NTZ-PML and to review relevant literature.
Methods: Case report and literature review.
Results: A 31-year-old right-handed woman with relapsing-remitting multiple sclerosis (MS) on natalizumab (JC virus index of 2.36; finished 96 infusions [personal choice]) with no evidence of MS activity for the past six years presented with subacute vertigo, dysarthria, left-sided weakness, and ataxia. The symptoms began six weeks earlier, and she was treated with high-dose steroids for presumed MS exacerbation with no improvement. Exam revealed severe ataxia, dysarthria, and multi-directional nystagmus with preserved cognitive functions. Brain magnetic resonance imaging (MRI) showed patchy T2 hyperintensity in the left cerebellar peduncle and the brachium pontis. Despite the unusual location, we suspected PML and started active management. Spinal fluid analysis showed 24 copies/mL of JC virus confirming the diagnosis. We used PLEX, mirtazapine, steroids, and maraviroc. However, she continued to clinically worsen. Weekly MRIs showed rapid progression of signal intensity (day 7) and patchy enhancement (day 24). She continued to show clinical and radiographic progression at day 33 despite continued steroids. We will provide clinical and radiologic follow-up data at ACTRIMS. A review of the literature retrieved nine detailed accounts of infratentorial NTZ-PML. We will discuss various diagnostic and management approaches including the utility of PLEX in these cases.
Conclusion: We presented a challenging case of infratentorial NTZ-PML, initially misdiagnosed as an MS exacerbation, and which rapidly progressed despite active management. Our case and other reports of infratentorial NTZ-PML suggest a predilection for cerebellar peduncles and pons. Furthermore, management of infratentorial NTZ-PML deserves further discussion especially

in the context of reports of good outcomes without the use of PLEX.

P079

B Cell Therapies and Conception: A Review of Risks

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Background: A 30 year-old nulliparous woman with relapsing remitting multiple sclerosis (RRMS) presented for advice about disease modifying therapy (DMT). She had previously stopped fingolimod prior to attempting conception but developed severe clinical and radiographic relapse. She restarted fingolimod but desires an option to protect herself from relapse while minimizing risk to a fetus. The use of a B cell-depleting agent prior to conception was discussed since B cell therapies have a mean terminal half-life of 19-22 days but a longer therapeutic impact.
Objectives: To analyze the available literature regarding the safety of B cell-depleting therapies in women before conception and during pregnancy.
Methods: A Pubmed search was completed using the following English-language MeSH terms: "Multiple Sclerosis", "Autoimmune", "Pregnancy", "Rituximab", "Ocrelizumab". 20 relevant articles were included.
Results: 186 pregnancies with rituximab exposure (n=2 neuromyelitis optica, n=2 MS, n=182 systemic autoimmune or oncologic diseases) are reported. Exposure to rituximab was 18 months to 1 week preconception (n=19), first trimester (n=6), or second or third trimester (n=161). Roughly half of mothers in the second-or third term group received additional chemotherapies. In the preconception exposure group, one neonate had self-limited B-cell depletion (total 2%, normal 5-24%) without corresponding infection. One neonate exposed to first trimester rituximab had mild, self-limited neutropenia without infection. Of those exposed to second or third trimester rituximab, 10 had B-cell depletion (one 29-week preterm neonate had severe sepsis, with B cell subsets of 10% and undetectable immunoglobulins at 37 weeks' gestation). 4 infants without evidence of B cell depletion had moderately severe neonatal infections. No teratogenicity of rituximab was noted.
Conclusion: Women with active RRMS who wish to conceive may encounter a decision to discontinue DMT prior to conception. Whether B cell therapies may be safely administered prior to conception to women with MS is not certain. The literature is limited regarding the safety of treatment with B cell-depleting therapy prior to pregnancy. While therapies targeting CD20 are known to cross the placenta, rituximab and ocrelizumab contain IgG1k components, which do not cross the placenta until after the first trimester. There is no consensus regarding timing of discontinuing B cell-depleting therapy in women desiring to conceive.

P080

Treatment of Natalizumab-Induced PML with Cidofovir or CMX001 (brincidofovir) and Mirtazapine

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Background: Progressive-multifocal encephalopathy (PML) is a viral brain infection caused by the JC polyomavirus (JCV) which is often fatal. Published case reports describe beneficial outcomes in PML treatment with cidofovir combined with mirtazapine in immunocompromised patients including autoimmune diseases (i.e. SLE, sarcoid). Cidofovir (CDV) was studied for treatment of HIV-related PML but had no statistically significant benefit in survival when added to antiretroviral therapy. To date, there have been no publications describing patients treated with cidofovir for PML associated with multiple sclerosis (MS) therapy such as natalizumab. CMX001 (Brincidofovir), a lipid conjugate of cidofovir was developed to provide oral bioavailability, and potentially increased antiviral potency against dsDNA viruses. Promising studies for its use against JCV DNA replication in vitro in human fetal brain SVG cultures were done, but only limited anecdotal data on its use for PML in vivo exists.
Objectives: To describe the clinical outcome of four MS patients who developed PML while on natalizumab treated with CDV or CMX001.
Methods: Retrospective chart review of 4 multiple sclerosis patients who were diagnosed with PML and treated with either intravenous CDV or oral CMX001.
Results: Two male and two female patients were treated for natalizumab-related PML in 2011. All 4 patients survived for more than 5 years after being diagnosed with PML. Three of the patients were treated with intravenous CDV (5mg/kg every 2 weeks for 4-7 cycles) and mirtazapine. One patient was treated with oral CMX001 and mirtazapine. Serial CSF analysis showed an initial rise in CSF JCV PCR after diagnosis with subsequent decrease in the copies after treatment with CDV or CMX001. Two patients developed significant diarrhea while on therapy. Three patients had significant neurologic recovery, but with mild to moderate residual cognitive deficits. One patient who remained significantly physically disabled after a delayed PML diagnosis died 5 years later.
Conclusion: The review of these 4 patient cases demonstrate that early initiation of treatment with CDV or CMX001 and concurrent mirtazapine can halt the progression of natalizumab –related PML and aid in neurologic recovery. More studies are needed to evaluate this combination of therapy for use in natalizumab-related PML.

P081

Pulmonary Sarcoidosis Following Treatment of Multiple Sclerosis with Interferon-Beta

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Background: Sarcoidosis is a rare multisystem noncaseating granulomatous disease affecting middle aged adults of unknown etiology. Elevated levels of interferon-gamma in alveoli and serum are associated with pulmonary sarcoidosis. While structurally different to interferon-gamma, Type 1 interferons have been uncommonly associated with development of sarcoidosis, possibly due to macrophage activation. In particular, sarcoidosis during treatment with interferon-beta for multiple sclerosis is an exceedingly rare complication.

Objectives: To present a case of incidentally discovered pulmonary sarcoidosis in a patient receiving interferon-beta for Relapsing Remitting Multiple Sclerosis (RRMS).
Methods: Case Study and Literature Review.
Results: A 54-year-old female with a 7 year history of RRMS was most recently treated with Interferon beta-1a for two years. Surveillance imaging of brain and spinal cord showed radiographic progression of multiple sclerosis while incidentally noting mediastinal lymphadenopathy in the absence of any pulmonary or systemic symptoms except occasional cough. Dedicated chest imaging confirmed mediastinal and hilar adenopathy without radiographic evidence of malignancy or infection. Biopsy revealed aggregates of epithelioid histiocytes consistent with granulomatous disease without evidence of mycobacterial or other infectious process. Interferon-beta1a was discontinued and the patient was transitioned to alternative disease modifying therapy for RRMS.
Conclusion: Sarcoidosis is a rare, but important to recognize, complication of interferon-beta therapy for RRMS. Early detection and discontinuation of interferon therapy is the mainstay of treatment.

P082

A Case Report of Asymptomatic Progressive Multifocal Leukoencephalopathy

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Background: Progressive multifocal leukoencephalopathy (PML) is the leading adverse effect for using natalizumab in the treatment of multiple sclerosis (MS). Very few cases have described a completely asymptomatic course of PML.
Objectives: We report the development of asymptomatic PML in a 24-year-old woman with MS treated with natalizumab.
Methods: The patient was diagnosed with PML based on characteristic MRI lesions after 27 infusions of natalizumab. She had no neurologic deficits at the time of diagnosis and John Cunningham virus (JCV) was detected at 15 copies/ml (NIH/NINDS, Bethesda, MD. USA). She was initially treated with mefloquine and mirtazapine.
Results: The patient remained asymptomatic for three months and later developed worsening MRI lesions related to immune reconstitution inflammatory syndrome (IRIS). At that time, she received intravenous immunoglobulin (IVIG) and high dose intravenous methylprednisone with radiographic improvement of the lesions.
Conclusion: Our report illustrates that early detection of asymptomatic PML and its subsequent treatment resulted in a benign clinical course. In consideration of the additional small number of asymptomatic PML cases that have been reported, we conclude that routine MRI surveillance is important for MS patients who are at high risk for developing natalizumab-associated PML.

P083

Rebound Relapse in Multiple Sclerosis after Ceassing Fingolimod

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Background: Rebound is defined as a relapse that is clinically severe accompanied by magnetic resonance imaging (MRI) lesion activity that surpassed the level of activity before starting the disease modifying therapy. It is usually related with the recovery of the lymphopenia induced by the medication once this is suspended.
Objectives: To highlight the importance of identifying this entity as a potential complication in the safety profile of the medication.
Methods: Case report. A 56 years old female with diagnosis of Multiple Sclerosis (MS) since 2013, initially treated with glatiramer acetate, switched to Fingolimod in May 2016 because of high disease activity on MRI, with an Expanded Disability Status Scale (EDSS) of 2.5. She started 45 days after cessation of Fingolimod with right hemiparesis and dysesthesia, 2 days later she developed disorientation, irritability, dysarthria and right cerebellar syndrome, with a new EDSS of 4.0. Lymphocites count increased from 600 to 1500. MRI showed multiple new T2 and FLAIR hyperintensities compared to the previous image control: on left cerebellar peduncle and multiple tumefactive lesions predominantly on left parieto-temporal lobes, all of them with intense gadolinium enhancement.
Results: She received 10 days of 1000mg methylprednisolone and intravenous human immunoglobulin at 1gr/kg, then she restarted fingolimod as usual. Two weeks later her lymphocite counts were reduced to 500 and after another two weeks she was recovered from the cerebellar syndrome and right weakness.
Conclusion: Rebound relapse in cessation of Fingolimod is comparable with the previously reported immune reconstitution inflammatory syndrome in patients with MS following cessation of Natalizumab therapy. This phenomenon must now be considered in its risk-benefit ratio when treating patients.

P084

Long-Term Lymphocyte Counts in Patients with RRMS Treated with Cladribine Tablets 3.5 Mg/Kg: Total Lymphocytes, B-, and T-Cell Subsets

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Background: In CLARITY, the cladribine tablets (CT) group (3.5 mg/kg) demonstrated significantly lower annualized relapse rates versus placebo (0.14 vs 0.33; <0.001) at 96 weeks. Lymphopenia was the most commonly reported adverse event, consistent with the proposed mechanism of action of CT.
Objectives: To investigate absolute lymphocyte counts (ALCs) up to 312 weeks and B- and T-cell subsets up to 240 weeks after the first administered dose of CT, in patients with relapsing–remitting multiple sclerosis (RRMS) receiving 2 annual courses of CT (3.5 mg/kg cumulative dose) and no further active treatment.
Methods: Data from patients with RRMS randomized 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 ALC was 1.86×10^9/L. During Year (Y)1, ALC reached nadir (1.00×10^9/L) at 9 weeks post-treatment

with CT 3.5 mg/kg before gradually increasing. During Y2, median ALC reached nadir at Week (Wk) 55 (0.81×10^9/L), recovered to normal values ($\geq1.00\times10^9$/L) by the end of Y2 (Wk96), and continued to increase thereafter. ALC had returned to normal values in 75% of patients by Wk144. Median CD4+ lymphocytes were 851 cells/μL at baseline. After treatment in Y1, CD4+ reached nadir at Wk16 (385 cells/μL) and then gradually increased. CD4+ reached nadir in Y2 of treatment at Wk60 (292 cells/μL). Values then gradually recovered, reaching the threshold of 350 cells/μL by approximately Wk120, continuing to improve thereafter. Median CD8+ lymphocytes at baseline were 378 cells/μL. CD8+ reached Y1 nadir at Wk16 (239 cells/μL), then gradually increased; 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); after Y2 treatment nadir was reached 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 recovering and 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.

P086

Effectiveness of Lymphocyte-Based Re-Treatment Criteria in Minimizing the Incidence of Severe Sustained Lymphopenia with Cladribine Tablets 3.5 mg/kg

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Background: In CLARITY the cladribine tablets 3.5-mg/kg group demonstrated lower annualized relapse rates versus placebo (0.14 vs 0.33, $p<0.001$) at 96 weeks. The most common adverse event was lymphopenia, consistent with the proposed mechanism of action.

Objectives: To evaluate whether lymphopenia persists following treatment and re-treatment with cladribine tablets 3.5 mg/kg.

Methods: Lymphopenia incidence rates by grade (National Cancer Institute Common Terminology Criteria for Adverse Events v3.0) for patients who were randomized to cladribine tablets 3.5 mg/kg in the 2-year CLARITY study and re-randomized to cladribine tablets 3.5 mg/kg in the 2-year CLARITY Extension study (7 mg/kg cumulative dose over 4 years; N=186) are reported. Patients with Grade 0 lymphopenia ($\geq1.0\times10^9$ cells/L) before the first course of cladribine tablets and Grade 0 or 1 lymphopenia ($\geq0.8\times10^9$ 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 or 1 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.

Conclusion: In patients who were treated according to re-treatment guidelines (i.e., having lymphocyte counts $\geq1.0\times10^9$/L before the first course and $\geq0.8\times10^9$/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 minimizing the incidence of severe, sustained lymphopenia during four years of treatment with cladribine tablets.

P087

Lymphocyte Subset Abnormalities in Predominantly Hispanic Multiple Sclerosis Patients Treated with Fingolimod or Dimethyl Fumarate

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Background: Abnormalities in lymphocyte subsets are noted in multiple sclerosis (MS) patients taking both fingolimod and dimethyl fumarate (DMF). In clinical trials, absolute lymphocyte counts (ALC) dropped by 20-30% in patients taking fingolimod and ALC dropped by about 30% with DMF use. We seek to better characterize these abnormalities in a predominantly Hispanic population in South Florida, USA.

Objectives: To examine the influence of fingolimod and DMF on lymphocyte subsets in a predominantly Hispanic MS population.

Methods: This retrospective, longitudinal observational study of MS patients taking either fingolimod or DMF evaluated lymphocyte subset values at baseline, 6 months, 1 year, 2 years after treatment start. Inclusion criteria were a definite diagnosis of relapsing MS, treatment with either fingolimod or DMF, and availability of baseline lymphocyte subset values with at least two lymphocyte subset values. Paired longitudinal analyses comparing treatment group and ethnic group were conducted for CD4 and CD8 counts at baseline and month 6, month 12 and month 24. Absolute lymphocyte count and lymphocyte subsets were examined by cross-sectional analysis. Paired *t* tests were used for longitudinal analyses and two-sample student *t* tests for cross-sectional analyses, with statistical significance set at *P* values < 0.05.

Results: 46 patients included 11 males and 35 females. Thirty-six patients (78%) were Hispanic, of which 100% self-identified as White-Hispanic. Ages ranged from 20 to 57 years, with a median age of 44.5 years. The median duration of disease was 8.3 years. Thirty-five and 11 patients were treated with DMF and fingolimod, respectively. Absolute lymphocyte counts decreased over time in both the fingolimod and the DMF groups. A reduction of ALC by 56.5% was statistically significant at 2 years of fingolimod therapy compared to baseline values (p=0.0012). In the DMF group, 2-year ALC was reduced from baseline ALC by 44.0% (p=0.0009). The mean reduction of CD8 (76.3%) was more pronounced than that of CD4 (63.2%) (p=0.0016, p=0.0015). CD8+ counts at 1 year and 2 years were not significantly different (p=0.21). No serious infections were reported.
Conclusion: In this predominantly Hispanic population treated with either fingolimod or DMF in an academic MS center, lymphocyte subset changes over time were observed in a large proportion of patients. The clinical significance of lymphocyte subset abnormalities in these patients is unclear. Further studies including Hispanics are needed.

Environmental Factors

P088
Two Cases of Pediatric Multiple Sclerosis after Human Papillomavirus Vaccination
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Background: The quadrivalent human papillomavirus (HPV) vaccine, Gardasil®, was FDA approved in 2006 for prevention of HPV infection (types 6, 11, 16, and 18) and related cancers. Few cases have been reported of central nervous system demyelinating disease including acute disseminated encephalomyelitis, neuromyelitis optica (NMO), clinically isolated syndrome and multiple sclerosis (MS) post-vaccination.
Objectives: To report two cases of MS in the pediatric population that developed after administration of HPV vaccination with Gardasil®.
Methods: Case reports and literature review.
Results: Case 1:14 year-old male presented with left retro-orbital pain and blurry vision in the left eye, diagnosed with left optic neuritis. He had a second attack of left optic neuritis two months after initial presentation. Third dose of Gardasil® was given two weeks prior to presentation.
Case 2: 17 year-old female presented with blurry vision in the right eye, diagnosed with right optic neuritis. MRI brain showed right frontal enhancing lesion. First dose of Gardasil® was given two weeks prior to presentation. She did not receive further doses. One week after discharge, she experienced intermittent numbness and weakness in her lower extremities, and blurry vision in the right eye. Repeat MRI brain showed new left parieto-occipital enhancing lesion.
For both patients, CSF showed presence of oligoclonal bands. MRIs of the brain showed presence of white matter lesions with periventricular and corpus collosal involvement. Rest of work-up was unremarkable including NMO antibody. Both patients were treated with IV steroids for relapses, and started on disease modifying therapy with interferon beta-1a for relapsing remitting MS after second event. They were followed for two years.
Conclusion: Despite a large Scandinavian study of almost 4 million girls and women, in which nearly 800,000 received HPV vaccination, no increased risk of MS or demyelinating disease were identified (JAMA, 2015; 313[1]:54-61). These 2 cases and the others that have been previously reported, suggest a temporal association between HPV vaccination and onset of MS. Although live, attenuated vaccines are generally not recommended in MS patients, Gardasil® is an inactivated and recombinant vaccine, and does not contain any viral DNA. Whether the vaccine increases the risk of the initial demyelinating event in an already predisposed population or triggers the onset of MS, by way of an immune response, remains to be studied.

Epidemiology

P089
Effect of Age at Puberty on Risk of Multiple Sclerosis: A Mendelian Randomization Study
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Background: Puberty attainment marks a dramatic increase in MS incidence and the emergence of a female predominant sex ratio, suggesting that it may be a defining period in MS etiology. Several epidemiological studies have reported an increased risk of MS with earlier age at puberty among females, although others found no association, or an opposite effect. However, these studies are subject to residual confounding from factors such as obesity which are associated with both puberty timing and MS susceptibility.
Objectives: To investigate the potential for a causal effect of age at puberty on MS susceptibility and whether such effects are mediated by obesity using Mendelian randomization (MR).
Methods: We used genetic variants strongly associated with age at menarche in a large genome wide association study (GWAS) meta-analysis involving 329,245 women. The genetic architecture of puberty timing across both sexes is highly correlated ($r_{genetic\ correlation}$=0.75, p=1.2x10^{-79}), allowing menarche variants to provide some insight into puberty timing in males as well. The effect of age at puberty on risk of MS was measured using the latest International MS Genetics Consortium (IMSGC) GWAS meta-analysis including 14,802 MS cases and 26,703 controls. The effect of each variant on MS was weighted by its association with age at puberty. Estimates were combined using an inverse-variance weighted meta-analysis. To test whether puberty effects on MS were mediated by body mass index (BMI), we performed a multivariable MR incorporating the same puberty-associated variants along with their effect on BMI, derived from a GWAS of 87,048 individuals.

Results: We selected 375 independent autosomal non-HLA variants strongly associated with puberty timing. Of those, 372 were ascertained either directly (n=345) or through a proxy (n=27, median r^2=0.99) in the IMSGC meta-analysis. The inverse-variance weighted analysis revealed that a 1 year decrease in the age at puberty increased odds of MS by 8% (OR=1.08, 95% CI 1.01-1.16, p=0.03). However, the multivariable MR analysis suggested that after accounting for mediating effects of BMI, there was no direct effect of age at puberty on MS susceptibility (OR=1.04, 95% CI 0.96-1.13, p=0.36).
Conclusion: This study demonstrates that genetically decreased age at puberty increases the risk of MS. This association is largely mediated by the effects of puberty timing on BMI. However, the pathways underlying a possible effect of age at puberty on disease course and severity remain unclear.

P090

Predicting Diagnostic Delays in Persons with Multiple Sclerosis

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Background: Diagnostic delays in multiple sclerosis (MS) negatively impacts long-term outcomes. Elucidating predictors of delay is imperative for the earlier initiation of therapeutics.
Objectives: To identify predictors of diagnostic delay in persons with MS (PwMS).
Methods: The study included of 1,497 PwMS participating in the Accelerated Cure Project. Detailed medical history, socio-demographics, and behavioral risk factors were collected. Diagnostic delay was the difference in age at diagnosis and age of 1st symptom. Diagnostic delay was non-normally distributed, therefore we conducted data simulations to compare poisson, quasi-poisson, negative binomial, zero-inflated poisson, zero-inflated negative binomial, and zero-inflated geometric (ZIG) distributions. Based on goodness-of-fit statistics, the ZIG model was selected. A zero-inflated model has two parts: the 1st part assesses probability of a delay; the 2nd part assesses the relationship between predictors and delay length. Backward stepwise selection was used to determine predictors relevant for each part of the ZIG regression model, with robust standard errors. Variables included gender, birth year, race, disease subtype, smoking status within 5yrs of onset, diagnosis of obesity, history of infectious mononucleosis (IM), education level, number of impaired functional domains (FDs; 1, 2-4, 5-8, and ≥9 FD[s] impaired), and era of onset (before 1983, 1983-2000, 2001-2004, ≥2005; to reflect landmark changes in diagnostic criteria).
Results: The number of impaired FDs and era of onset were the only significant predictors of probability of a delay. Polysymptomatic PwMS were significantly more likely to have no delay than monosymptomatics (odds ratio $(OR)_{2\text{-}4\ FDs}$=3.0, p<0.01; $OR_{5\text{-}8\ FDs}$=2.6, p<0.05, and $OR_{\geq 9\ FDs}$=6.0, p<0.01). As expected, PwMS with more recent onset were more likely to also have no delay compared to those with onset in 1983-2000 ($OR_{2001\text{-}2004}$=17.9; $OR_{\geq 2005}$=34.1; p<<0.001).
Length of diagnostic delay was influenced by multiple predictors. Older age of onset (p<<0.001), history of IM (p<0.01), being black (p<0.01) or other race (p<0.05), experienced shorter delays. Primary progressives had a 31% increase in delay length compared to relapsing at onset PwMS. There was suggestive evidence for a 13% increase in delay length among smokers (p<0.1).
Conclusion: We identified multiple predictors of probability of a diagnostic delay, and predictors contributing to the length of delay in PwMS.

P091

Distinct Effects of Obesity and Vitamin D on Risk of Multiple Sclerosis: A Mendelian Randomization Study

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Background: Several lines of evidence support a causal role for obesity in the development of MS. Although several candidate pathways have been identified to explain this association, it remains unclear which is most critical. Vitamin D has been proposed as a possible mediator since increased adiposity leads to lower levels of circulating 25-hydroxyvitamin D, which in turn predisposes to MS. Mendelian randomization (MR) studies have informed the causal effect of obesity on adult-onset MS, but possible mediation by vitamin D has yet to be assessed.
Objectives: To investigate the direct causal effect of obesity as measured by body mass index (BMI) on MS susceptibility independent of variations in vitamin D levels through MR.
Methods: We selected as instrumental variables genetic variants strongly associated with BMI in the genome wide association study (GWAS) meta-analysis by the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which studied 322,105 European individuals. Corresponding effect estimates for these variants on MS susceptibility were obtained from the latest International MS Genetics Consortium (IMSGC) GWAS meta-analysis (14,802 MS cases and 26,703 controls). The effect of each variant on MS was weighted by its association with BMI. Estimates were combined using an inverse-variance weighted meta-analysis. Next, the effect of the BMI-associated variants on vitamin D was obtained from a recent study combining whole genome sequencing and GWAS data in 42,274 individuals. The BMI and vitamin D effect estimates were combined in a multivariable MR analysis to measure the direct effect of BMI on MS adjusting for vitamin D levels.
Results: We identified 77 genome-wide significant BMI-related variants in GIANT. A variant in chromosome 1 was excluded following linkage disequilibrium assessment, leaving 76 independent instruments for analysis. We confirmed the association between genetically determined BMI and MS susceptibility, with a standard deviation increase in BMI raising odds of MS by 34% (OR=1.34, 95% CI 1.10-1.64, p=0.003). This association remained largely unchanged after adjusting for vitamin D levels in the multivariable MR, with a standard deviation in BMI remaining associated with a 33% increase in odds of MS (OR=1.33, 95% CI 1.09-1.63, p=0.005).

Conclusion: This study demonstrates that the effect of obesity on MS risk is not mediated only by lowered vitamin D levels. These findings provide motivation to better understand how obesity increases the risk of MS.

P092

Use of the New Oral Disease-Modifying Therapies for Multiple Sclerosis: The First Five Years

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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.
Objectives: To describe the uptake of the new oral DMTs and to compare their use with that of the established first- and second-generation parenteral DMTs.
Methods: We used prospectively collected population-based health administrative data from British Columbia, Canada to identify persons with multiple sclerosis (PwMS) between 2011 and 2015. They were selected using a previously validated algorithm based on hospital and physician generated diagnostic (International Classification of Disease) codes. Using province-wide prescription records, we estimated the rate of uptake for each oral DMT and the proportion of PwMS using DMTs annually and over the five-year period. Changes in the annual rates and proportions were examined using Poisson and Log-Binomial regression. Findings were stratified by sex, age, and socioeconomic status (SES).
Results: Of the 14,148 PwMS identified, 1,019 started an oral DMT during the study period; equivalent to a rate of 16.6/1,000 person-year (95%CI: 15.6-17.7). On average during this period, the proportion of PwMS who filled at least one prescription for an oral DMT was 83/1,000. There was a three-fold increase in uptake between the first year that each of the oral drugs became available to the end of 2015. Similarly, the proportion of PwMS who had used an oral or second-generation parenteral DMTs increased, while use of the first-generation DMTs decreased by 30%. While no difference was observed between men and women (p-value > 0.5), uptake and use of several of the DMTs was associated with younger age or higher SES (p-value < 0.001).
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.

P093

Using Claims-Based Algorithms to Identify High Disease Activity for Relapsing Remitting Multiple Sclerosis Patients in US Healthcare Data

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Background: Relapsing Remitting Multiple Sclerosis (RRMS) accounts for about 85% of all diagnosed multiple sclerosis (MS) cases. RRMS is characterised by periods of increased disease activity followed by periods of recovery. High disease activity (HDA)-RRMS can be characterized, in part, by frequent relapses or a high burden of brain lesions. Valid identification of patients with HDA-RRMS in healthcare claims data sources allows deeper insight into characteristics and predictors of HDA-RRMS, and may lead to more effective treatment options.
Objectives: To develop and validate a healthcare claims-based algorithm for HDA-RRMS patient identification in an U.S. Integrated Delivery Network (IDN).
Methods: Study criteria included MS diagnosis, age ≥ 18 years, ≥ 1 year baseline history, RRMS subtype identified, no progressive MS disease, no other demyelinating diseases and no pregnancy in the IDN data for period 2010-2014. In the follow-up year after index date, the developed HDA-RRMS algorithm required at least one of the following: i) ≥ 2 relapses regardless of DMT use or not, and by a presence of either: hospitalisation or neurology visit with MS as primary diagnosis; MS symptoms/treatment; plasmapheresis; or high dose corticosteroid or ACTH use within 7 days after admission/visit; ii) ≥ 2 ER visits or hospitalizations with MS as primary admission or discharge diagnosis; iii) ≥ 3 neurology visits; or iv) ≥ 3 brain or spinal MRIs. A random sample of 141 medical chart reviews of patients with at least 2 relapses in the follow-up year regardless of treatment status identified as HDA-RRMS patients by the algorithm was the "gold standard" for validation and positive predictive value (PPV) calculations. HDA cases were assessed by a clinician as Certain, Likely, Possible, or No. Sensitivity analyses were also conducted.
Results: Of the 141 unique patients randomly sampled from the 2,271 RRMS patient cohort for medical chart reviews for HDA, 123 (87.2%) patients were Certain; 0 Likely, 6 (4.3%) Possible, and 12 (8.5%) No HDA. The algorithm had PPV of 91.5% (95% CI: 85.2-95.3%) if including Certain, Likely, and Possible cases as positive for HDA vs No. The algorithm had PPV of 91.1% (95% CI: 84.7-95.1%) when excluding Possible or both Likely and Possible as positive HDA cases.
Conclusion: The algorithm had high PPVs for identifying HDA among RRMS patients. The developed HDA-RRMS claims-based algorithm is a promising method for future research for high disease activity RRMS patients in the healthcare claims databases.

P094

To Identify Relapses in Relapsing Remitting Multiple Sclerosis Patients Using United States Integrated Delivery Network Claims-Based Algorithm

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Background: Many patients have multiple sclerosis (MS) present with Relapsing Remitting Multiple Sclerosis (RRMS), a subgroup of MS characterised by exacerbations of disease and periods of remission. Claims-based algorithms to identify relapses have been validated previously but only with moderate performance.
Objectives: To develop and validate an operational claims-based algorithm for relapse identification among RRMS patients in an Integrated Delivery Network (IDN).
Methods: IDN data (2010-2014) were queried for study inclusion criteria: MS diagnosis, ≥18 years old, ≥1 year baseline history, and no other demyelinating diseases. The claims-based algorithm for identifying MS relapses was developed using criteria combined with an algorithm ascertaining RRMS patients and excluding progressive MS. The criteria included any of the following during 1-year follow-up after the index date: hospitalization or neurology visit with MS as primary diagnosis; MS symptoms/treatment; plasmapheresis; or high dose corticosteroid or adrenocorticotropic hormone (ACTH) use within 7 days after admission/visit. A random sample of medical chart reviews of relapses in the follow-up year as RRMS relapses by the algorithm was the "gold standard" for validation and positive predictive value (PPV) calculations. Relapse cases were assessed by a clinician as Certain, Likely, Possible and No. Sensitivity analyses were also conducted.
Results: Of the 2,271 RRMS patients identified using the claims-based algorithms, 11,362 unique relapse episodes among 2,029 patients were identified. Of the 89 unique patients randomly sampled from the 2,029 RRMS patient cohort for medical chart reviews for relapses, 69 (77.5%) relapses were Certain, 6 (6.7%) Likely, 10 (11.2%) Possible and 4 (4.5%) No relapse. The algorithm had PPV (95% CI) of 95.5% (88.9 - 98.8%) if including Certain, Likely, and Possible cases positive relapses vs No. The algorithm had PPV of 94.9% (87.3 - 98.4%) when excluding Possible, and PPV of 94.5% (86.3 - 98.3%) when excluding both Likely and Possible as positive relapses.
Conclusion: The algorithm using claims codes performed well for identifying relapses among RRMS patients. Clinical manifestations of relapses were often captured under codes of the US IDN data, and are rich sources for the algorithm development. The developed relapse claims-based algorithm is a promising method for future MS research to study relapse and disease activity using the healthcare claims databases.

P095

Investigating the Contribution of Susceptibility Factors on Early Clinical Expression of Multiple Sclerosis

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Background: There is evidence suggesting early clinical expression may predict long-term multiple sclerosis (MS) outcomes; however, little is known about factors influencing onset heterogeneity. Given temporality, we hypothesize MS risk factors contribute to early clinical expression.
Objectives: To investigate the relationship between MS risk factors and age of onset (AOO), number of impaired functional domains (NIFDs) at onset, and early relapse activity (ERA).
Methods: The study consisted of 1,524 persons with MS (PwMS) participating in the Accelerated Cure Project. Detailed medical history, socio-demographics, and behavioral risk factors were collected. Genotypic data were available for a subset (N=1,054). The outcomes were: **1.** AOO (age of 1st symptom); **2.** NIFDs (based on 31 symptoms at onset which were classified into FDs by two neurologists); and **3.** ERA (number of relapses in the 2yrs after onset). For each outcome, we conducted variable selection using least absolute shrinkage and selection operator (LASSO). Variables included gender, birth year, race, disease subtype (relapsing remitting (RR) or primary progressive (PP) at onset), smoking status within 5yrs of onset, diagnosis of obesity by onset, history of infectious mononucleosis, education level (as a proxy for socioeconomic status [SES]), and *HLA-DRB1*15:01*. The relationships between the LASSO selected variables and their respective outcomes were investigated using linear (AOO) and negative binomial (NIFDs & ERA) regressions with robust standard errors. The ERA analysis was restricted to RRMS.
Results: AOO: As expected *HLA-DRB1*15:01* was associated with earlier AOO, and PwPPMS were older at onset. Lower SES and being a smoker were significantly associated with earlier AOO. The obese were 8% older at onset ($p=3x10^{-4}$). Results did not vary by disease subtype, except among PwPPMS where males were 12% older than females.
NIFDs: Having RRMS, lower SES, and an older AOO increased the NIFDs. Obesity was associated with a 15% increase (p=0.04), while smoking was suggestive of an 8% increase (p=0.07) in NIFDs.
ERA: The obese had a 30% increase in ERA compared to those who were not (p<0.01). Younger AOO and lower SES were also associated with greater ERA. There was suggestive evidence for a 13% increase among smokers (p=0.06).
Conclusion: We conducted a comprehensive investigation of early clinical expression in PwMS. There were multiple significant associations; of note, obesity was associated with older AOO and increases in NIFDs and ERA.

P096

Patterns and Trends of Healthcare Utilization Among People with Multiple Sclerosis in the Age of Disease-Modifying Modifying Therapy

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Background: Multiple sclerosis (MS) has high socioeconomic burden. Cost of disease-modifying treatments (DMT) is a major contributor to the healthcare expenditure.
Objectives: To investigate healthcare utilization in people with MS in relation to DMT usage.
Methods: We performed retrospective analyses of aggregate administrative claim data from a large commercially insured

population. MS cohort entry is defined as having >=3 separate occurrences of the International Classification of Diseases (ICD)-9 code for MS. We assessed the trend of healthcare expenditure: (1) 6 months before to the12 months after MS cohort entry, (2) 6 to 36 months after DMT initiation. For all available DMTs, we compared the mean healthcare expenditure during the study period and mean treatment duration. For a given DMT, we calculated the incidence rates per 100 person years of the following: hospitalizations, outpatient doctor visits / neurology visits, magnetic resonance imaging (MRI) studies of brain and spinal cord, and steroid infusions. We then calculated the incidence rate ratios (IRR) of a given DMT with interferon-beta as reference and compared incidence rates among DMTs using Poisson Regression, adjusting for total healthcare expenditure at 6 months prior to MS cohort entry and Bonferroni correction.

Results: We assessed 55,520 people with MS from a population of >10 million people across the US between 2004 and 2013: mean age = 45 years, female to male ratio = 3.24:1, period prevalence = 525 per 100,000 (0.52%). Mean healthcare expenditure is significantly higher at 6 and 12 months after MS cohort entry than at the 6 months prior entry ($p<0.001$). Among DMTs following treatment initiation, patients receiving interferon-beta have the lowest mean healthcare expenditure at each time period, whereas those who receive natalizumab have the highest cost at 24 and 36 months after DMT initiation ($p<0.001$ for all comparisons). For incidence rates of healthcare utilizations outcomes across DMTs with interferon-beta as reference, patients receiving mitoxatrone had the highest incidence rate in doctor visits and steroid infusions ($p<0.001$ for all comparisons), whereas patients receiving natalizumab showed the highest incidence rate in neurology visits and MRIs of the brain ($p<0.01$ for all comparisons).

Conclusion: This large-scale examination of healthcare utilization in relation to MS treatments highlights the need for prospective comparative studies towards value-based medicine.

P097

The North American Registry for Care and Research in Multiple Sclerosis

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Background: Numerous databases exist internationally and have been ongoing for several years. Until recently, a database linking Multiple Sclerosis (MS) centers in North America (NA) has been absent. The North American Registry for Care and Research in MS (NARCRMS) was developed to allow stakeholders to freely access de-identified data and is the first database to link MS Centers in NA. This database captures clinical records and patient-reported and clinician-reported outcomes.

Objectives: To develop a clinician-based registry and database linking many MS centers across NA to acquire longitudinal outcomes of people with MS. NARCRMS aims to be a repository of clinical, genetic and radiological data, and biomaterials for developing biomarkers. NARCRMS plans to develop Research Interest Groups from within participating centers to promote collaborations to address specific unanswered questions related to MS.

Methods: NARCRMS is a special project of the Consortium of Multiple Sclerosis Centers (CMSC) and is overseen by the CMSC Board of Governors. The NARCRMS Steering Committee, comprised of key leaders in the field, sets policies for operations and is developing strategies for expanding collaborations with other registries. Inclusion criteria require disease onset of CIS or MS within the prior 10 years, age at enrollment of 18-50, inclusive, and EDSS < 6.5. This HIPAA-compliant registry uses the OpenClinica application with password policies, audit history, role based access control, and a user access log. NARCRMS currently receives funding from the CMSC and several industry supporters.

Results: Eight MS centers are currently NARCRMS sites. As of September 1, 2017, 83 people with CIS or MS are enrolled. 17 are males, 65 are female, and 1 is transgender male. Self-identified races represented are: African American (11), Caucasian (53), African American/Caucasian (2), native American (1), Pacific Islander (1), Asian (2) and no information (NI, 13). Eleven self-identify as Hispanic with the remainder non-Hispanic (53), unknown (2) or NI (11). Ages at diagnosis range from teenage (17 aged 15-19 years) to middle-age (6 aged 50 years or more). Birthplaces include 17 different US states, and 4 other countries (Jordan, Canada, Bahamas, Saudi Arabia).

Conclusion: NARCRMS is in operation and actively enrolling people with MS who meet inclusion criteria. We expect to eventually have 20 sites, chosen to geographically represent all regions of NA.

P098

Mortality and Comorbidity Distribution in MS By Race/ Ethnicity, Age, Sex: An Analysis of a US Population-Based Cohort

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Background: Multiple Sclerosis (MS) is a chronic demyelinating disease of the CNS where comorbidities increase the risk of morbidity and mortality in MS. Whether such comorbidities differ from the general population in US based cohorts is still lacking, in particular racial and ethnic-specific estimates that could be helpful in identifying groups at risk.

Objectives: To examine the distribution of multiple causes of death as a proxy of comorbidity among MS vs. non-MS related deaths in the US by sex, age, race/ethnicity (Non-Hispanic White, Black, Hispanic, Other).

Methods: We used the 2011-2015 Multiple Cause-of-Death Mortality Data of the National Center for Health Statistics for analysis. We identified deaths in the US with MS listed as underlying

or contributing cause of death and other US deaths excluding MS. We examined the distribution of all other causes of death as recorded in their death certificates by age, sex, and race/ethnicity using ICD-10 codes as proxies for comorbidities.
Results: A total of 28,861 MS related deaths were identified compared to 12,989,666 non-MS related deaths. The most common comorbidities in the MS cohort, were diseases of the circulatory (25.4%) and respiratory system (16.9%) compared to 31.5% and 11.6% respectively for the non-MS cohort. Neoplasms were more common in the non-MS cohort (13.5% vs. 7.1%). When examining comorbidities by race and ethnicity in those with MS, diseases of the respiratory system (16.9%) were reported more in non-Hispanic white males (17.8%). Diseases of the circulatory system were more frequently reported in MS blacks (28.5%) throughout all age ranges with cardiac arrest being the most recurrent sub classification. MS-related injury and poisoning (3%) at the time of death was more common in Hispanics than in any other race/ethnicity. In general, patients with MS who die young (age 20-29) were more likely to have diseases of the respiratory system (22.3%) compared to non-MS individuals of the same age group where external causes of morbidity (35.4%) such as environmental events and circumstances (e.g. falls, accidents, assaults) were more common.
Conclusion: This nationwide population-based study confirms prior observations that disorders of the cardiovascular and respiratory systems remain the most common underlying or contributing cause of death in MS and non-MS individuals. It also exposes that a significant difference in comorbidity distribution by age exists between MS specific ethnic groups.

P099

Epidemiology of Multiple Sclerosis in the Andean Region of Ecuador

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Background: Multiple sclerosis (MS), the etiology of which is still unknown, is a common autoimmune disease in Caucasian populations. Ecuador is a country with a low prevalence of MS. Ecuador is made up of 4 regions, one of them, the Andean Region at 3500 meters above sea level has the highest concentration of Amerindian population. To date, there are no epidemiological studies on MS in the Andean Region of Ecuador.
Objectives: To analyze the epidemiological behaviour of MS in the Andean Region of Ecuador.
Methods: We performed a descriptive study of patients with MS who visited reference centres in the Andean region for diagnosis and treatment of MS. These centres of reference are Carlos Andrade Marín Hospital, Eugenio Espejo Hospital y Militar Hospital in Quito and José Carrasco Hospital in Cuenca. Patients included in the study were those who met the McDonald 2010 diagnostic criteria for MS and who lived for at least one year in the Andean Region of Ecuador. Demographic data of the populations were obtained from the database of the National Institute of Statistics and Censuses (INEC).
Results: We identified a total of 157 MS patients. The mean age of the population was 41.85 years old (DS +/- 12.38). The female / male ratio was 2: 1. Ninety one percent of the cases were relapsing remitting MS. The provinces of Pichincha and Azuay, where the lowest percentage of indigenous population (5.1% and 2.3%, respectively) were found, had the highest diagnostic rates of MS per 100,000 inhabitants, 4.49 and 4.08, respectively. Provinces in which the indigenous population is larger such as Bolivar and Cotopaxi (21-24%) have the lowest number of MS cases, with rates of 0.75 and 0.64 per 100,000 inhabitants respectively. Seventy seven percent of MS patients come from cities in which the population is Caucasian and Mestizo (Quito and Cuenca). We did not find patients with MS who were born or lived in Amerindian communities. Twenty five percent of the patients are first, second and third-degree descendants of European migrants.
Conclusion: This is the first study of MS in the Andean region of Ecuador. The greatest number of cases of MS come from provinces and cities where the population is Mestizo and Caucasian. None of the patients came from Amerindian communities. This suggests that the presence of MS in Ecuador may be due to the introduction of MS susceptibility genes during European migrations. It is necessary to carry out genetic studies to confirm what was observed in the presented study.

P100

Preferences Regarding Research Study Attributes Among People with MS Belonging to Different Racial and Ethnic Groups

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Background: Racial and ethnic disparities in medical research participation have been documented for many diseases, and these disparities exist in multiple sclerosis (MS) research as well. The multi-stakeholder MS Minority Research Engagement Partnership Network was formed to better understand and address the problem of underrepresentation of minority participants in MS research. To support their objectives, network members identified a need for MS-specific information on factors that influence minority participation in research.

Objectives: The objectives of this study were to (1) survey people with MS about research perceptions and preferences, including preferences regarding specific study attributes; and (2) analyze preference data to identify the most preferred and disliked study attributes overall, as well as differences in responses among racial and ethnic groups.
Methods: Network members developed a Web-based survey with English and Spanish versions to gather data on research experience, concerns, and preferences among people with MS. Invitations to take the survey were distributed by network members and partner organizations.
Results: The survey was completed by 2611 participants with MS (2114 Caucasian, 216 African-American; 188 Hispanic; year of birth 1965 ± 12; 521 diagnosed > 20 years ago; 869 treated at an MS center; 1026 previously participated in MS research). Study attributes consistently preferred across all groups (no difference between the groups) included benefits of the study to people with MS; interest in the research topic; and provision of study results and of individual test results to the participant. Study attributes disliked similarly across all groups included the potential for harms to health; inconvenient study clinic location; lack of payment for out-of-pocket costs; and confusing study information. Study attributes in which preferences differed between racial and/or ethnic groups included being compensated for participation (p= 0.04); study information being sent via the Internet (p= 0.006); family support for participating in the study (p= 0.01); and benefits of the study to the respondent's racial group (p= <0.001).
Conclusion: Through an Internet survey we have gathered data about research attitudes and preferences among people with MS from different races and ethnicities. Our findings about preferences for research study attributes can be applied by investigators aiming to recruit a diverse study population.

P101
Clinical Features of Multiply Sclerosis in Adult Patients in High Mountain Area of Kyrgyz Republic
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Background: The high altitude is one of the factors for hypoxia development, which changes immunoreactivity under long-term conditions. 90% of the territory of the KR is above 1500 m above sea level, the climate is sharply continental
Objectives: The objective of this study is to determine the features of the course of MS, clinical polymorphism in the mountainous terrain conditions of the KR
Methods: The study was conducted at the base of the National Hospital of the Kyrgyz Republic on the basis of the database (47 persons, 27 of them are women) with a reliable diagnosis of MS by the criteria of C.M. Poser et al and McDonald et al., all patients lived in a mountainous area, the average altitude above the sea level was 1700± 200 m.
Results: The debut of RS was averagely 27.4 ±0.4 years (min-16, max-48). The remitting course of the disease was 69.8%, the second-progressive was 26%, the primary-progressive was 4.2%. The typical course was observed in 65.3% of patients, the atypical one was in 34.65%. The atypical course of MS manifested in the form of long-term remission (more than 30 years), malignant or vice versa benign course, the presence of concomitant vascular diseases of the brain, which clinically blurred the aspect of MS. When analyzing the altitude of living above the sea level, the following results were obtained: 6.8% of patients lived at an altitude less than 1000 m, 55.3% - at the level of 1500 m, 12.7% - 1800 m, 25.53% - more than 2500 m above sea level.
When analyzing the degree of dependence between disability of patients and level of the sea at which they permanently live, it was found that in patients living at an altitude of less than 1500 m at sea level, the course of MS has a steadily progressive type. Patients who permanently live at an altitude of more than 2500 m have atypical forms of disease course, with a tendency to long-term stabilization, a benign course, which is probably due to the presence of relative hypoxia in the highlands, which causes changes in the immunoreactivity of the organism.
Conclusion: In view of the heterogeneity of the etiology and pathogenesis, as well as the influence of exogenous factors affecting the course and development of MS, the study of the features of the course of MS in high altitude conditions remains highly topical. Distinctive features of MS in high-mountainous areas of the Kyrgyz Republic can be considered as slow progression of the disease, which is possibly associated with climatogeographic features.

P102
Overview of the North American Registry for Care and Research in MS (NARCRMS)
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Background: Multiple Sclerosis (MS) is a highly variable disorder with an unpredictable course in every patient. While much can be learned from the care of individual patients, factors that modify the course of MS can only be understood from population studies. Registries have been helpful in understanding other widely diverse disorders like cancer and stroke, but a MS registry in the United States is lacking.
Objectives: The North American Registry for Care and Research in MS (NARCRMS) was created to collect population-based information on MS. Patients from across North America will participate. Objectives include collecting information in an organized manner and generating knowledge about every aspect of MS.
Methods: NARCRMS is a project of the Consortium of Multiple Sclerosis Centers (CMSC). The project was conceived in 2013 and implemented by 2016. It is a collaborative partnership of industry, MS centers in universities and general practice and patients. Social & Scientific Systems, Inc. in Silver Spring, MD serves as the Operations Center, Information Technology (IT) Core and Data Management Center. NARCRMS will enroll 1,000 patients in a longitudinal follow up study across 20 centers over the next 5 years with each center contributing data on 50 patients. The database is

cloud-based and all stakeholders including patients will have access to the de-identified data through a reporting portal. The IT, Clinical, and Health Economics and Outcome Research (HEOR) cores are operational. Neuroimaging, Biomarker, Genetics, Experimental Therapeutics, Epidemiology & Biostatistics, Bioinformatics, Brain-Banking and Neuropathology Cores will be implemented. The Neuroimaging core is expected to go live by Q4 2017 and the Biomarker core in mid-2018. To date, 92 patients from nine sites have been enrolled. Enrollment of the first 100 patients is expected by the end of 2017, with one-year follow up data available for 21 patients. Comprehensive environmental, socioeconomic, mental and cognitive information will be collected to assess the impact of current therapies and estimate the cost of MS care on an on-going basis.

Results: From a concept in 2013, NARCRMS, the first national MS database in North America is now a reality.

Conclusion: A viable model to sustain a national MS database has been developed and implemented. NARCRMS in conjunction with other international databases is expected to provide valuable information on MS and help eradicate this disorder.

P103

Multiple Sclerosis at Onset and Its Relationship to Endocrine Comorbidities

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Background: Multiple Sclerosis (MS) is an autoimmune disorder of variable clinical presentation. Several subsets of endocrine diseases (ED) have an autoimmune component in their etiology. MS and some ED have similar symptom presentation including fatigue, weakness, sensory dysfunctions, and depression. This can cause masking of diagnosis of either disease by the other. Some MS disease modifying therapies (DMTs) affect ED and should not be prescribed to affected patients. Vitamin D (VitD) deficiency has been related to autoimmune conditions such as MS, diabetes mellitus (DM), and hypothyroidism. It has previously been reported that Hispanic MS (HMS) patients have abnormal levels of VitD.

Objectives: Establish the number of HMS patients that present at diagnosis a chronic ED

Methods: Cross-sectional study was performed on a sample of MS patients in Puerto Rico. The population data was obtained from data recorded at San Juan MS Center. Data was obtained at onset from patients that were diagnosed from 2014-2016 and it included disease comorbidity information. Descriptive statistics were used to analyze the dataset

Results: 320 MS patients diagnosed from 2014-2016 were analyzed for chronic ED previous to their MS diagnosis. 24.4% (78/320) of patients had an ED comorbidity. Specifically, 6.9% had DM, 13.4% had thyroid disease, 6.3% had hyperlipidemia, 2.5% had hypoglycemia, and 0.3% had osteoporosis. The majority of these patients were women, 76.3% (244/320), with only 23.8% (76/320) male patients. Important to note that one patient could have more than one comorbidity. The average age of the analyzed patients was 38. For females, the average age was also 38 and for males it was 37. The average age of patients diagnosed with ED and MS was 43. The average age for males with ED was 46 and for women it was 42.

Conclusion: MS and several chronic ED are autoimmune disorders. Here we show that there is a high prevalence of ED among HMS patients before MS diagnosis (24.4%). MS and ED share some symptom presentation and could lead to masking of the diagnosis. It is important to treat these conditions simultaneously because MS could progress faster for patients with uncontrolled ED. VitD abnormities are common in Hispanic populations and it has been associated with MS and ED. Further analysis is needed to establish a possible link between VitD, MS, and ED. It is critical to establish the relationship between them in order to provide better DMT prescription and efficacy.

P104

The Current Situation of the Multiple Sclerosis in the Department of Tlemcen

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Background: The current situation of the Multiple Sclerosis in the Department of Tlemcen (ALGERIA)

Objectives: Determining the epidemiology, clinical and developmental MS patients for three years, hospitalized at the Neurology Department of the University Hospital of Tlemcen.

Methods: Retro-prospective study of patients with MS confirmed by the 2010 McDonald criteria hospitalized at neurology department during three years, the period January 2013 to December 2015. All ages confused. All patients received a spinal MRI cerebrospinal complemented by a study of CSF.

Results: 93 patients documented during the study period:

-Department of Tlemcen 76 patients

-South West 07 patients

-Neighboring Departments (Ain Temouchent, SBA, Mostaganem, Saida, Relizane) 10patients

—74 ♀(79,57%) / 19 ♂(20,43%) => sex ratio = 3,89 (female predominance)

—Average age 32,6 years

—Familial cases 10%

—The low incidence could be explained :

—geographical location known to be low with average prevalence: 5-30 /100 000 H (Kurtzke ,1980),and 26.3 /100 000 H (Barka, 2013 Tlemcen CHU),

—Low density in neurologists, lack of diagnostic means, and nature of the population studied (oftenhospital cohort),

—Net female predominance in our cohort , sex ratio = 0.26 (Cohort Pr Barka - Tlemcen: 0.5, Cohort Dr.Benabadji - Tlemcen: 0.42, Agnes Fromont. 2012: 0,37(epidemiological Study of the multiple sclerosis in France)

Conclusion: The Multiple Sclerosis is a crippling disease affecting especially the young subject. The region of Tlemcen stays a zone of low incidence (stable incidence between 2 and 3/100.000 H/ year) and of average prevalence (26,3/100.000 H).

According to our study, we confirm the very significant North-South gradient. Each year, on average of 30 patients have MS in the department of Tlemcen.

P105

Mood Disorders in Multiple Sclerosis: About 100 Patients Collected in the Service of Neurology University Hospital of Tlemcen

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Background: Mood disorders in multiple sclerosis: About 100 patients collected in the service of Neurology University Hospital of Tlemcen (ALGERIA)
Objectives: To study the prevalence of mood disorders in type of major depression, dysthymia and hypomania in patients with multiple sclerosis.
Methods: Cross-sectional study on 100 patients with confirmed multiple sclerosis (MRI Clinic + cerebro-spinal + / - PL). The evaluation of symptoms is made using a questionnaire: the MINI DSMIV. The MINI DSMIV is a structured interview exploring the major psychiatric disorders of Axis I DSM IV. The expected responses are binary (yes or no). The collection and analysis of data is done on SPSS. Statistical tests used: For the comparison of means: The test of x^2 and for the comparison of percentages: Does the student.
Results:
-100 Patients included in the study with a mean age of 36.6 ± 10, 78, 80% are women and 20% men.
- 26% of patients have a family member with MS (aunt, uncle, niece or nephew).
-86% Are put under interferon type of treatment (Rebif, Avonex and Betaferon).
-The Pattern of the first consultation varies, motor disorders (40%), visual disturbances (28%), sensory disturbances (21%) and balance disorders (11%).
-Seniority Disease is on average 7.38 ± 6 years, 52.
-The Mood disorders were present in 85% of patients were as follows: - The dysthymia (63.8%)
- A hypomania (20.2%)
- A major depressive episode (16.3%)
- The features are:
-81% Are women and whose ¾ want one doctor.
-85% Are under interferons whose distribution by type of treatment is: Avonex (35.29%), Betaferon (29, 41%) and Rebif (35, 29%)
-15% Refused any medication.
-the beginning of treatment was 4.3 ± 3.73 [1-16]
- 79,01% of patients have disease evolution under 10 years old with a leading two chi is 0.26.
-Number of hospitalization 2.32 ± 2.22 [0-10] and an odds ratio of 1, 417 [0.369 -5.432]
Conclusion: Our results emphasize the importance of mood disorders in MS population and their correlation with interferons to detect as soon as possible. Because of their frequency and impact on quality of life, it seems necessary to pay special attention to these disorders.

Experimental Models

P106 Hindlimb Clasping-Onset EAE Models Secondary-Progressive Multiple Sclerosis

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Background: Experimental autoimmune encephalomyelitis (EAE) is a common animal model of multiple sclerosis (MS) that has been instrumental in understanding the events that can lead to MS relapses. Typical EAE has been a less effective model of progressive MS. Though axon injury does occur, it is very rapid and acute, making it difficult to intervene with neuroprotective therapies. In the course of examining the role of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) on EAE development, we made the serendipitous observation that female 2D2$^+$ (myelin oligodendrocyte glycoprotein T cell receptor transgenic) mice on the PPARα heterozygote (Het) background developed an atypical presentation of EAE that was characterized by hindlimb clasping.
Objectives: To characterize the immunological and pathological basis of this neurological presentation in Het 2D2$^+$ mice.
Methods: Mice were scored for the severity of clasping signs until 9 months of age and performance on rotarod and hanging grip tasks was measured at 3, 6, and 9 months of age. Histopathological analysis of inflammation, demyelination, and neuron loss was conducted. High-resolution 3D MR images were acquired in middle-aged (8 month old) mice and used to measure spinal cord volume and structural alterations in the brain. Immune studies were performed to understand the immunological basis of the hindlimb clasping phenotype.
Results: We observed that female Het 2D2$^+$ mice exhibited a waxing and waning of hindlimb clasping signs with a concurrent gradual increase in neurological disability with age. This neurological progression correlated with a worsening of performance on rotarod and hanging grip tasks. Histological analysis revealed that clasping onset associated with the presence of mild inflammation in the dorsal spinal cord and adjacent nerve roots. The brain was largely spared from inflammation with the exception of the optic nerves that were consistently infiltrated by T cells. By middle age, CNS inflammation became more sporadic, but compared to Het mice that did not carry the 2D2 transgene, Het 2D2$^+$ mice exhibited a loss of neurons and atrophy of the spinal cord and brain regions that were contiguous with affected axon tracts. Immunological studies revealed that the higher penetrance of the clasping phenotype in Het compared to WT 2D2$^+$ mice associated with a T helper 17 bias in the immune response.
Conclusion: Clasping-onset EAE with age models the neuron loss associated with progressive MS.

P107

Experimental Autoimmune Encephalomyelitis (EAE) Exacerbates Visual System Pathology Relative to Cuprizone (CPZ) Induced Demyelination

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Background: Visual pathology, a prevalent feature of multiple sclerosis (MS), is characterized by impaired visual function, inflammation, demyelination, and axonal damage. Although minimally-invasive visual assessments are increasingly used clinically to assess disease course in MS patients, longitudinal studies investigating visual pathology in mouse models are lacking. The lymphocyte-mediated chronic experimental autoimmune encephalomyelitis (EAE) model and the non-lymphocyte mediated cuprizone (CPZ) demyelination model may have differential effects on visual pathway pathology due to the enhanced inflammatory environment characteristic of EAE. Because MS is an inflammatory, demyelinating and neurodegenerative disease, understanding differences in visual pathology in these two models is vital for developing pharmacological targets and testing potential pharmaceuticals.
Objectives: To assess longitudinal visual pathway dysfunction in the lymphocyte mediated EAE and non-lymphocyte mediated CPZ demyelination mouse models of MS.
Methods: Minimally invasive longitudinal optical coherence tomography (OCT), electroretinograms (ERG), and visually evoked potentials (VEP) data were collected on PLP-eGFP and C57BL/6 mice fed 0.2% CPZ or induced with EAE at early, peak, and late disease stages. Immunohistochemistry was performed for assessment of visual pathway structures.
Results: OCT indicated decreased thickness of whole retina and retinal nerve fiber layer (RNFL) of EAE mice at late timepoints. ERG and VEP amplitudes and latencies were impaired in EAE mice at early and peak disease timepoints, but improved at late disease stages. Immunohistochemical analysis showed significant demyelination in visual pathway areas of EAE mice, coupled with axonal damage and inflammation in other visual pathway areas. Conversely, CPZ demyelination induced no change in RNFL thickness but increased retinal thickness at all timepoints. VEP amplitudes and latencies were also impaired in CPZ mice but to a lesser extent than in EAE.
Conclusion: Longitudinal assessment of retinal structures and visual pathway function reveal significantly increased visual pathway pathology and severity in the MOG-EAE mouse model compared to the CPZ demyelination model. This indicates that inflammatory lymphocytes, a key aspect of EAE pathology absent from CPZ pathology, may exacerbate demyelination-induced changes to visual pathway conduction.

Gender Differences, Hormones and Sex Chromosomes

P108 Disease Type in a Spontaneous Transgenic Mouse Model for Multiple Sclerosis Is Dictated By the Gender of the Immune Cells

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Background: The majority of MS patients present with a relapsing-remitting form of the disease (RRMS) gradually evolving into a secondary progressive phase (SPMS). In primary progressive MS (PPMS) there is a steady worsening of neurological function without intermittent recovery. Women mostly develop RRMS and are affected more often (2-3:1) than men, who mostly suffer from PPMS.
The transgenic TCR1640 mice express a T cell receptor specific for $MOG_{92\text{-}106,}$ and spontaneously develop disease. Females have a higher incidence and develop RR followed by SP disease, while males develop PP disease, perfectly reflecting the gender differences and disease course diversity seen in human MS.
Objectives: To investigate if type of disease is gender intrinsic and driven by immune cells.
Methods: Immune cells isolated from the spleen and lymh node of presymptomatic male and female TCR1640 mice were injected intravenously into WT SJL/J mice (male into male (n=12), male into female (n=23), female into male (n=15), female into female (n=19)). The mice were scored daily for 60 days and were sacrificed at specific time point (relapse, remission, chronic) to isolate central nervous system (CNS), spleen and lymph nodes to perform immunohistochemistry and flow cytometry.
Results: Injection of female transgenic immune cells into male or female WT SJL/J mice resulted in a relapsing-remitting disease course followed by a stable secondary progressive phase while injection of male transgenic immune cells into male or female WT SJL/J mice led to a stable progressive disease course without remission. Preliminary results show that in both recipients that received male cells and recipients that received female cells a disruption in their ZO-1 and an upregulation of VCAM-1 and laminin was present. In addition, perivascular spaces were filled with activated macrophages, T cells and fibrinogen. However, microglia activation remained only high in recipients that received male cells while recipients that received female cells have a higher infiltration of Foxp3 cells and a lower amount of fibrinogen during remission although the absolute number of $IL17^{+}IFNy^{-}$ cells transgenic cells that infiltrated the CNS were comparable.
Conclusion: Using adoptive transfer we showed that the gender of injected transgenic immune cells can dictate the disease type in the recipient animal; that is female transgenic cells dictate a RR disease while male transgenic cells prompt a PP disease.

P109

Human Chorionic Gonadotrophin As a Potencial Immune Modulator in Patients with Multiple Sclerosis

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Background: Multiple sclerosis (MS) is 2-3 times more common in women than men. It is well known that pregnancy has a strong influence on MS disease activity and a reduced relapse frequency (70%) is seen during pregnancy. After delivery, MS symptoms often worsen, with frequent relapses in the postpartum period and highest relapse frequency within 3 months after

delivery. Hormonal factors are thus assumed to be involved in regulating the course of the disease. Human chorionic gonadotropin (hCG) is synthetized by the placenta during pregnancy and the presence of its receptor has been described in immune cells, such as B and T cells.

Objectives: To evaluate the potential capacity of hCG to regulate activation and cytokine production by immune cells in a context of MS.

Methods: We recruited women suffering MS from 20-40 years old to obtain whole blood samples. PBMC were isolated and then cultivated with hCG (third trimester levels), either urinary (u, 100 IU/ml) or recombinant (r, 5 ug/ml) or without hCG (control) for 24 h. PMA, Ionomycin and Brefeldin A were added, in some wells, for the last 5h of culture. Flow cytometry was used for the phenotypical characterization of the lymphocytes subset: CD19, CD80, CD86 (B cells), CD4 and Foxp3 (T cells) and to evaluate intracellular cytokines levels: TNF-α and IL-10.

Results: We observed that treatment with hCGu significantly reduced the relative numbers of $CD19^+CD86^+$ B cells as compared to control group. No changes were observed concerning $CD80^+$ expressing B-lymphocytes. Interestingly, addition of either hCGu or hCGr induced a significant increase in the total number of $CD4^+Foxp3^+IL\text{-}10^+$ regulatory T cells upon stimulation, when compared to controls. Similarly, IL-10 production by $CD19^+$ B cells stimulated with either type of hCG, showed a slight no significant increase. On the other hand, treatment with either hCGu or hCGr, also induced a significant reduction in the total numbers of $CD19^+TNF\text{-}\alpha^+$ B cells as well as $CD4^+TNF\text{-}\alpha^+$ cells, as compared to controls (data were analyzed by One-way ANOVA).

Conclusion: Overall, we demonstrated here that treatment with hCG *in vitro,* lowers the expression of the costimulatory molecule CD86 in B cells, increases the production of IL-10 by $CD4^+Foxp3^+$ regulatory T cells and decreases the production of TNF-α, in both $CD4^+$ and $CD19^+$ B cells. These results open new avenues to explore the use of hCG as a potential treatment in MS patients, especially for those that do not respond to conventional therapies.

Genetics and Epigenetics

P110

Epigenomic Analysis of T Cells in Multiple Sclerosis

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Background: Multiple sclerosis (MS) is a genetically mediated autoimmune disease in which activated auto-reactive effector CD4+ T cells (Teff) cause CNS damage by targeting myelin. Regulatory T cells (Treg) are dysfunctional in MS, exhibiting a pro-inflammatory phenotype. Genetic variants that contribute to MS risk may interact with environmental risk factors such as salt exposure through epigenetic mechanisms in T cells.

Objectives: This study will characterize the genetic and epigenetic alterations that occur in Treg and Teff cells in MS. This data will be used to identify transcriptional regulators that underlie MS pathogenesis.

Methods: Mononuclear cells were isolated from the peripheral blood of MS patients (n=22 to date) and healthy donors (n=16 to date). Treg and Teff cells were isolated with fluorescence-activated cell sorting and subjected to RNA-seq and ATAC-seq assays in parallel. RNA-seq reads were aligned to hg38 with STAR and quantitated to the gene level with RSEM. Raw counts were transformed with voom, and differentially expressed genes were identified with limma.

ATAC-seq provides a genomewide measure of chromatin accessibility. To identify peaks of chromatin accessibility, reads were aligned with Bowtie2. Peaks were called on pooled samples with MACS2 and quantitated with featureCount. Limma-voom was used to identify differentially accessible peaks between MS patients and controls.

Results: To date, we have identified 3 genes (BLK, BCL3, PRDM1) that are differentially expressed in MS Tregs at FDR < 0.05; BLK, the most significant of these, exhibits 16-fold overexpression ($P_{adj} = 0.0070$). A total of 61 genes were found to be differentially expressed in Teffs. Gene set enrichnment analysis and integrated pathway analysis highlighted the importance of several pathways, including IL6 signalling and microRNA processing.

ATAC-seq analysis revealed multiple differentially accessible regions of chromatin accessibility. Linear regression of these peaks against gene expression revealed several candidates for transcriptional regulation.

Conclusion: Using RNA-seq, we identify significant transcriptional alterations in both Treg and Teff cells between MS patients and healthy controls. ATAC-seq analysis of the same cells highlighted chromatin regions that are likely to exert a regulatory influence on expression of these genes. Current studies aim to identify the particular transcription factors responsible for the observed transcriptional changes.

P111

Network-Based Evaluation of Genetic Predictors of Changes in Low Contrast Letter Acuity

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Background: While genome-wide association studies (GWAS) have successfully identified over 200 variants associated with multiple sclerosis (MS) risk, there are no consistently-identified variants that predict MS course. Low-contrast letter acuity (LCLA) correlates with magnetic resonance imaging outcomes and clinical disability and may serve as a sensitive, easily obtainable outcome to track the course of MS.

Objectives: To assess genetic predictors of visual acuity loss in people with MS.

Methods: We conducted a GWAS of longitudinal LCLA changes in 836 people with MS pooled from two well-characterized cohorts – participants from the CombiRx Trial (n=582; mean

follow-up 3.1 years) and from the Johns Hopkins MS Center (n=254; mean follow-up 3.96 years) who were genotyped on genome-wide arrays. We assessed the association between individual variants and a sustained 5-letter loss in LCLA, adjusting for age, MS duration, and optic neuritis history using Cox proportional hazards models. Analyses were conducted separately within cohorts, and summary effect measures were calculated using meta-analysis methods pooling results from all 836 individuals. Using results from individual variant analyses and excluding variants showing statistical heterogeneity between the cohorts, we calculated a gene-based p-value using the VEGAS algorithm and mapped the corresponding gene p-values to an existing protein-protein interaction network. We extracted novel, potentially biologically relevant subnetworks using a bioinformatics algorithm and tested for enrichment in those subnetworks.

Results: While no variant achieved genome-wide significance in individual analyses, network analyses extracted several subnetworks with significant biological enrichment. We identified a complement pathway network consisting of 12 genes (P for enrichment= 2.2 $x10^{-11}$), with *CR1* (P=0.008) being the strongest associated gene and rs61822967 (P=2. $x10^{-4}$) being the strongest associated variant within *CR1*. We also identified a WNT-signaling network (14 genes; P for enrichment=$6.38x10^{-18}$) with *WNT1* being the strongest associated gene (P for enrichment=0.001) and rs833842 being the strongest associated variant (P=$3.3x10^{-4}$) in *WNT1*.

Conclusion: These preliminary results suggest a novel role of complement and WNT-signaling that may underlie visual outcomes in people with MS. Complement is relevant to synapse formation and retinal degeneration in other diseases and thus is of particular interest.

P112

No Significant Genetic or Transcriptomic Predictors of Severe and Prolonged Lymphopenia in MS Cases Treated with Dimethyl Fumarate

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Background: It is not known whether clinically relevant genetic risk factors exist for developing severe and prolonged lymphopenia (SPL) in MS patients treated with delayed-release dimethyl fumarate (DMF).

Objectives: To perform exploratory genomic analysis of SPL in MS patients treated with DMF from the pivotal phase 3 DEFINE/CONFIRM trials.

Methods: We genotyped DNA from 1,258 patients (HumanOmnichip2.5-V1.2) and analyzed whole blood RNA samples from 1,133 patients collected at baseline (Affymetrix HGUplus 2.0 Array). Patients' absolute lymphocyte count (ALC) were categorized into: SPL, <500 cells/μl for ≥6 months; moderate and prolonged lymphopenia (MPL), <800 cells/μl for ≥6 months, excluding SPL; mildly reduced lymphocytes, < LLN at any point, excluding SPL+MPL; and no lymphopenia, ≥910 cells/μl (lower limit of normal range (LLN)). A genome-wide association study (GWAS) was performed on ~1 million DNA variants using logistic regression (adjusted for ancestry, baseline ALC), excluding the "mildly reduced lymphocytes" phenotype. The GWAS had 80% power to detect odds ratios of 4.0 and 1.8 in the SPL and SPL+MPL analyses, respectively. Gene expression profile analyses were adjusted for ancestry, baseline ALC, age, gender and disease duration.

Results: None of the variants tested reached genome-wide significance (*P*<5e-8). Analysis of the major histocompatibility complex (MHC) did not identify strong associations. There was no overlap between our GWAS peaks and GWAS loci associated with white blood cell counts in published studies. Gene expression profiles were not associated with lymphopenia (FDR<5%). A classification model including gene expression features was not more predictive of lymphopenia status than clinical covariates.

Conclusion: No common variants of large effect that would be clinically useful in predicting SPL were identified. Gene expression profiles were not associated with lymphopenia. This GWAS of DNA variants and RNA expression profiles did not provide additional insight into the mechanism of action of SPL or relevant genetic risk factors in DMF-treated patients. Monitoring ALC as per label recommendations remains the most effective way to identify patients at risk for developing SPL.

P113

Vitamin D Receptor Gene Polymorphism in Patients with Multiple Sclerosis

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Background: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. There are studies which show that low 25(OH)D levels are associated with the increasing MS risk and increasing disease severity. The action of Vitamin D is mediated by the nuclear vitamin D receptor (VDR).

Objectives: In this study, the role of VDR gene polymorphisms (Taq I, Bsm I, Apa I) and vitamin D levels in the etiopathogenesis of the disease and their relationship with clinical, and demographic characteristics of patients diagnosed with MS in the Black Sea region were investigated.

Methods: 124 cases who were diagnosed with MS in accordance with the 2010 Mc Donald criteria in the Multiple Sclerosis outpatient clinic of the Neurology Department of Medical school of Ondokuz Mayıs University in Turkey were evaluated 87 cases in whom gene regions were determined by polymerase chain reaction (PCR) and DNA isolation were included in the study. The Control group consisted of 100 healthy volunteers with the demographics similar to patients.

Results: Demographic data of patients and seasonal distribution of VDR polymorphism testing are shown in the table. Genotype and allele frequency of APA 1 Bsm I and Taq 1 polymorphisms of vitamin D receptor gene of the patient and control groups are shown in Table 2. No significant difference was found in patient and control groups for Apa 1 and Taq 1 mutation. (P=0,208, P=0,113). According to the Vitamin D gene polymorphism which was tested separately for the genes Apa 1, Bsm 1 and Taq 1 in multiple sclerosis patients no significant relation was found between disease onset age, gender, clinical subtype, EDSS, clinical onset finding, number of attacks, immunomodulator treatment response. Vitamin D level was low in 77 patients (87.5%) and

high in 10 patients (12.5%). No difference was found between groups with low and normal vitamin D levels for Apa 1, Bsm and Taq 1 receptor polymorhism (P:0,892, 0,645, 0,899).
Conclusion: No relationship was found between MS development with VDR polymorphism and clinical course of the disease. Studies that investigate the possible effect of VDR polymorphism and vitamin D on MS pathogenesis and clinical course of the disease in higher number of people and in different societies are needed.

P114

Tumor Necrosis Factor Alpha and Beta Receptor Gene Polymorphism in Multiple Sclerosis Patients

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Background: Multiplex sclerosis (MS) is an inflammatory, autoimmune, demyelinating disease of the central nervous system. Tumor necrosis factor (TNF) α and β has an important role in the pathogenesis of disease.
Objectives: In this study, we investigated the role of TNF-α and TNF-β receptor gene polymorphism in the etiopathogenesis of the disease and the clinical and demographic characteristics of patients in MS patients.
Methods: 206 cases with definite MS diagnosed according to the 2010 McDonald criteria followed in the Multiply Sclerosis polyclinic of Neurology Department of Medical Faculty of Ondokuz Mayıs University. The control group consisted of 142 healthy volunteers with similar demographic characteristics to the study subjects.
Genotyping of TNF-α (-308 G/A) Polymorphism
The alleles of the G/A polymorphism at position -308 in the promoter region of the TNF- α gene were distinguished by cutting with the NcoI restriction enzyme. The polymorphic site was amplified using forward (5'- GAG GCA ATA GGT TTT GAG GGC CAT-3') and reverse primers (3'- GGG ACA CAC AAG CAT CAA G-3').
Genotyping of TNF-β (+252 A/G) Polymorphism
The alleles of the G/A polymorphism at position -308 in the promoter region of the TNF- β gene were distinguished by cutting with the NcoI restriction enzyme. The polymorphic site was amplified using forward (5'- CCGTGCTTCGTGGTTTG GACTA-3') and reverse primers (3'- AGAGGGGTGGATG CTTGGGTTC-3').
Results: There was no difference in TNF-α and TNF-β receptor gene polymorphism between patient and control groups (P=0.063, P=0.120). There was no significant relationship for TNF-α and TNF-β receptor gene polymorphism in MS patients between disease age at onset, sex, clinical subtype, EDSS, clinical onset, number of attacks, immunomodulator treatment response. Detailed analysis is given in table 1.
Conclusion: TNF-α and TNF-β receptor gene polymorphisms were not associated with MS development and clinical course of disease in MS patients. There is a need for investigations into the possible effects of TNF-α and TNF-β receptor gene polymorphisms on MS pathogenesis and disease clinical course.

Imaging

P115

Longitudinal MRI History of Lesion Repair Based on the Presence or Absence of a 7T Paramagnetic Rim

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Background: Paramagnetic rims on 7T susceptibility-based MRI pathologically identify MS lesions with smoldering inflammation at the lesion edge, remyelination failure, and often ongoing axonal degeneration. However, the long-term effects of rim persistence at the lesion level in vivo (e.g., slow expansion) are still uncertain.
Objectives: To assess whether the presence of rims affects the long-term longitudinal history of MS lesions.
Methods: Twenty-four MS patients (12 relapsing/12 progressive) with archival 3T yearly scans for ≥10 years underwent a 7T MRI acquisition. Twenty-seven discrete supratentorial chronic lesions with rim and 27 without rim were selected for a retrospective yearly evaluation of lesion volume (mean follow-up duration 13.0±5.4 years). Based on the compound annual growth rate of adjusted volume, lesions were classified as shrinking (≤-1%), steady (between -1 and 1%) or expanding (≥1%) over time. For each lesion, T1 values at 7T were determined.
Results: Chronic lesions with and without rim had a compound annual volume growth rate of 2.5% (expansion) and -3.6% (shrinkage), respectively ($p<0.0001$). At last MRI time point, lesions with rim were bigger than those without ($p<0.0001$), but not at baseline ($p=0.08$). Of 54 analyzed lesions, 30 lesions were shrinking (7 with rim/23 without), 9 were steady (8 with rim/1 without) and 15 were expanding over time (12 with rim/3 without). Lesions with rim were more frequently steady or expanding in comparison to lesions without rim (Fisher's exact test $p<0.0001$). Eight of 12 expanding lesions with rim showed re-enhancement of the lesion edge (6 lesions) or subsumed adjacent WM abnormalities (2 lesions) during follow up. On 7T T1-map, lesions with rim had higher T1 values (suggesting more tissue destruction) than lesions without rim ($p=0.0003$).
Conclusion: Persistent inflammation at the lesion edge is not only a major barrier for remyelination, but can exert ongoing damage to the surrounding tissue.

P116

Effects of Disease-Modifying Therapy on Brain Compartment Atrophy Rates - a 5-Year Study

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Background: The armamentarium of multiple sclerosis (MS) disease-modifying therapies (DMTs) has dramatically expanded over the past decade and now includes DMTs with high efficacy at reducing inflammatory disease activity. The substrate of long-term disability in MS is neuro-axonal loss, which is not captured by conventional MRI measures. Whole brain atrophy may reflect global neuro-axonal loss in MS and has been utilized as an outcome measure in clinical trials, but data are typically limited to short-term follow-up. Furthermore, measures of gray matter (GM) integrity, such as thalamic and cortical GM volumes, are reduced early in the disease course and exhibit stronger associations with clinical disability than whole brain and white matter (WM) measures. However, data regarding long-term follow-up and effects of DMTs on rates of GM measure atrophy is limited.
Objectives: To determine the differential effects of DMTs on rates of brain compartment atrophy over 5 years.
Methods: A cohort of MS patients followed with annual 3T brain MRI was evaluated. A validated pipeline was used to obtain thalamic, cortical GM, cerebral WM, and cerebral volume fractions. DMTs were categorized as high (DMT-H: natalizumab, rituximab, fingolimod, and dimethyl fumarate) and low-potency (DMT-L: interferon-beta and glatiramer acetate). Patients were included if they had been on a DMT for ≥6 months and had imaging follow-up of ≥1 year while in the same DMT class. Data were censored at discontinuation or switch of DMT class. Analyses were performed with mixed-effects linear regression and adjusted for demographics and clinical characteristics.
Results: Sixty subjects were identified that fulfilled the study criteria (23 DMT-H, 37 DMT-L). Mean follow-up was 5.0 years. The majority of DMT-H subjects were on natalizumab (83%). The DMT-H group had greater disability at baseline (median EDSS 3.5 vs. 2.0; p=0.02), but otherwise the groups did not differ in age, sex, race, and disease subtype. DMT-H subjects exhibited slower annual rates of thalamic (-0.24% vs -0.66%; p=0.006), cortical GM (-0.35% vs -0.53%; p=0.02), and whole brain atrophy (-0.27% vs -0.46%; p=0.01) than DMT-L subjects. Cerebral WM rates of atrophy did not differ between groups.
Conclusion: DMT-H treatment is associated with slower rates of GM atrophy, especially of the thalamus. Thalamic volume is a promising imaging biomarker of neurodegeneration in MS and future studies should further evaluate its clinical significance and potential for use as a trial outcome measure.

P117

Assessing Fingolimod Axonal Protection Efficacy in Mouse Optic Neuritis Using Diffusion Basis Spectrum Imaging

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Background: Optic neuritis (ON), frequently the first clinical manifestation of multiple sclerosis (MS), can lead to impaired vision in MS patients. The severity of axonal loss is believed to play a critical role in the degree of subsequent visual impairment. Previous studies demonstrated that diffusion basis spectrum imaging (DBSI) noninvasively quantified optic nerve axonal loss at onset of ON in mice with experimental autoimmune encephalomyelitis (EAE). Herein, we employed DBSI to noninvasively assess fingolimod therapeutic efficacy on axonal preservation.
Objectives: To assess whether fingolimod treatment protects axons from irreversible damage.
Methods: MOG_{35-55} EAE was induced in 18 female C57BL/6 mice. Daily visual acuity (VA) with Virtual Optometry System and clinical scores were assessed. To approximate the situation in the case of human ON, treatment did not commence until clinical signs were seen. When VA ≤ 0.25 cycle/degree, defined as the clinical onset of ON in EAE mice, fingolimod (1mg/kg) or saline was administrated by oral gavage for ten weeks. DBSI was performed to assess optic nerve axonal integrity prior to immunization (baseline), and at two, six, and ten weeks after treatment (four time points in total). Immediately after the last in vivo DBSI scan, mice were perfusion-fixed for histology.
Results: The VA of fingolimod-treated mice was better than saline-treated mice but worse than normal mice. Based on DBSI parameters, mice with ON treated with fingolimod exhibited reduced inflammation (less hindered and restricted isotropic diffusion fraction) and less axonal injury and loss (higher DBSI-determined fractional anisotropy, higher fiber fraction in optic nerves), compared to mice receiving placebo. Axonal pathologies detected by DBSI in vivo were validated by the corresponding immunohistochemistry markers.
Conclusion: This 'proof-of-concept' study demonstrates that it is feasible to use DBSI as a noninvasive imaging biomarker to assess the effect of a drug (in this case fingolimod) on underlying pathologies. DBSI could potentially be used as an outcome measure in clinical studies to monitor disease progression and treatment responses.

P118

Deep Learning-Based Synthesis for Normalization of FLAIR Imaging

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Background: FLuid-Attenuated Inversion Recovery (FLAIR) MRI is often used to quantify the difference in T2-weighted lesion load over the course of a multiple sclerosis (MS) patient's history, and can influence treatment decisions. As MRI technology has improved, higher quality 3D-FLAIR imaging has become possible for clinical use, leading to increased resolution and conspicuity of T2-hyperintense lesions. However, this creates a problem in longitudinal settings, where existing 2D-FLAIR scans are not comparable to the newer 3D-FLAIR scans, especially when using automated segmentation algorithms.
Objectives: To determine the feasibility of deep learning-based image synthesis as a normalization tool for FLAIR imaging.

Methods: 10 MS patients underwent two standard research MRI protocols on two different scanners within 1 month of each other. Two U-Net models were developed using leave-one-out training from the acquired T1-, PD-, T2-weighted and FLAIR images of each session and trained against an acquired 3D-FLAIR. Synthesis was incorporated into a MS-specific pipeline using Bridging Radiology And Investigative Neurology using Modular, Automated Pypelines (BRAINMAP). The T1-weighted scan from the first protocol was used for both segmentations. In addition, 9 scans where the FLAIR images were motion-corrupted underwent synthesis and segmentation results were compared to the next follow-up. The Dice coefficient (DSC) was used to assess overlap of lesion masks and the Wilcoxon Signed Rank Test was used to assess differences in volumes.
Results: Lesion volumes were significantly different (p=0.007) when using acquired FLAIR images; however, the difference was no longer significant with synthetic images (p=0.575). The median and interquartile range DSC between lesion masks increased from 0.42 (0.24, 0.50) to 0.70 (0.61, 0.76) with synthetic images and percent difference in volume decreased from 44.8% (36.0%, 62.0%) to 7.7% (4.3%, 26.8%). Lesion volume difference with follow-up was statistically significant comparing motion-corrupted FLAIRs to synthetic images (p=0.02).
Conclusion: By using synthetic 3D-FLAIR images, lesion load measurements between two scans with different or corrupted FLAIR acquisitions were normalized and reached acceptable variability that is consistent with two manual raters. With further validation, this method can be used to normalize or generate any structural contrast where differences in MRI acquisition parameters or image artifacts would normally preclude meaningful longitudinal analyses.

P119

Obesity and Increase of Demyelinating Lesions in Magnetic Resonance Imaging in Multiple Sclerosis Apilot Study in a Hispanic Cohort

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Background: Obesity is highly common in Hispanic population due to genetic and type of diet. In industrialized countries, obesity has been described as risk factor to develop multiple sclerosis (MS).
Objectives: Quantify demyelinating lesions on Magnetic Resonance Imaging in patients with definite MS and analyze its relation to the body mass index (BMI)
Methods: Our cohort includes 126 patients with definite MS hospital admitted during the last 15 years. The number of lesion were quantified and a descriptive analysis of the lesions in different brain locations were analyzed according to their BMI (defined by World Health Organization). An ANOVA test was performed, to analyze number and localization of demyelinating lesions and T-test for independent samples.
Results: In our cohort predominate female patients (69.6%), median age 35 years (15 – 64) and mean weight 68 kilograms (44 – 150), and height 1.64 meters (1.38 – 1.92), The median BMI was 24.1 (16.51 – 52.39) and were allocated according to BMI. MS patients were 18.4% pre-obesity, 16.8% obesity class I and 3.2% obesity class II and III. Median number of demyelinating lesions was 20 (0 - 327) most of them were periventricular 6 (0-62) and juxtacortical 13 (0 – 278). When comparing the number of total lesions and BMI we found statistical significant differences between pre-obesity and obesity class II (p= 0.001) and higher number of lesions in obesity class II compared to class I (p=0.011). The number of periventricular lesions were higher in obesity class II, (p= 0.006) in Obesity class I and class II.
Conclusion: In our Hispanic cohort of MS patients, obesity class II showed a higher number of demyelinating lesions on MRI. In our population, a further analysis relating BMI, number of lesion, response to treatment and prognosis is needed.

P120

Mimosa: An Automated Method for Inter-Modal Segmentation of Brain T2 Hyperintensities and T1 Black Holes in Multiple Sclerosis

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Background: Magnetic resonance imaging (MRI) is crucial for *in vivo*detection and characterization of white matter lesions (WML) in multiple sclerosis. The most widely established MRI outcome measure is T2-weighted lesion (T2L) volume. Unfortunately, T2L volume is non-specific for the level of tissue destruction and shows a weak relationship to clinical status. Consequently, some researchers have focused on T1-weighted hypointense lesion (T1L) ("black holes") volume quantification to provide more specificity for axonal loss and a closer link to neurologic disability.
Objectives: This study aimed to adapt and assess the performance of an automatic T2L segmentation algorithm for segmenting T1L. First, to ensure the method performed well on the images of interest, we compared the automated T2L segmentation with gold standard manual T2L segmentations. We then adapted the pipeline and compared the automated T1L segmentation with gold standard manual T1L segmentations.
Methods: Brain high-resolution 3D T1, T2, and FLAIR sequences were acquired from 40 MS subjects on a Siemens 3T Skyra unit at the Brigham and Women's Hospital (Boston, MA). Trained observers under the supervision of an experienced observer manually segmented T2L and T1L. We automatically processed the data by N4 inhomogeneity correction, rigid registration, skull stripping, and intensity normalization. We then employed MIMoSA, an automated segmentation algorithm, which has previously shown competitive performance for segmenting T2L. MIMoSA utilizes complementary MRI pulse sequences to emphasize different tissue properties, which can help identify and characterize interrelated features of lesions, in a local logistic regression to model the probability that any voxel is part of a lesion.

Results: Using bootstrap cross-validation, we found that MIMoSA is a robust method that can be applied to segment both T2L and T1L. For T2L, we found a Sorenson's dice coefficient (DSC) of 0.61, a partial AUC (pAUC) up to 1% false positive rate of 0.69, and a correlation of 0.93. For T1L, we found 0.48 DSC, 0.63 pAUC, and correlation 0.83.
Conclusion: Though originally designed to segment T2L, MIMoSA is a fully automated segmentation algorithm that shows promise in segmenting T1 black holes with both sensitivity and specificity in patients with MS.

P121
Validation of Fully Automated Machine-Learning Algorithm for T2 Lesion Segmentation from Clinical MRI in Multiple Sclerosis
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Background: 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.
Objectives: 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).

P122
Clinical and MRI Course of Multiple Sclerosis Patients Treated with Disease Modifying Treatments (DMTs) in a Tertiary Care Center
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Background: The goals of the multiple disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) are to reduce the inflammatory process (MS relapses and new MRI lesions) and to reduce the progression of disability. As in clinical trials, most clinicians now equate MRI activity and clinical activity. Several guidelines have been proposed to evaluate the response of these agents. In general, three outcomes are used for monitoring: clinical relapses, EDSS score and MRI. Tolerance and toxicity must also be taken into account. Depending on the frequency and severity of clinical relapses, EDSS score and new T2 and gadolinium-enhancing lesions, switching thepary is advised.
Objectives: These guidelines need to be confirmed and appreciated in a real-world setting. The objective of this study is to look at the utilisation of the MRI in our tertiary care center MS clinic and to evaluate if the MRI monitoring is a tool that guides the therapeutic plan.
Methods: In our MS clinic, we use the iMed database. We currently have close to 4 thousand patients registered. Patients are seen once or twice a year. We selected patients with RRMS who were started on a DMT between January 2013 and March 2017. Usual demographics are described. We extracted data on clinical relapses, EDSS score, MRI (frequency, clinical information, radiological activity) and tolerance of DMTs.
Results: A total of 179 MS patients were identified. The mean age was 38,4 years (range 15-64 years) and 138 (77%) were female. For the first DMT, 50% were on orals and 50% on injectables. Out of the 179 patients, 118 (66%) had the first imaging follow-up an average of 493 days after the initiation of the agent. The reasons for the follow-up imaging was a routine control in 88 cases (75%), clinical events in 15 cases (13%), new baseline in 7 cases (6%), PML monitoring in 2 cases (2%), study follow-up in 1 case (1%) and unknown in 5 cases (4%).
During the study period, 53 (30%) patients had a DMT switch: 37 (70%) because of radiological concern, 11 (21%) due to adverse effects, 3 (6%) pregnancy, 1 (2%) personnal choice and 1 (2%) clinical deterioration. According to the guidelines, the level of concern (LOC) of patients that did not switch was low for 13 patients (10%), moderate for 8 (6%) and high for 11 (9%).
Conclusion: This study shows that the MRI activity addresses response to DMTs better than clinical follow-up and helps guide the therapeutic plan.

P123

Correlating the Presence of Rim Positive Lesions on Quantitative Susceptibility Mapping (QSM) with PK11195 Expression on PET Imaging

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Background: Quantitative susceptibility mapping (QSM) is a novel sequence used for quantification of iron. Imaging techniques have demonstrated that iron accumulates in chronic lesions of MS patients, especially in the rim. Histopathology reveals the presence of microglia and macrophages (MG/MΦ) in the rim of chronic active lesions. The source of iron in MG/MΦ in lesions are likely oligodendrocytes and myelin debris. The tracer [11C]PK11195 selectively binds translocator protein (TSPO) on activated MG/MΦ, making PET an *In vivo* proxy of innate inflammation.

Objectives: To identify chronic lesions as being QSM rim+ or rim- in a cohort of MS patients and to compare the uptake of PK11195 in QSM rim + lesions as compared to QSM rim- lesions.

Methods: 33 patients (26 with relapsing remitting, 7 with progressive MS) with PK-PET and corresponding QSM sequences were included. QSM rim+ and rim- lesions were identified. Individual lesion masks were created, and co-registered to PK-PET images. PK uptake was quantified by volume of distribution (VT). VT for individual lesions was calculated in reference to white matter, to consider physiologic variability, and Vt ratio (VTr) was obtained. 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 age.

Results: The included 33 patients had a mean age of 43.8 years, a mean disease duration of 13.4 years and a mean EDSS of 2.7. 488 T2 lesions were identified, 45 lesions were QSM rim+, and 443 lesions were QSM rim-. VTr value for rim+ lesions was 1.01, versus 0.93 for rim- lesions. The difference between rim + and rim- VTr values was significant (p =0.002) after controlling for multiple lesions per patient, patient age, and lesion volume.

Conclusion: A difference of VTr was found between QSM rim+ and rim- lesions and increased PK signal is associated with rim+ lesions. This provides evidence that lesions containing iron have a higher presence of activated MG/MΦ. MG/MΦ in the border of MS lesions are consistent with the classification of chronic active lesions. QSM +rim lesions can be used to identify a subset of chronic MS lesions with activated MG/MΦ, represented by the presence of iron. Differentiating chronic MS lesions with the use of novel sequences may provide a biomarker for inflammation and a therapeutic target to reduce on-going disease progression.

P124

A Fully Automated Statistical Technique for Counting Pathologically Distinct Multiple Sclerosis Lesions

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Background: Lesion load is a commonly used biomarker of disease status in multiple sclerosis (MS), yet it has historically shown a modest association with clinical outcomes. Additional information relevant to disease severity is thought to be captured in the natural history of lesion formation, but this feature is difficult to assess in patients with confluent (i.e., spatially overlapping) lesions.

Objectives: To address this issue, the current study introduces a novel statistical technique for cross-sectionally counting pathologically distinct lesions regardless of confluence, and seeks to demonstrate the validity, reliability, and clinical relevance of the proposed count.

Methods: To obtain the proposed lesion count, conventional MRI scans are used to segment white matter lesion tissue, yielding lesion probability maps. Lesion texture is then quantified using the eigenvalues of the Hessian matrix at each voxel of the probability map, and a thresholding procedure is carried out to select voxels exhibiting the texture expected of the center of a lesion.

Results: Validity of this technique was demonstrated by comparing the proposed count to a gold-standard count in 60 subjects observed longitudinally. The proposed count was highly correlated with the gold standard ($r = .97$, $p < .001$) and no significant difference was found between the counts ($t_{59} = -0.83$, $p > .40$). Reliability was determined using 14 scans of a clinically stable subject acquired at 7 sites. The variability of the 14 count estimates was approximately equivalent to that of lesion load in both fully automated and manually segmented contexts. Accounting for lesion load and age, the proposed count was negatively associated ($t_{58} = -2.73$, $p < .01$) with the Kurtzke Expanded Disability Status Scale (EDSS), suggesting that for a given lesion load, a higher lesion count is associated with lower disease severity. Additionally, average lesion size, operationalized as lesion load divided by the proposed count, was found to have a higher association with EDSS ($r = .35$, $p < .01$) than lesion load ($r = .10$, $p > .40$) or lesion count ($r = -.12$, $p > .30$) alone.

Conclusion: We introduce a novel technique for obtaining a count of pathologically distinct lesions from a single cross-sectional study, and show it to be valid, reliable, and clinically relevant. These findings demonstrate that it is possible to recover important aspects of the natural history of MS lesion formation without longitudinal data.

P125

The Primate Meninges Harbor Lymphatic Vessels That Can be Visualized Noninvasively By MRI

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Background: A network of dural lymphatic vessels in rodents has recently been described, but whether a similar network is present in primates is unknown.
Objectives: Here, we report the existence of meningeal lymphatic vessels in human and nonhuman primates (common marmoset monkeys) and the feasibility of noninvasively imaging and mapping them in vivo with high-resolution, clinical MRI.
Methods: High-resolution (in-plane resolution 270 x 270 μm or finer) brain MRI, including post-gadolinium contrast T2-FLAIR and T1-weighted black-blood scans, was obtained in 5 healthy volunteers and 3 common marmosets. MRI scans were performed with two distinct gadolinium-based contrast agents (gadobutrol and gadofosveset), with different propensity to extravasate across the capillary endothelial barrier. Comprehensive neuropathological examination assessed with immunohistochemistry and immunofluorescence the presence of lymphatics in human and marmoset dura mater samples; results were compared with MRI.
Results: On T2-FLAIR and T1-weighted black-blood imaging, lymphatic vessels enhance with gadobutrol, a gadolinium-based contrast agent with high propensity to extravasate across a permeable capillary endothelial barrier, but not with gadofosveset, a blood-pool contrast agent. The topography of these vessels, running alongside dural venous sinuses, recapitulates the meningeal lymphatic system of rodents. In primates, meningeal lymphatics display a typical panel of lymphatic endothelial markers by immunohistochemistry.
Conclusion: Pathologically verified, noninvasive visualization of dural lymphatics is feasible in human beings and primates by applying high-resolution MRI and standard gadolinium-based contrast material. This discovery holds promise for better understanding the normal physiology of lymphatic drainage from the central nervous system and potential aberrations in neurological diseases.

P126

Cervical Spinal Cord Normal-Appearing White Matter Tissue Integrity Progression Correlates with Sensorimotor Functional Changes in Multiple Sclerosis

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Background: Tract-specific cervical spinal cord diffusion tensor imaging (DTI) has shown a strong and consistent relationship with clinical sensorimotor outcomes in cross-sectional studies of multiple sclerosis (MS) patients with remote cervical spinal cord disease. Due to the dynamic nature of MS pathophysiology, longitudinal investigation of such relationships is required to demonstrate cervical spinal cord DTI as meaningful imaging biomarkers for clinical trials in MS.
Objectives: To evaluate the relationship between DTI-measured tissue integrity progression in the cervical spinal cord posterior columns (PC) and lateral corticospinal tracts (CST) and the corresponding sensorimotor functional changes in relapsing-remitting multiple sclerosis (RRMS) patients.
Methods: Longitudinal cervical spinal cord imaging (at acute onset, 1, 3, 6, 12, and 18 months) was performed on 7 RRMS patients (mean age 36, 5 females, mean EDSS 2.4) at 3T. Clinical functions, including finger vibratory thresholds, 25-foot timed walk (25FTW) and 9-hole peg test (9HPT), were assessed at each visit. Lesions were identified using sagittal T2-weighted and short-TI inversion recovery (STIR) images. Tract-specific cervical spinal cord (C1 to C6) tissue integrity was measured using high-resolution (0.9×0.9 x 5 mm^3) axial spinal cord DTI. Percent changes from the baseline or values of the DTI measures at each time point in the PC or CST (averaged over slices) for lesional or normal-appearing white matter were correlated (Pearson's r) to that of the functional assessments.
Results: All cervical spinal cord lesions (one lesion for 5 subjects and two lesions for 2 subjects) regressed (i.e., reduced lesional T2/STIR signal intensity and size) over time. Functional assessment changes ranged from -40 to 35 % (vibratory threshold), -23 to 10% (25FTW), and -36 to 25% (9HPT). Radial diffusivity and fractional anisotropy changes in the normal-appearing, but not lesional, PC significantly correlated ($|r|>0.4$, $p=0.01$) with vibration sensation changes. There was no significant correlation between DTI changes and 25FTW or 9HPT changes. Axial diffusivity values (not changes) in normal-appearing PC or CST were significantly correlated with 25FTW or 9HPT assessments ($|r|>0.6$, $p<0.01$).
Conclusion: Cervical spinal cord normal-appearing, but not lesional, white matter tissue integrity progression, measured by tract-specific DTI, could be potential longitudinal imaging biomarkers for clinical trials in MS.

P127

Magnetization Transfer Time Courses in the Grey and White Matter Volumes of Gadolinium-Enhancing Leukocortical Lesions

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Background: Cortical lesions (CLs) in multiple sclerosis (MS) have been described as having little inflammation in ex-vivo pathology studies. However, there has been evidence of cortical acute inflammation confirmed by brain biopsy. Our previous work has shown that gadolinium-enhancing leukocortical lesions (LCLs), although not frequent (6% of all enhancing lesions in our cohort) do affect a considerable number of recently diagnosed relapsing-remitting MS patients (36% of our subjects).
Objectives: To compare magnetization transfer evolution in the grey (GM) and white matter (WM) voxels of previously identified gadolinium-enhancing LCLs, before and after the gadolinium-enhancement event.
Methods: Data from 25 early-stage MS patients with 12 to 24 monthly scans using 3T MRI with triple-dose gadolinium were analyzed. WM and GM voxels were separately classified for 78 gadolinium-enhancing LCLs, using all available MRI contrasts. T1-weighted images with and without fat saturation pulses that exhibit magnetization transfer (MT) effects were used to produce MT ratio (MTR) images.
A mixed effect model was used to assess the relationship between MTR and three predictors (fixed effects) 1) *gadolinium-enhancement event* (pre-event/post-event), 2) *tissue type* (WM/GM), and 3) *lesion resolution* on all image contrasts (resolved/non-resolved). We also assessed interactions between 1) time and gadolinium-enhancement-event, 2) tissue type and gadolinium-enhancement-event, and 3) tissue type and lesion resolution. *Subject* and *lesion* were included as random effects.
Results: GM and WM voxels of enhancing LCLs experienced a significant drop in mean MTR post-enhancement. In lesions that resolved, GM voxels of enhancing LCLs experienced a significant drop in mean MTR post-enhancement (-1.2 units; $p = 0.002$); WM voxels experienced a significantly greater drop (-1.79 units; $p = 0.04$).
Conclusion: Decreases in MTR suggest that at least some cortical tissue damage is a consequence of gadolinium-enhancing LCLs. These low values persist over time, even in the LCLs that show resolution of the signal abnormality in all the conventional MRI images, and may underlie observations of low normal-appearing cortical MTR in MS patients.

P128

Longitudinal Assessment of Rates of MRI and Retinal Atrophy in African American Versus Caucasian American Patients with Multiple Sclerosis

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Background: African Americans with MS (AAMS) demonstrate higher inflammatory disease activity, faster disability accumulation and greater visual dysfunction as compared to Caucasian Americans with MS (CAMS). AAMS have been shown to have more pronounced brain tissue damage, in addition to higher lesion volume loads. Optical Coherence Tomography (OCT) is a non-invasive and reliable tool for measuring structural retinal changes. Recent studies support its utility for tracking neurodegeneration and disease progression *in-vivo* in MS. AAMS have been found to have greater retinal structure injury cross-sectionally and longitudinally in the peripapillary retinal nerve fiber layer (p-RNFL) and ganglion cell+ inner plexiform layer (GCIP). Despite prior work, there is a paucity of study of differences in brain sub-structure volumes over time in AAMS relative to CAMS. Similarly, longitudinal assessment of deeper retinal changes by race remain incompletely characterized
Objectives: To assess differences in brain MRI and retinal OCT atrophy rates between AAMS and CAMS
Methods: Twenty AAMS and 20 matched CAMS were tracked with brain MRI for a mean duration of 5.2 years. In addition, 115 AAMS and 115 matched CAMS were tracked with retinal OCT for a mean duration of 4.4 years. Annual contrast enhanced 3T brain MRI and 6-month OCT scans were performed. Validated image segmentation algorithms developed at Johns Hopkins University were used to analyze both the MRI and OCT data. Mixed-effects linear regression models were used in statistical analyses
Results: Significant whole brain and brain sub-structure atrophy was observed across both cohorts over the study duration ($p<0.001$ for all). Whole brain, gray and white matter atrophy rates were significantly different between both cohorts, with AAMS exhibiting atrophy rates twice as fast as CAMS patients (p-values 0.030, <0.001 and 0.050 respectively). In addition, thalamic atrophy was markedly faster in AAMS patients (-1.50%/year in AAMS vs -0.51% in CAMS, p-value 0.010). GCIP and p-RNFL annual rates of change were significantly faster in AAMS vs. CAMS (-1.13% vs -0.76% (p-value 0.014) and -0.74% vs -0.44% (p-value 0.010) respectively)
Conclusion: AAMS exhibited more rapid neurodegeneration than CAMS with significantly faster brain and retinal tissue volume loss as compared with CAMS. These results corroborate the more rapid clinical progression observed in AAMS vs CAMS, and raise the question of whether AAMS may benefit from a more aggressive therapeutic approach

P129

Calibrated fMRI Study Reveals Neural-Vascular Uncoupling in the Visual Cortex of Multiple Sclerosis Patients

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Background: Multiple Sclerosis (MS) results in visual cortex (VC) dysfunction, even in the absence of ophthalmic pathologies. The precise mechanism of this dysfunction remains elusive. Our previous studies have shown associations between white-matter microstructure (WMMS) insult and reduced Blood-Oxygen-Level-Dependent (BOLD) signal in the VC of MS patients when compared to healthy controls. However, the physiologic basis of this phenomenon remains unknown.
Objectives: We hypothesized that WMMS damage affects communication between neurons and cerebral vasculature (i.e.., neurovascular coupling) and in turn, disrupts neural function. In this study, we sought to isolate the origin of MS-related BOLD changes by comparing components of the hemodynamic response function (blood-flow and oxygen metabolism) using dual-echo calibrated functional magnetic resonance imaging (cfMRI).
Methods: We conducted a case-control study comparing relapsing-remitting MS patients with matched healthy controls. Participants were scanned using a 3T MRI scanner. We utilized a dual-echo pulse sequence that permitted near-simultaneous measurement of cerebral blood flow (CBF) and BOLD signal. In the scanner, participants performed a hypercapnia inhalation challenge while being scanned. They subsequently performed a visual task in which they responded with bilateral button- press whenever a fixation cross at center-screen changed in luminance; during stimulation blocks (32 sec), flickering checkerboards were presented at 6Hz. Individual data were preprocessed and convolved to obtain functional regions of interest (ROI). BOLD and CBF time series were obtained from these ROIs. Cerebral metabolic rate of oxygen (CMRO2) was calculated using the deoxyhemoglobin dilution model.
Results: Whereas healthy controls exhibited stimulation-induced BOLD signal increases that were sustained across the block, MS patients exhibited stimulation-induced BOLD signal increases that declined across the block. Estimated maximum blood-oxygenation (the factor M) was higher in MS patients than healthy controls. During stimulation, increases in CBF and CMRO2 were lower in MS patients than healthy controls, suggesting that reductions in neural metabolism plays a key role in MS-related neural-vascular coupling alterations.
Conclusion: These results support the hypothesis that MS-related visual cortex dysfunction stems from neural pathology arising more from neural and glial deficits than from vascular deficits.

P130

Ultrasmall Superparamagnetic Iron Oxide Nanoparticle-Enhanced MRI at 7-Tesla in MS

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Background: Ferumoxytol is a suspension of ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles that can be phagocytized by peripheral monocytes. The USPIO-monocyte complex can be detected by MRI, and USPIO signal in the brain suggests active monocyte targeting. However, prior studies of USPIO used descriptive outcomes, short follow-up times, and lower field-strength magnets, limiting the interpretation of their results. 7-tesla MRI provides increased spatial resolution and sensitivity to paramagnetic substances, thus improving the ability to detect small changes in USPIO-related MRI signal.
Objectives: To determine the safety and utility of ferumoxytol-enhanced MRI at 7-tesla.
Methods: 5 healthy volunteers and 5 MS patients underwent a single 510-mg intravenous dose of ferumoxytol. This was followed by MRI at baseline, within 2 hours of ferumoxytol infusion ("immediate"), 24-48 hours ("delayed"), 1 month, and 6 months, all at 7T. Gadolinium contrast was administered at baseline, 1 month, and 6 months. Sequences included 8-echo gradient echo ($1mm^3$), which was used to generate R2* maps, and MP2RAGE ($0.7\ mm^3$) with quantitative T1map. Images were also visually inspected for evidence of USPIO enhancement.
Results: All subjects tolerated the ferumoxytol infusion. There were no significant changes in R2* between baseline and 6-month MRI scans in the globus pallidus, putamen, and white matter/normal appearing white matter (Mann-Whitney t-test, all $p > 0.05$). USPIO enhancement was seen in 2 patients, 1 lesion each. One lesion had focal USPIO enhancement within portions of a resolving tumefactive lesion that was gadolinium-enhancing for > 1 year. The second lesion was <2 weeks old (by MRI) and showed nodular USPIO-enhancement on the immediate scan, changing to peripheral enhancement after 48 hours. Across the 5 patients, 39 chronic, non-gadolinium enhancing MS lesions, and none of them showed USPIO-related signal change.
Conclusion: Ferumoxytol was safe and well tolerated. Quantitative MRI did not show significant changes in iron-related signal intensity in deep gray nuclei or within white matter. Chronic, non-gadolinium-enhancing MS lesions do not show evidence of USPIO enhancement, suggesting that peripheral monocyte targeting of these lesions is minimal or nonexistent. However, USPIO enhancement in 2 MS lesions – one chronic and the other new gadolinium-enhancing – suggests that USPIO identify distinct pathophysiological processes from gadolinium.

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Optical Coherence Tomography Measures Correlate with Cognitive Function in Progressive Multiple Sclerosis

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Background: Optical coherence tomography (OCT) provides high-resolution imaging of the retina. OCT is a quick, cheap, and reproducible method for assessment of tissue injury in multiple sclerosis (MS). There is evidence that some OCT measures are markers of whole brain injury. OCT measures of retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness have been shown to be associated with cognition in MS. Most of these studies focused on relapsing forms of MS. Although cognitive dysfunction is a prominent feature of progressive forms of MS,

there are few studies examining the relationship of OCT and cognition in progressive MS cohorts.
Objectives: To investigate the association between OCT measures and cognitive function in patients with progressive MS.
Methods: We analyzed data obtained at baseline in the NN102/SPRINT-MS randomized trial comparing ibudilast to placebo in primary progressive (PP) or secondary progressive (SP) MS. OCT measurements included RNFL and GCL thickness. Cognitive testing included the Symbol Digit Modality Test (SDMT), Selective Reminding Test, SF36 Mental Component, and EDSS Cerebral Score. Baseline clinical and MRI data were also collected. Data were analyzed using Pearson and Spearman correlation tests, and linear models using JMP Pro 13.0.0 statistical software.
Results: Baseline characteristics (N=286) included SPMS:N=142,*49.65%*; Male: N=137, 47.9*%*; Age: Avg=55.5, *SD=7.3*; Disease duration (years): Avg=14.9, *SD=9.05*. SDMT was correlated with RNFL thickness (p=0.0007, β=0.309, N=266) and GC thickness (p=0.0002, β=0.418, N=191). No other cognitive tests correlated with OCT measures. Consistent with previous findings, OCT measures correlated with T1 and T2 lesion volumes, magnetization transfer ratio (Gray matter and whole brain), brain parenchymal fraction (BPF), and corticospinal tract diffusion tensor imaging measures. Using linear regression modeling including age, sex and low contrast letter acuity, RNFL correlated with SDMT (p=0.0127) independent of visual acuity. In a single model including other known predictors of cognition, T2 lesion volume (p=0.00125) and BPF (p=0.0426) were the strongest predictors of SDMT.
Conclusion: OCT measures of RNFL and GC thickness correlated with clinical measures of cognition, specifically SDMT, in progressive multiple sclerosis. The correlation of change in OCT measures and in SDMT and the ability of OCT to predict SDMT over time require further investigation.

P132

Automatic Cerebrospinal Fluid Zero Reference for Quantitative Susceptibility Mapping of Multiple Sclerosis

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Background: Quantitative susceptibility mapping (QSM) is becoming widely used in studying multiple sclerosis (MS), where both iron and myelin pathologies cause magnetic susceptibility changes. Conventional QSM (Morphology Enabled Dipole Inversion, MEDI) determines susceptibility up to an arbitrary constant and requires a tissue reference for longitudinal and cross-center studies. MEDI reconstructed with automatically segmented cerebrospinal fluid (CSF) in ventricles as zero reference (MEDI+0) solves this tissue reference problem. Both MEDI+0 and MEDI postprocessing can be performed on the same gradient echo data.
Objectives: To evaluate the clinical feasibility of MEDI+0 in MS patients by comparing it with MEDI.
Methods: First, all 44 consecutive MS cases in a month (7/2017) from three of the scanners in our medical center were identified for image quality evaluation by a neuroradiologist using three scales: excellent agreement between MEDI+0 and MEDI, good agreement with marginal discrepancy, and poor agreement with substantial disagreement. Second, 43 MS cases, having all lesions segmented (total 405 lesions) and normal appearing white matter (NAWM) identified, were analyzed with ROI measurements of lesion susceptibility values, as well as image quality assessment. Lesion contrasts, $|S_{lesion}-S_{NAWM})|$, were also determined.
Results: Of the consecutive 44 cases, 43 (97.73%) were scored excellent agreement between MEDI+0 and MEDI, 1 good agreement (idiopathic artifacts in magnitude images), and none poor agreement. The CSF susceptibility variations in MEDI (range [-15.074, 29.742] ppb, mean 7.297ppb, standard deviation 9.620ppb) were reduced by MEDI+0 to ([-3.915, 2.130], -0.201, 0.833) ppb. All of the 43 cases with segmented lesion ROIs were scored excellent agreement. Among the 405 MS lesions, there were good correlations between MEDI+0 and MEDI for lesion susceptibility values referenced to CSF (R= 0.81, P< 0.001) and for lesion contrast with NAWM (R=0.73, P<0.001).
Conclusion: Compared with MEDI, MEDI+0 provides the same image quality, lesion to NAWM contrasts, and reliable susceptibility value in multiple sclerosis.

P133

MD1003 in Progressive Multiple Sclerosis: 24-Month Brain Volume Changes of the MS-SPI Trial

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Background: MS-SPI was a 12-month (M), randomized, double-blind, placebo-controlled trial of the effects of MD1003 (high-dose pharmaceutical biotin) in patients with progressive, non-clinically active multiple sclerosis (MS). In the open-label extension phase, all patients received MD1003.
Objectives: A brain volumetric magnetic resonance imaging (MRI) follow-up sub-study was conducted to evaluate the impact of MD1003 on MRI-measured safety parameters and to explore the mechanism of action of MD1003.
Methods: Sequences were standardized and tested between the six centers included. Images were centralized to the Shanoir platform and analyzed in two independent centers (INSERM, Toulouse, France; NeuroRx, Montreal, Canada).
MRIs were performed at M0, M12, and M24 on 74 patients (MD1003>MD1003: 49; placebo>MD1003: 25). Normalized volumes of the whole brain (WBV), white matter (WMV) and grey matter (GMV) at baseline were analyzed using SIENAX in 66

patients (MD1003>MD1003: 44; placebo>MD1003: 22). Subsequent volume changes were analyzed using SIENA and paired Jacobian integration.

Results: A decrease in WBV and GMV measures was observed at M12 in the MD1003 arm compared with the placebo arm. Differences were statistically significant for the WBV percentage change and for the GMV percentage change. No differences were observed for the WMV percentage change. At M24, the change from baseline in WBV, GMV, and WMV was relatively constant in the MD1003 group, which continued on treatment, compared with M12. The placebo group, in which changes from baseline had been moderate in the first 12 Ms, experienced a decrease across all volumetric measures when switched to MD1003 at M12; this was maintained for 12 Ms. At M24, the decrease was similar in the placebo>MD1003 group and in the MD1003>MD1003 group.

Conclusion: Volumetric analyses performed independently and blindly by two different reading centers indicated a decrease in WBV and GMV in the MD1003 arm compared with the placebo arm. These volume changes were recapitulated when the placebo group switched to MD1003. No differences between groups were observed at M24, after the placebo arm had been switched to active treatment.

Overall, these results are consistent with a pseudo-atrophy phenomenon linked to a decrease in brain water volume after the initiation of treatment with MD1003. This pseudo-atrophy phenomenon may be a consequence of increased energy production triggered by high doses of pharmaceutical biotin.

P134

Brain Atrophy after High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Multiple Sclerosis (HALT-MS)

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Background: High-Dose Immunosuppressive Therapy (HDIT) and Autologous Hematopoietic Cell Transplantation (HCT) for Multiple Sclerosis (HALT-MS) was a phase II clinical trial of HDIT/HCT for patients with relapsing-remitting (RR) MS who experienced relapses with disability progression while on MS disease-modifying therapy. High rates of short-term brain volume loss have been observed following similar treatments.

Objectives: To model the time-courses of whole-brain (WB), grey-matter (GM), and white-matter (WM) volume loss in HALT-MS subjects to better understand the effect of this treatment on brain atrophy in MS.

Methods: We measured percentage WB, GM, and WM volume changes (Pairwise Jacobian Integration) over up to 5 years in twenty-four RRMS patients who underwent BEAM (BiCNU, Etoposide, Ara-C, Melphalan) chemotherapy-based HDIT and HCT. A non-linear mixed-effects model was applied to the volume trajectory data, with the total dose of BEAM chemotherapy and the baseline volume of T1-weighted WM lesion (T1LV) as predictors of treatment-related volume loss. We estimated the rates of both short-term treatment-related and long-term volume loss. Subgroup analysis included comparing the short-term and long-term rates of volume loss between the patients with and without gadolinium-enhancing lesions at baseline.

Results: Rapid short-term volume loss occurred in all compartments: 0.98% (SE: 0.60), 1.2% (0.77), and 1.6% (0.84) in WB, GM, and WM, respectively. Total BEAM dose was a significant predictor of the rate of volume loss in all compartments. T1LV was a significant predictor for WB and WM volume loss. The average long-term rates of volume loss after the initial treatment-related effects slowed to -0.22%/y (SE: 0.075), -0.12%/y (0.081), and -0.15%/y (0.11) in the WB, GM, and WM, respectively.

Patients with gadolinium-enhancing lesions at baseline had significantly higher short-term rates of GM volume loss (-1.83% vs. -0.40%, p=0.003) and WB volume loss (-1.90% vs. -0.76%, p=0.002) at 1-year follow-up, and significantly higher long-term rate of GM volume loss (-0.26%/y vs. -0.0051%/y, p=0.025). The difference in long-term WB loss did not reach significance (-0.32%/y vs. -0.13%/y, p=0.081).

Conclusion: Brain volume loss may accelerate for months after HDIT/HCT due to the effects of chemotherapy-related toxicity and progression of WM lesion-related degeneration. However, over the long-term, adequate immunosuppression and HCT can reduce rates of brain volume loss to the range observed in normal aging.

P135

Radiomic Prediction of Clinical Outcome in Multiple Sclerosis Patients from the Combirx Cohort

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Background: Radiomics allows the conversion of digital medical images into mineable data, by extracting quantitative imaging features. Machine learning models trained on radiomic features can help predict important clinical outcomes and uncover novel information for a variety of diseases. Magnetic resonance imaging (MRI) is routinely obtained in people with multiple sclerosis (MS) to monitor disease activity. These images may contain latent information linked to clinical outcomes that could be elucidated via radiomic analysis.

Objectives: To evaluate the predictive performance of machine learning models constructed from MRI radiomic features at baseline to predict clinical outcomes at 3 years in relapsing-remitting (RR) MS.

Methods: A subset of 33 RRMS patients from the CombiRx trial, a multi-center, phase-III investigation of combination therapy, with available T1 and FLAIR baseline MRI scans and Expanded Disability Status Scale (EDSS) scores at 3 years were selected for the analyses. MS lesions were semi-automatically segmented and used as masks to compute radiomic features related to shape, intensity, and texture. These features were then utilized to

construct supervised machine learning classification models to predict EDSS at 3 years (EDSS < 2 vs. EDSS ≥ 2) via repeated cross validation. Models were also constructed from baseline clinical data (age, sex, baseline EDSS) and lesion volume alone for comparison. All computational tools utilized were open-source to foster reproducibility of results.

Results: A gradient boosting machine learning model constructed with radiomic features achieved an accuracy (± standard deviation) of 0.867 ± 0.024 when evaluated via repeated cross validation. The accuracy of the radiomic model was significantly higher than models built with clinical data (0.548 ± 0.023, $p < 0.001$) or lesion volume alone (0.634 ± 0.018, $p < 0.001$).

Conclusion: Machine learning models trained on the MRI radiomic features of MS lesions demonstrate high and reliable performance to predict EDSS at 3 years. The radiomics model performed better than models constructed from clinical features or lesion volume alone. Radiomics applied to clinically available MRI data could be a powerful tool in MS predictive analytics. We plan to expand our study to the entire CombiRx dataset to increase training data and improve generalizability of our results.

P136

Evidence for Neural-Vascular Uncoupling in Multiple Sclerosis: A Calibrated fMRI Study in Motor Cortex

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Background: Multiple Sclerosis (MS) symptomology is known to include fatigue and motor slowing that has been attributed to motor cortex (MC) dysfunction. The neural-vascular coupling system, composed of cerebral blood vessels, glial cells, and neurons coherently function to maintain effective neural function. Previously, we have found reduced blood-oxygen-level dependent (BOLD) signal in the motor cortex of MS patients. However, the relative contributions of each neural-vascular component to reduced BOLD signal remain unknown.

Objectives: We performed a cross-sectional study comparing BOLD, cerebral blood flow, and cerebral metabolic rate of oxygen in relapsing-remitting MS patients and healthy controls to elucidate each component in the neurovascular coupling system.

Methods: All subjects who met inclusion criteria were scanned using a 3T MRI scanner with a dual-echo calibrated functional MRI (cfMRI) sequence which provided near-simultaneous measures for both cerebral blood flow (CBF) and BOLD signal. During imaging, subjects performed a motor task which required bilateral button presses in time with a 2Hz auditory rhythm. An additional hypercapnia gas challenge involving periodic inhalation of room air (4 min) and 5% CO_2 (6 min) permitted measures of cerebral metabolic rate of oxygen ($CMRO_2$). Data were preprocessed and average percent signal change from baseline was calculated in each voxel providing BOLD and CBF time series. The anatomical region of interest (ROI) was defined as the precentral region after cortical parcellation using Freesurfer in native space.

Results: During active blocks, MS patients displayed an initial rise in CBF followed by a gradual decline, whereas healthy controls exhibited a similar initial rise and a subsequent sustained plateau. CBF decreased in MS patients but BOLD signal was not different from healthy controls, suggesting lower $CMRO_2$ in MS patients. Estimated maximum blood-oxygenation (the factor M) was higher in MS patients than healthy controls.

Conclusion: These results suggest that, with persistent stimulation of the motor cortex, MS patients exhibit progressive uncoupling between glial cells, neurons, and blood vessels. Such uncoupling, provides a plausible mechanism for MS-related motor cortex dysfunction, fatigue, and motor slowing.

P137

Novel Techniques for MS Lesion Segmentation Algorithm Evaluation

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Background: Automated segmentation of lesions is increasingly being utilized in MS research studies and clinical trials. The Dice score (the ratio of overlapping volume to average volume) is popular for evaluating the performance of segmentation algorithms. Although it is useful as a standardized measure, it offers a very limited picture of segmentation quality since algorithms may perform quite differently in ways not reflected by their Dice score.

Objectives: We propose a new set of evaluation techniques that offer improved insights into the behavior of MS lesion segmentation algorithms.

Methods: T1w, T2w, PD and FLAIR 3T MRI images of the brains from 70 MS patients were used in this study. Lesions were manually segmented by an expert. The performance of two popular automated algorithms, OASIS and LesionTOADS, were compared. For each image, we identified the connected components as distinct lesions. Comparing the lesions in the automated and manual segmentations, we classified lesions into 6 categories: Correct Detection (1-1 match), False Alarm (0-1), Detection Failure (1-0), Merge (N-1), Split (1-M), Merge-Split (N-M). For each lesion, we computed the Dice score, which we analyze per lesion size, class, and spatial distribution. We also reported lesion counts.

Results: OASIS and LesionTOADS had nearly identical image-wide Dice scores (median Dice: 0.547 vs. 0.544). The number of distinct lesions was 2,461 (manual), 1,340 (OASIS) and 2,810 (LesionTOADS). In all classes, LesionTOADS had a higher per-class Dice score than OASIS; however, LesionTOADS resulted in far more False Alarm lesions than OASIS, which led to a low image-wide Dice score. LesionTOADS performed better for small and large lesions, whereas OASIS performed better for medium-size lesions. Both algorithms had many detection failures in the septum area, and OASIS had a secondary problem area around the temporal horn of the ventricles. False alarms were most common around the lateral ventricles as well as in the inferior temporal lobes for both algorithms.

Conclusion: The proposed performance analysis per lesion class, size, and spatial distribution allows novel insights into algorithm performance that image-wide summary metrics cannot provide.

This enables scientists to choose algorithms better suited for a specific study, as well as allow for algorithm development and tuning by revealing their specific strengths and weaknesses.

P138

Pattern Separation Deficits Strongly Predict Dentate Gyrus Hippocampal Atrophy in Relapsing Remitting MS

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Background: Memory impairment is common in multiple sclerosis (MS) and is associated with volumetric changes (atrophy) in the hippocampus. Traditional neurocognitive measures may be less sensitive to hippocampal atrophy compared to lab-based measures. Pattern separation, the ability to differentiate similar yet distinct memories, is sensitive to hippocampal changes (localized to the dentate gyrus) in both animal and human models and may help in understanding the underlying mechanisms of memory impairment in MS.
Objectives: To investigate how whole hippocampal and hippocampal subfield volumes are related to pattern separation in MS.
Methods: Sixteen relapsing-remitting MS participants completed a behavioral measure of pattern separation (the Mnemonic Similarities Test; MST), traditional neurocognitive assessments of verbal (Hopkins Verbal Learning Test) and visuospatial (Brief Visuospatial Memory Test) memory and 3T structural magnetic resonance imaging scans. Volumetric estimates and segmentation were derived using FreeSurfer 6.0. MS participants' pattern separation performance was compared to published parameter estimates from a sample of healthy control and amnestic mild cognitive impairment participants. Bilateral hippocampi and dentate gyri volumes served as *a priori* regions of interest and were correlated with traditional neurocognitive assessments of memory and pattern separation (computed as lure discrimination index) scores using partial correlations, adjusting for age, disease duration, and intracranial volume.
Results: Pattern separation performance in MS was worse than age-matched healthy controls (p=.005), and did not differ from older adults or amnestic mild cognitive impairment groups (p's=n.s). Bilateral hippocampi volumes correlated significantly with visuospatial memory (R^2_{Left}=.47; R^2_{Right}=.36) and pattern separation (R^2_{Left}=.67; R^2_{Right}=.67) but not with verbal memory. Bilateral dentate gyri volumes were only significantly correlated with pattern separation (R^2_{Left}=.38; R^2_{Right}=.39).
Conclusion: Pattern separation assessed using the MST may be more sensitive to dentate-specific hippocampal atrophy in relapsing-remitting MS than traditional neurocognitive assessments.

P139

Histopathological Correlation of Diffusion Basis Spectrum Imaging in Human Brain Biopsy Tissue of an Inflammatory Demyelinating Lesion

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Background: There is a need to develop imaging biomarkers capable of differentiating and quantifying the heterogeneous pathological components in multiple sclerosis (MS). Diffusion basis spectrum imaging (DBSI) models diffusion-weighted MRI signals as a combination of discrete anisotropic diffusion tensors (representing the integrity of axon fibers and myelin while resolving for crossing fibers), and a spectrum of isotropic diffusion tensors (reflecting the extra-axonal environment associated with inflammation and tissue loss).
Objectives: To assess the histopathological correlates of DBSI metrics in MS-affected brain tissue.
Methods: DBSI was performed on a 53 year-old man three weeks after biopsy of a contrast-enhancing right parietal white matter lesion for further evaluation of new onset seizures. The biopsy showed inflammatory demyelination with relative axonal sparing, typical of MS. DBSI metrics including axial diffusivity (AD), radial diffusivity (RD), restricted and non-restricted isotropic fractions, and fiber fraction were calculated in the biopsied lesion identified on FLAIR images and were compared with the same region in a healthy control. Results were also compared to diffusion tensor imaging (DTI) and magnetization transfer ratio (MTR) values.
Results: DBSI-derived RD (marker of demyelination), but not DTI-derived RD, was significantly (>2 SD than the mean for healthy control) increased in the entire lesion from which the biopsy was taken. Non-restricted isotropic fraction (marker of edema) was diffusely elevated in the lesion. Restricted isotropic fraction (marker of cellularity) was increased in the lesion adjacent to the biopsy site, but decreased in the actual biopsy site (few cells). Neither DBSI- nor DTI-derived AD (marker of axonal integrity) was significantly altered in the lesion surrounding the biopsy site. MTR values in the lesion were consistent with demyelination and edema, but MTR could not assess cellularity or axonal integrity.
Conclusion: The observed changes in DBSI metrics including increased RD (demyelination), unchanged AD (axonal integrity), and elevated restricted isotropic fraction (cellularity) were consistent with histopathology finding of inflammatory demyelination with axonal sparing. DBSI more accurately reflected the underlying pathologies than DTI and MTR. This study provides preliminary evidence for the feasibility of DBSI to differentiate the pathological processes in acute MS lesions.

P140

Characteristics of Brain PET-CT FDG in Anti NMDAR Encephalitis

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Background: In the NMDAr encephalitis, the brain PET-CT FDG findings are heterogeneous. Initially, temporal lobe hypermetabolism was reported in limbic paraneoplastic encephalitis.

Later, a heterogeneous pattern with hypermetabolism in the base nuclei and hippocampus hypometabolism was described. Finally, a series of 22 patients with predominance of lobar hypometabolism with a higher frequency in the parietal lobe, followed by occipital were reported.
Objectives: To identify the characteristics of brain PET-CT FDG in patients with defined anti-NMDAr encephalitis.
Methods: We documented the findings observed in each of the patients, describing the presence of hypo or hypermetabolism in each brain cut and nuclei of the base using the visual (qualitative) method with validation of the institution's Nuclear Medicine department. Finally, we calculated the proportion of hypo or hypermetabolism of each region of interest and in the case of patients with a control study, we contrasted with the clinical evolution of the patient. The mean time elapsed from onset of symptoms to brain FDG PET-CT was calculated.
Results: The brain PET-CT FDG was performed in 30 patients with anti-NMDAr encephalitis, being observed abnormal in all of them. The mean time to onset of symptoms was 138 days (95% CI 48-227). An abnormality of the occipital metabolism was observed in 27 patients (88% hypometabolism vs 3% hypermetabolism), followed by temporal cortex affection in 24 (hypometabolism 53% vs 47% hypermetabolism) and parietal in 26 patients (hypometabolism 77% vs hypermetabolism 33 %). The alteration in the nuclei of the base was observed in only 23 patients, (52% hypermetabolism vs 48% hypometabolism).
Conclusion: The findings identified by the visual method (qualitative) in brain PET-CT FDG, suggests an evolutionary radiological pattern characterized by initial affection of temporal and occipital cortex, followed by parietal cortex, frontal and finally nuclei of the base; observing the biological coherence of the dynamic brain pattern PET-CT FDG and the evolution of the disease. This qualitative observation was possible by the observation of the clinical status of the patient, the time of disease evolution and the findings were presented in the brain PET-CT FDG;as well as visual analysis of changes observed in PET-CT FDG brain control in 5 of the 30 patients with anti-NMDA encephalitis during their hospitalization.

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Automated Segmentation of Multiple Sclerosis Brain Lesions – a Simple Step in the Complicated Problem of Clinical Imaging Standardization

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Background: Assessment of magnetic resonance imaging (MRI) related disease activity, new and enlarging T2 fluid attenuation inversion recovery (FLAIR) lesions or gadolinium-enhancing lesions, is an integral component of Multiple Sclerosis (MS) management, but is fraught with technical hurdles in clinical practice. Agreement on new lesion counts is suboptimal; with one study reporting up to 45% of clinical readers disagreed with an expert reader using standardized image acquisition.[1] Additionally, lesion segmentation volume assessments are not readily available in most clinical practices.[2] A reliable, accurate, and reproducible automated technique for segmentation and analysis of MS lesions is needed in clinical practice.
Objectives: To evaluate automated segmentation of lesion counts and volumes as a reliable and reproducible tool for clinical practice.
Methods: A retrospective comparison of MRI scans acquired at 3.0 Tesla was performed to evaluate LesionQuant (CorTechs Labs), a method of automated 3D T1 and T2 FLAIR lesion identification, segmentation, and measurement. Lesions were segmented as unique based on gaps of either 1mm or 2mm. Blinded manual analysis of total and new lesions by an expert image reviewer (gold standard) was compared to a neuroradiologist, an MS clinical fellow, and the automated analysis derived via LesionQuant.
Results: Scan-rescan reproducibility for LesionQuant lesion counts (Median Difference = 3.0 lesions) and volumes (Median Volume Difference <0.2 cc) was good. Comparisons between manual and automated lesion volume segmentation showed good agreement (R>0.85). Manual and automated lesion counts were highly correlated (R>0.85) and automatic lesion counts using a minimum lesion distance of 2mm better reflected the gold standard evaluation of lesion counts. Concordance correlation of lesion counts and new disease activity between expert readers and LesionQuant will be presented.
Conclusion: While MRI is a universally accepted tool for both the diagnosis and monitoring of MS, its current usage lacks standardization and reproducibility in clinical settings. Automated segmentation of MS lesion volumes and counts by LesionQuant provides reproducible results and correlates well with manual segmentation. This report will present the correlation of manual lesion counts and MRI activity by an expert reader with assessment by other clinical evaluators and LesionQuant automated analysis.

P142

Vesicular Appearing Multiple Sclerosis Initially Diagnosed As Neurocysticercosis

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Background: Atypical presentations of Multiple Sclerosis (MS) can lead to initial misdiagnosis, especially when the neuroimaging characteristics overlap with other diseases, such as Neurocysticerosis (NCC), in a patient demographic at risk for both diseases.
Objectives: To review the literature on the neuroimaging features of atypical MS compared to NCC.
Methods: Case report and literature review.
Results: The initial diagnosis of NCC was based on the clinical presentation of seizure combined with neuroimaging that was only consistent with probable NCC, not definitive NCC. Further analysis of the clinical course, which included multiple relapses despite appropriate anti-parasitic treatment, combined with neuroimaging that met both McDonald criteria and was consistent with documented subtypes of atypical demyelination, ultimately led to the diagnosis of atypical MS.
Conclusion: Judicious application of neuroimaging criteria is required to accurately diagnose MS in a young Latino population that is also at risk for NCC.

Internet and Social Media

P143

Evaluation of a Web-Based Fall Prevention Program Among People with Multiple Sclerosis

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Background: More than half of people with multiple sclerosis (PwMS) report falling at least once every 3-6 months and over one-third report multiple falls in this timeframe. Currently there is no accepted standard of care for fall prevention in PwMS. Several approaches are used and have been studied including physical therapy, group exercise and fall prevention education, but all of these have limitations in efficacy and implementation. Free from Falls (FFF), is a group based exercise and education program for PwMS, developed by the National MS Society (NMSS). FFF consists of eight 2-hour instructor-led group sessions, comprised of didactics and discussion, and exercises designed to improve balance and postural control. Though FFF may improve mobility, balance and balance confidence, access to this program is limited by time, space and budgetary constraints. We therefore developed a web-based version of FFF to improve access to this program.
Objectives: The aim of the study is to describe the development and beta-testing of a web-based fall prevention program.
Methods: We developed Free from Falls Online (FFFO) by adapting the original FFF program into a web-based format using Wix. We presented educational material as 8 narrated, 30-minute webinars with supplementary, reading material. The exercise component was adapted into a narrated video with persons of varying levels of disability demonstrating the exercises. We then conducted beta testing of FFFO among 6 people with MS in the community, with varying impairments including motor and visual problems to evaluate usability and functionality.
Results: Observations from beta testing demonstrated that the individual components (links, modules, contact form) of FFFO was functional across different web-browsers (Internet Explorer, Firefox, Google Chrome and Safari). Modifications were made to address MS-specific barriers to internet use, such as low contrast, small font, cluttering of content and poor navigational design. The program is now hosted on the NMSS website and will be freely available to the public. We are currently evaluating its efficacy for fall prevention in a pilot randomized controlled trial.
Conclusion: Comprehensive fall prevention programs can be delivered online to address limitations in access by delivering MS health education and exercise programs at relatively low cost to a much wider audience. The adoption, adherence, efficacy and effectiveness of online delivery require further study.

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Social Network in People at Risk for Multiple Sclerosis: Network Composition but Not Network Structure Is Associated with Self-Reported Disability

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Background: Social relations contribute to environmental or experiential risk factors for multiple sclerosis (MS) such as diet, physical activity, smoking, and exposure to Epstein-Barr virus.
Objectives: We examined the social networks of participants in the Genes and Environment in Multiple Sclerosis (GEMS) Project, a prospective cohort study of MS first-degree family members.
Methods: In a cross-sectional study, we used a questionnaire to ascertain the social network features of 1493 first-degree family member: 1378 asymptomatic individuals without MS and 115 with MS at the time of examination. We quantified each person's social network structure (e.g., network size and constraint) and composition (e.g., proportion of kin, a range of health habits within a network). We performed regression analyses to discover associations between network features and the multiple sclerosis rating scale (MSRS), a self-reported measure of functional disability validated for MS.
Results: Overall, the composition ($p < 0.0001$) but not the structure ($p=0.067$) of personal networks was associated with the MSRS score. Deconstructing the network composition features, we found the proportion of people in one's network that do not go to a doctor regularly to have the strongest correlation with MSRS (beta=7.24, $p=7.4E-8$, FDR=$9.6x10^{-7}$). In addition, the proportion of people in the network perceived to have a negative health impact was strongly correlated with MSRS (beta=1.74, $p=0.00085$, FDR=0.0055). Leveraging previously reported genetic and environmental risk factor data available among a subset of the participants, we noted an intriguing positive correlation between Genetic & Environmental Risk Score (GERS) and a larger personal network size ($p=5.0x10^{-5}$). This finding appears to be driven primarily by the larger network size of women participants relative to men ($p=1.0x10^{-5}$). Among asymptomatic participants, both a history of mononucleosis ($p=0.0048$) and a higher genetic risk score for MS susceptibility ($p=0.0059$) were correlated with a larger network size.
Conclusion: In this largest examination of social networks in people at risk for a chronic neurological disease, characteristics of people around a person at risk for MS are associated with that individual's functional disability. This study highlights the importance of social environment on neurological function. The intriguing modest association of MS genetic risk with an increased network size requires further exploration.

P145

Identifying Factors for Diverse Participation in Multiple Sclerosis Patient Networks

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Background: Over 80,000 individuals participate in multiple sclerosis (MS) patient networks such as Accelerated Cure Network, Health Care Journey, iConquerMS, and the Alliance for Research in Hispanic MS (ARHMS). We identified the different

levels of patient participation in these communities from more passive (Category 1 - email list and Category 2 - patient-clinician interaction) to more active (Category 3 - MS Patient Powered Research Network (PPRN) and Category 4 - MS for clinical research). A particular challenge is to engage more numerous and diverse demographic participation in MS patient research networks (MSPRN), such as iConquerMS and ARHMS - which involves patient data sharing (surveys and EHR) and blood samples for research.

Objectives: We address the following questions: *What are individuals' views of MS patient networks? What encourages or discourages them to participate in these networks? What are the factors to increase underrepresented participation?* Our aims are to: Understand factors influencing participation in MS patient networks and identify the factors most likely to impact active patient participation in MS research with underrepresented communities.

Methods: Using the framework of the Learning Health System (LHS) we identify values affecting MSPRN participation (Survey) to research MSPRN participation and non-participation (Interview and 2nd Survey). We will conduct predictive modeling of factors in participation and nonparticipation. We use a culturally aware MS research model to identify predictive factors affecting diverse and inclusive participation and nonparticipation in MSPRNs. We aim to determine predictive factors for diverse participation in Category 3 and 4 MSPRNs.

Results: Data from a recent MS patient online survey of 2,611 responses demonstrated that 7.2% of the patient respondents were Hispanic. Among Hispanic participants, 35.6% had participated in a research study. Among the total participants of the online survey, 9.3% were African American/Black, and within the group, 37.3% had participated in a research study. Further results on participant factors will be forthcoming at the poster session.

Conclusion: The long-term impact of this research is to provide new approaches to increasing underrepresented patient participation in the MS research community. Ideally this study will contribute to inclusive evidence-based practices to develop new innovations benefiting all patients with MS.

P146

Low Dose Naltrexone in Multiple Sclerosis: Web-Presence Versus Scientific Evidence

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Background: Naltrexone is an oral semi-synthetic opiate receptor antagonist, licensed in a 50–100 mg daily dose for the treatment of heroin and alcohol addiction. Preclinical studies identified several mechanisms by which low dose naltrexone (LDN), less than 5 mg daily, can benefit patients living with multiple sclerosis (MS). Those included the ability of LDN to upregulate opioid receptors, increase endogenous opiate production, prevent oxidative damage and glutamate-mediated cytotoxicity to neurons/oligodendrocytes and inhibit T-cell/glia replication

Objectives: To compare readily available web information for patients on the use of LDN in MS to published research on the subject

Methods: We searched Google for terms such as "low dose naltrexone," and "multiple sclerosis." We searched PubMed for: "naltrexone," "low dose naltrexone," "naloxone," "experimental autoimmune encephalomyelitis" and "Multiple Sclerosis." We navigated relevant websites and reviewed the scientific literature

Results: We screened a total of 24 articles and included 18 publications (7 clinical investigations, 6 preclinical studies, 1 medical hypothesis, 4 commentaries). We excluded 6 studies irrelevant to MS. We found 3 clinical trials for LDN in MS patients which suffered limitations, and none provided conclusive evidence on the subject. However, all studies agreed on the safety of LDN. Google searches for the term "naltrexone and MS" yielded about 413,000 results and for "low dose naltrexone and multiple sclerosis" yielded about 184,000 results. Numerous patient-oriented websites discussed LDN and MS with phrases used such as "Overcoming Multiple Sclerosis" or "A Wonder Drug that Eases Multiple Sclerosis Side Effects," among other claims. A limited number of websites, such as the National Multiple Sclerosis Society, provided evidence-based information for patients and caregivers on the subject and acknowledged the limitations of the scientific evidence

Conclusion: It remains challenging for health care providers to answer various patient queries regarding potential effects of LDN in MS due to the inadequacy of clinical evidence. We identified a gap between readily available information off the internet for MS patients and actual scientific evidence. Preclinical investigations showed promising effects on inflammation and disease modification. Further studies are needed to determine the effect of LDN as an add-on therapy on quality of life measures such as pain, energy, social, cognitive and sexual functions in patients living with MS

Microbiome

P147

Examination of the Intestinal Microbiome in Early Stage of Multiple Sclerosis in a Prospective Cohort of High-Risk Family Members

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Background: Intestinal microbiome is a novel arena to investigate in relation to MS onset.

Objectives: To examine the baseline intestinal microbiome profiles in asymptomatic first-degree family members at high and low risk for MS susceptibility.

Methods: In a prospective cohort study of MS first-degree family members, we previously assessed each participant's risk for MS using a weighted score ($GERS_{MS}$) that integrates an individual's genetic burden with environmental exposures associated with MS susceptibility. We collected baseline fecal samples from 93 participants across the MS risk distribution ($GERS_{MS}$) as well as healthy cohabitants. We performed shotgun whole metagenome sequencing using the Illumina HiSeq 2500 platform at a median sequencing depth of 2Gb per sample, obtained species-level classification based on marker genes using MetaPhlAn, and

transformed the proportions of bacterial counts using arcsine square root. We used linear modeling to discover association of bacterial abundance and host meta-data: age, gender, race, ethnicity, body mass index (BMI), geographic location (i.e., state), and $GERS_{MS}$.

Results: Based on the diversity of bacterial species identified across samples and the concordance with previously described microbiome correlations, we have generated high-quality intestinal metagenomics data from people at risk for MS. For instance, we observed the expected positive correlation between BMI and *Ruminococcus torques* abundance (t-statistic=2.84, *P*=0.006), which has been reported in microbiome studies of human obesity. Of relevance, $GERS_{MS}$ is inversely correlated with the abundance of Lachnospiraceae family (t-statistic=-2.51, *P*=0.014), which includes the *Roseburia* and *Butyrivibrio* genera that produce short-chain fatty acids (SCFA). SCFAs promote the generation of anti-inflammatory regulatory T cells and provide metabolic benefits through the gut-brain axis. Additional analyses of the metagenomics data (e.g., alignment of sequencing reads to reference metagenomes, de novo discovery of bacterial genes, and measure of alpha diversity based on gene abundance rather than species abundance) will be presented.

Conclusion: In this examination of the intestinal microbiome in asymptomatic people at risk for MS, we found loss of abundance in bacteria organisms that are implicated in promoting peripheral immune tolerance among individuals at higher risk for MS, consistent with prior human microbiome studies in MS and other autoimmune diseases.

Neuro - Ophthalmology

P148

Isolated and Progressive Myelin Oligodendrocyte Glycoprotein (MOG-IgG) Mediated Optic Neuritis Masquerading As Malignant Optic Nerve Glioma

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Background: Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been recognized as a cause of optic neuritis (ON), distinct from multiple sclerosis and aquaporin-4 IgG (AQP4-IgG). MOG-IgG optic neuritis often presents bilaterally and involves the optic chiasm. Malignant optic nerve gliomas typically present with features of optic neuritis, along with progressive visual deterioration over five to six weeks and death in less than a year.

Objectives: The purpose of this study is to present a case of MOG-IgG ON initially concerning for malignant optic nerve glioma.

Methods: Case report

Results: A 34 year-old, Caucasian, previously healthy male presented with a 3 week history of progressive vision loss bilaterally. His initial symptoms were pain behind the right eye that worsened with eye movements and loss of temporal vision in the right eye. One week later he developed temporal vision loss in the left eye. On the initial exam his visual acuity was count fingers at one foot in the right eye and 20/80 in the left. There was no afferent pupillary defect and he had reduced color vision in both eyes. He had grade 1 optic disc edema with a nasal disc hemorrhage on the right and trace optic disc edema on the left. MRI orbits showed enlargement and enhancement of the optic chiasm and prechiasmatic optic nerves bilaterally, compatible with optic glioma. Diagnostic studies included normal serum inflammatory markers, negative CV2 antibody, and negative aquaporin-4 antibody. Cerebrospinal fluid studies were significant for a mild pleocytosis of 9/uL, negative cytology, normal IgG index, and absent oligoclonal bands. MRI cervical spine showed no abnormalities. Radiation treatment of the presumed optic glioma was considered, but not performed. He was treated empirically with steroids and prednisone taper. Repeat MRI one week later showed a decrease in the size and enhancement of the optic chiasm lesion. His visual acuity improved to 20/200 in the right and 20/25 in the left. Several days later MOG-IgG returned positive and treatment with mycophenolate mofetil was initiated.

Conclusion: Malignant optic nerve gliomas may present with features of optic neuritis, including optic nerve head swelling. It is important to recognize that MOG-IgG ON is known to present with swelling of the optic nerves, longitudinally extensive optic nerve lesions, and involvement of the optic chiasm. Given the drastically different prognosis and treatment, it is important to consider MOG-IgG ON along with malignant optic nerve glioma.

Neuromyelitis Optica

P149

Relationship between Physical Activity Level, Fatigue and Depression in Paediatric Neuomyelitis Optica Spectrum Disorder and Recurrent Optic Neuritis

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Background: Moderate-to-vigorous physical activity (MVPA) has been associated with better psychosocial outcomes in pediatric multiple sclerosis, but has not been evaluated in youth with other recurrent demyelinating diseases such as neuromyelitis optica spectrum disorder (NMOSD) and recurrent optic neuritis (RON).

Objectives: To describe MVPA as it relates to fatigue and depression in children with NMOSD/RON as compared with healthy controls. We hypothesized that youth with NMOSD/RON would report higher depression and fatigue and lower MVPA levels compared to sex and age matched healthy controls.

Methods: This cross-sectional study included consecutive youth (≤18 yrs.) with NMOSD or RON who completed the Pediatric Quality of Life Multidimensional Fatigue scale, Center for Epidemiological Studies Depression Scale, and the Godin Leisure

Time Exercise Questionnaire at a Neuroinflammatory Clinic (Hospital for Sick Children, Toronto, ON). Previously collected healthy control data were used for comparison. NMOSD/RON outcomes were examined by antibody profile.
Results: The sample included 30 NMOSD/RON patients (77% female, mean age 13.0 years, 24 NMOSD/6 RON, avg. EDSS=1.0) and 30 healthy controls (77% female, mean age 13.6 years.). MVPA in the NMOSD/RON group was similar to healthy controls (49.3 and 53.6 METs/week, respectively). Total fatigue (mean=69.6 and 70.6, respectively) and depression (mean=12.7 and 12.0, respectively) were similar between groups. Higher MVPA was associated with less total fatigue (r=0.420, p=0.026) in the NMOSD/RON group. AQP-4-ab positive youth (n=6) reported lower MVPA levels (mean=29.0 METs/week) and higher fatigue levels (mean=59.3) than MOG-ab positive (n=16, 56.8 METs/week, 72.7) or ab negative (n=8, 51.5 METs/week, 71.1) youth (NS p=0.129, p=0.338).
Conclusion: Youth with NMOSD/RON report similar fatigue, depression and MVPA compared with healthy controls. AQP-4-ab positivity may confer increased risk for low MVPA, but larger studies are needed to confirm this finding. MVPA and total fatigue correlated moderately in youth with disease, suggesting MVPA may contribute to reduced fatigue in this group.

P150

Obstetric Outcomes in Mexican Patients with Nmo-IgG (+) Nmo

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Background: The influence of neuromyelitis optica (NMO) in pregnancy is still unclear. A retrospective study found that, in women positive for NMO-IgG (NMO-IgG [+]), 13% of pregnancies ended in spontaneous abortion. There are potential ethnic influences in NMO. The obstetric outcome of Mexican patients with NMO-IgG (+) NMO is currently unknown.
Objectives: To describe the obstetric history of Mexican patients with NMO-IgG (+) NMO.
Methods: We identified patients with diagnosis of NMO-IgG (+) NMO from the database of the clinic of demyelinating diseases. These patients were interviewed by telephone about their obstetric history.
Results: Out of a total of 39 female patients, 28 (71%) were successfully contacted and completed the survey. Of these, 18 (64%) reported at least one previous pregnancy. At the time of the survey, the mean age of these patients was 45.8±10.5 years. Mean age at which they presented their first clinical manifestation was 37.1±9.3 years, in 1 patient this information was missing. Mean age at diagnosis was 38.3±9.1 years, in 2 patients this information was missing. In total, 45 pregnancies were reported: 39 (86%) of them occurred ≥3 years before the first manifestation of NMO, 1 occurred ≥1 years before the first manifestation, and 1 occurred after the first manifestation. The temporality of the rest is unknown. Of all pregnancies, 10 (22%) were pregnancy losses: 4 were classified as miscarriages and 2 as stillbirths. The temporality of the rest is unknown. Of all pregnancy losses, 8 occurred ≥3 years before the diagnosis of NMO, 1 occurred after the first manifestation of NMO. The temporality of the remaining loss is unknown. All pregnancy losses occurred in 7 patients. Only one patient reported a history of preeclampsia, and it occurred ≥3 years before the first manifestation of NMO. Another patient reported a death associated with premature birth, which happened ≥3 years before the first manifestation of NMO. This patient also reported an intrapartum death associated with breech delivery at term, which happened ≥3 years before the first manifestation of NMO.
Conclusion: More than one-third (38%) of the patients with previous pregnancies reported at least one pregnancy loss, most of these occurred ≥3 years before the diagnosis of NMO.

P151

Vitamin D Supplementation May Have Therapeutic Effects in Neuromyelitis Optica Spectrum Disorder

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Background: Neuromyelitis optica Spectrum Disorder (NMOSD) is an inflammatory disorder of the central nervous system that presents typically with relapses of optic neuritis or transverse myelitis, in which IgG autoantibodies against aquaporin-4 water channel protein probably play a pathogenic role. NMOSD is a progressive disease that increases disability. Previous studies were shown that vitamin D play an important role in autoimmune and inflammatory diseases and patients with NMOSD has vitamin D deficiency and there was negative correlation with serum vitamin D and Expanded Disability Status Scale (EDSS) in NMOSD.
Objectives: The aim of this study is to investigate the effects of vitamin D supplementation on IgG-NMO and disability in patients with NMOSD.
Methods: 29 patients with newly diagnosed of NMOSD were involved to present randomized clinical trial study. Serum 25(OH) vitamin D, IgG-NMO, EDSS, Fatigue Scale, dietary vitamin D intake and Sun Exposure Status were assessed in patients with NMOSD. Then, 15 patients that randomized selected, consumed 50000 International Unit (IU) of vitamin D3 per week for 15 weeks. Other 14 patients received placebo. In finally, were assessed serum 25(OH) vitamin D, IgG-NMO, EDSS and Fatigue Scale after intervention and investigated changes after intervention. This present clinical trial study was approved by Iranian Registry of Clinical Trials.
Results: Mean ± SD of vitamin D intake, sun exposure scale, serum 25(OH) vitamin D3 levels, IgG-NMO titration, EDSS and

fatigue scale no had significant difference between intervention and placebo groups before intervention. We observed significant decreases in EDSS and fatigue scale after intervention in intervention group. (EDSS before= 4.91±1.85, after= 3.54±0.97, p=<0.001 – Fatigue Scale before= 50.47±4.21, after= 38.57±3.12, p=<0.001). Also IgG-NMO titration decreased after supplementation but this was marginally significant. (p=0.069). Too, we observed a significant negative correlation between serum vitamin D and EDSS (r=-0.717, p=0.004), fatigue scale (r=-0.410, p=0.027) and IgG-NMO (r=-0.564, p=0.001) in all participants after intervention. Age, gender, disease duration and latitude were not confounder variables.

Conclusion: Physiological variation in vitamin D may exert a major impact on autoimmune and inflammatory disease. We observed that vitamin D supplementation can decrease IgG-NMO, EDSS and fatigue scale in participants with NMOSD and vitamin D supplementation may have therapeutic effects in NMOSD.

P152

Salt Intake and Disability in Neuromyelitis Optica Spectrum Disorder

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Background: Neuromyelitis optica Spectrum Disorder (NMOSD) is an inflammatory disorder of the central nervous system (CNS) that presents typically with relapses of optic neuritis or transverse myelitis, in which IgG autoantibodies against aquaporin-4 water channel protein probably play a pathogenic role and IgG-NMO levels had correlation with disability in this patients. Previous studies demonstrated high salt intake may be associated with pro-inflammatory changes in the immune response, and increased clinical and magnetic resonance imaging (MRI) activity and aggravates T helper cell (Th) 17 responses and neuroinflammation in adults with multiple sclerosis.

Objectives: The aim of this study was to examine the association between salt intake and disability in patients with NMOSD.

Methods: 68 patients with diagnosed NMOSD with MRI assessment of brain and spinal cord, clinical symptoms and IgG-NMO test were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran include from present cross-sectional study. A 168-item semi-quantitative food frequency questionnaire (FFQ) was used for assessment of dietary intakes of salt. Medical history questionnaire, Expanded Disability Status Scale (EDSS) and Fatigue questionnaire were recorded and IgG-NMO was assessed in all participants.

Results: Mean ± SD of salt intake, EDSS and fatigue scale in IgG-NMO positive group was significant higher than IgG-NMO negative group. There was a positive significant correlation between dietary intakes of salt with EDSS (r=0.418, p=0.023), salt and fatigue scale (r=0.323, p=0.044) in IgG-NMO positive group. Correlation between dietary intakes of salt and EDSS in IgG-NMO negative group was marginally positive significant (r=0.265, p=0.059) and was a positive significant correlation of dietary intake of salt with EDSS in all participants (r=0.341, p=0.041).

Conclusion: This present study is a first report about dietary intake of salt and disability in neuromyelitis optica spectrum disorder. Our study demonstrated that there is a positive significant correlation between salt intake and EDSS in patients with NMOSD. In addition, dietary intakes of salt can increase fatigue status in NMOSD patients with positive IgG-NMO. These data may further fuel our understanding on the dietary impact on different immune cell subsets in autoimmune diseases. Further studies with larger sample sizes and other population needed to prove this correlation.

P153

Severe Optic Neuritis: 72 Cases from Turkey

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Background: Severe optic neuritis (ON), also considered as atypical ON, is characterized by agressive course, lack of response to steroids, and recurrence during steroid tapering.

Objectives: Our aim was to evaluate the clinical features, laboratory findings, treatment modalities and outcomes of the patients with severe ON from Turkey, seen over the last 10 years.

Methods: Clinical files of 6 university hospitals were evaluated retrospectively to define cases with severe ON. Patients who show clinical involvement of other sites of the nervous system were excluded.

Results: There were 72 patients, aged 16 to 65 years (mean 38 ± 12): 52 (72%) were female, 18 had bilateral involvement, 37 (51%) had only one attack, 35 (49%) had 2 or more attacks. Anti-aquaporin-4 antibody was positive in only 4/72. Twelve patients were tested for MOG antibodies, and one was positive. All the patients received IV methylprednisolone (IVMP) for the acute attack, 9 had monthly IVMP, 8 had IVIg, and 20 patients who did not respond to corticosteroids had plasma exchange. Of the 35 with recurrence had 29 azathioprine, 2 had rituximab, 2 had methotrexate, and 2 had mycophenolate mofetil. Final outcome: 23/72 patients had no recovery of vision, 17 had full recovery, the other 22 had partial recovery.

Conclusion: It is important to recognize and treat severe ON early since prognosis can be poor, and treatment could lead to

significant improvement. Plasma exchange should be considered in patients unresponsive to corticosteroids. IVIg could be an option in those patients who cannot receive plasma exchange.

P154

Lumbosacral Radiculomyelopathy- a Rare Presentation in an Established Case of Neuromyelitis Optica Spectrum Disorder

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Background: Lumbosacral Radiculomyelopathy is an uncommon presentation of Neuromyelitis Optica (NMO). It has been reported in 2 patients with NMO Spectrum Disorders (NMOSD). We present a patient with diagnosed NMOSD and lumbosacral Radiculomyelopathy.
Objectives: Classically NMO tends to spare the conus. One report suggests that lesions in the conus medullaris were seen in 1.58% in NMOSD, and 9.6% in anti-AQP4 antibody positive cases. In myelin oligodendrocyte glycoprotein (MOG) antibody-positive NMO/NMOSD, conus involvement on spinal magnetic resonance imaging is 75%, whereas in AQP4-Ab-positive cases it is only seen in 17%.
Methods: Case: A 21-year-old female presented with Area Postrema syndrome; following imaging and a positive serum anti-aquaporin 4 antibody, she was diagnosed with Neuromyelitis optica spectrum disorder (NMOSD). She was started on disease modifying agent Rituximab which was administered at 6 monthly intervals or if her CD19 counts increased whichever came earlier.
She presented to clinic with urinary incontinence and saddle anesthesia just after having missed her Rituximab infusion at the 6-month mark. The MRI spine demonstrated a lesion in the conus medullaris and contrast enhancement of the nerve roots in the cauda equina. Work up for other etiologies was negative.
Results: The patient had an NMO flare constituting Myeloradiculopathy, a rare presentation of NMOSD. She received plasmapharesis with near complete resolution of her symptoms. She has had no recurrence of symptoms since restarting on Rituximab infusions.
Conclusion: Lumbosacral Myeloradiculopathy is an uncommon presentation of NMO /NMOSD. There are only 2 other cases reported in the literature.
If lumbosacral myeloradiculopathy is the initial presentation, it is imperative to check the antiaquaporin-4 antibody.
If anti-aquaporin-4 antibody is negative, it is necessary to check for anti-myelin oligodendrocyte antibody as the incidence of lumbosacral myeloradiculopathy is higher in anti-MOG positive patients.
Conus lesions are overlooked as neuroimaging obtained typically in suspected NMO includes only the cervical and thoracic spinal cord looking for LETMs. In addition, lower motor neuron lesions are typically not suspected in NMOSD. In patients with diagnosed NMO/NMOSD, it is important to suspect conus / cauda lesions especially if presentation includes bowel, bladder, or sexual dysfunction – leading to imaging of the lumbosacral spinal cord.

P155

Neuromyelitis Optica Relapses 17 Years Apart after Empiric Treatment for Neurosarcoidosis

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Background: Neuromyelitis optica (NMO) is an uncommon demyelinating disorder, preferentially affecting the spine and optic nerves. It shares overlapping features with multiple sclerosis, neurosarcoidosis and other autoimmune conditions. However, the discovery of aquaporin-4 antibodies (AQP4-Abs), greater MRI resolution, and the establishment of criteria have tremendously improved diagnostic accuracy.
Objectives: Highlight the difficulty in diagnosing NMO, especially before the discovery of serum biomarkers. Discuss similarities to other neuroinflammatory conditions
Methods: obtaining images and serum lab studies during hospitalizations. Obtaining past medical records.
Results: We present a patient with acute longitudinally-extending transverse myelitis, found to be seropositive for AQP4-Abs. 17 years prior, gadolinium-enhancing lesions in the spine and brainstem were attributed to possible neurosarcoidosis, and she received immunomodulatory treatment. To date, there is no evidence of optic neuritis.
Conclusion: This case adds to the growing body of evidence that NMO is characterized by frequent misdiagnosis, and is highly variable in both disease course and areas of demyelination. Moreover, treatment regimens between neuroimmunological conditions are not identical, and therefore, the correct diagnosis is imperative.

P156

Diet and Neuromyelitis Optica Spectrum Disorder; Association between Food Group Intakes and Disability in Patients with Nmosd

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Background: Neuromyelitis optica Spectrum Disease (NMOSD) is an inflammatory disorder of the central nervous system (CNS) that presents typically with relapses of optic neuritis or transverse myelitis, in which IgG autoantibodies against aquaporin-4 water channel protein probably play a pathogenic role and IgG-NMO levels had correlation with disability in this patients. Assessment of dietary intakes of food groups is an approach that has been used to evaluate diet-disease and diet-disability association.
Objectives: To investigate of Association between food group intakes and disability in patients with NMOSD.
Methods: 68 patients with diagnosed NMOSD with MRI assessment of brain and spinal cord, clinical symptoms and IgG-NMO

test were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran include from present cross-sectional study. A 168-item semi-quantitative food frequency questionnaire (FFQ) was used for assessment of dietary intakes of food groups. Medical history questionnaire, Expanded Disability Status Scale (EDSS) and Fatigue questionnaire record from all participants.

Results: Mean ± SD of EDSS and fatigue scale in IgG-NMO positive group was significant higher than IgG-NMO negative group. There was a negative significant correlation between intakes of whole grain (r=-0.312, p=0.031), fish (r=-0.452, p=0.018) and fresh fruits (r=-0.365, p=0.026) with EDSS in all participants and intakes of fresh vegetables (r=-0.394, p=0.038) and EDSS in IgG-NMO negative subgroup. In addition, there was a negative significant correlation between intakes fresh vegetables (r=-0.302, p=0.034) and fresh fruits (r=-0.372, p=0.023) with fatigue scale in all participants. Correlation between red and processed meats with EDSS (r=0.512, p=0.002) and fatigue scale (r=0.439, p=0.020) was significantly positive in all participants. Although correlation between dietary intakes of dairy and vegetable oil with EDSS and fatigue scale in all participants and subgroups were negative, but was not significant.

Conclusion: Our study demonstrated that there is a positive significant correlation between intakes of red and processed meat with EDSS and fatigue scale in all participants. In addition, dietary intakes of whole grain, fish and fresh fruits can decrease EDSS in all patients with NMOSD. This is first report of dietary intakes of food groups in NMOSD patients. Further studies with larger sample sizes and other population needed to prove this correlation.

P157

Rituximab Therapy during Course of Pregnancy in Neuromyelitis Optica: Case Report

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Background: Neuromyelitis optica (NMO) is a rare demyelinating autoimmune disorder of central nervous system where increased relapse rates have been reported during pregnancy and postpartum stages. Immunosuppressive therapy such as rituximab (RTX), an anti CD20 agent, is commonly used to control the disease.

Objectives: However, little is known about NMO and pregnancy treatment management.

Methods: We present a 35 year-old Japanese-American female diagnosed with NMO April 2015 after presenting with transverse myelitis followed by bilateral optic neuritis shortly after delivery of her first child. Brain/spinal cord MRI were consistent with typical NMO-lesions in thoracic segment at T2-T4 and normal brain MRI, complete laboratory work-up showed anti-NMO antibody titers >1:160 and mimickers and other autoimmune diseases were ruled out. RTX was started and continued at 6 month intervals. After one year on RTX she was without evidence of disease activity, the B cell count remained <1% and the NMO antibody titers were 1:14. She conceives in December 2016 and has been maintained on RTX until delivery (Sept 2017) due to high postpartum risk of relapse and NMO titer rising during first trimester. Currently, she remains stable in regard to her NMO and her adequate materno-fetal well-being

Results: RTX during pregnancy is controversial due to scarce data in the literature. Previous case reports in NMO patients have shown that RTX might be safe and effective during the pregnancy, nevertheless there are very few cases published and to date there is no published case of RTX during the entire course of pregnancy with associated NMO titers and B cell counts

Conclusion: Herein, we describe a patient with NMO who remained on RTX therapy during her complete pregnancy course with good outcome suggesting that RTX in NMO patients during pregnancy may be safe and useful for the management of these high-risk patients. Long term effects to the mother and newborn remain to be looked into.

P158

Multiphasic Disseminated Encephalomyelitis in an Adult with Serological Markers of Autoimmunity: A Co-Existing Entity or a Nmo Spectrum Disorder

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Background: Multiphasic Disseminated Encephalomyelitis (MDEM) has been defined as two distinct episodes of acute disseminated encephalomyelitis (ADEM), separated by three months apart. The recurrent episode may have new or a re-emergence of prior neurological symptoms, signs and MRI findings. While rare in adults, possible auto-immune mechanisms of the disease with existing antibodies, including the recently described myelin oligodendrocyte protein antibody (anti MOG), have been proposed.

Objectives: We discuss a case of MDEM in an adult with co-existing positive SS-A and anti-thyroglobulin antibodies.

Methods: Case report

Results: A 37-year-old Hispanic female presented with 2 weeks of progressive vertigo, nausea, vomiting and diplopia. Two weeks prior to the symptom onset, she reported nonspecific gastrointestinal and upper respiratory tract symptoms which resolved spontaneously. Her exam demonstrated nystagmus, right lateral rectus and facial palsy along with dysesthesia of the right face. There was no dysmetria or ataxia. MRI of the brain showed demyelination of the left cerebellar vermis and right medial pons. She was treated with intravenous methylprednisolone with near total resolution of her symptoms. The etiology remained undetermined despite the initial work up including lumbar puncture (LP). One year later, she presented with similar complaints with new onset significant dysmetria and ataxia. Repeat MRI brain showed prior lesions without any contrast enhancement. Repeat LP once again revealed lymphocytic pleocytosis with normal protein, glucose and 2 oligoclonal bands. Neuromyelitis optica (NMO) antibody, cerebral angiogram and infectious work up were negative. However, SS-A antibody and anti-thyroglobulin antibodies were positive. Though she did not fit the complete criteria for Sjogren's syndrome (SS), she did report dry eyes, swollen glands, and trouble swallowing. She had also begun to show signs of hypothyroidism. There was improvement in her ataxia after another round of intravenous steroids and she was discharged home.

Conclusion: The question lies in whether our case was a co-existing entity of a multiple autoimmune syndrome (MAS), or a part of

the NMO spectrum disease. There have been several cases reported on co-existing SS and Neuromyelitis Optica. However on our literature review, no case of MDEM with positive SS-A and anti-thyroglobulin antibodies has been clearly reported. This leads us to the common belief of co-existing autoimmune diseases in a patient with genetic predisposition.

P159

Comparison of Fats/Oils Intake and Disability in Patients with MS and Patients with Nmosd

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Background: Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) are two neurodegenerative, autoimmune and inflammatory diseases that involve central nervous system (CNS). Assessment of dietary intakes of fats is an approach that has been used to evaluate diet-disease and diet-disability association.
Objectives: To investigate of fats/oils intake and disability in patients with MS and patients with NMOSD.
Methods: 126 patients with diagnosed MS (84 RRMS, 21 PPMS and 21 SPMS) and 68 patients with diagnosed NMOSD with MRI assessment of brain and spinal cord were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran include from present case control study. A 168-item semi-quantitative food frequency questionnaire was used for assessment of dietary intakes of fatty acids. Medical history questionnaire, Expanded Disability Status Scale (EDSS) and Fatigue questionnaire record from all participants.
Results: Mean ± SD of EDSS, fatigue scale, and dietary intakes of saturated fatty acids (SFAs) in patients with MS were lower than NMOSD patients, but were not significant. Total fat, Mono Unsaturated fatty acids (MUFAs) and Poly Unsaturated Fatty Acids (PUFAs) intakes in MS patients were higher than patients with NMOSD without any significant differences. There was a negative significant correlation between dietary intakes of total fats (r=-0.975, p=0.025) and PUFAs (r=-0.986, p=0.014) with EDSS, total fats (r=-0.995, p=0.005) and MUFAs (r=-0.964, p=0.036) with fatigue Scale in patients with MS. In addition, there were negative significant correlation between dietary intakes of PUFAs (r=-1.054, p=0.001) with EDSS, total fats (r=-0.951, p=0.046) and PUFAs (r=-0.991, p=0.009) with fatigue Scale in patients with NMOSD. There were positive significant correlation between SFAs with EDSS (r=0.998, p=0.003) in patients with MS and positive significant correlation between SFAs with EDSS (r=1.125, p=<0.001) and fatigue scale (r=1.218, p=<0.001) in patients with NMOSD.
Conclusion: Our study demonstrated that there is a positive significant correlation between intakes of SFAs with EDSS in patients with MS and patients with NMOSD. In addition, dietary intakes of PUFAs can decreases EDSS in all patients with MS or NMOSD and decreases fatigue scale in NMOSD patients. Dietary intakes of fats and types of fatty acids may impress on disability in MS and NMOSD.

Neuroprotection and Neuroregeneration

P160

Ozanimod (RPC1063) Potentially Confers Neuroprotective Benefit through Modulation of S1P1R on Astrocytes

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Background: Ozanimod (RPC1063) is an oral, once-daily immunomodulator that selectively targets $S1P_{1R}$ and $S1P_{5R}$ and has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS). Ozanimod down-regulates $S1P_{1R}$ and retains autoreactive lymphocytes in peripheral lymphoid tissues. Furthermore, ozanimod penetrates the blood-brain barrier, potentially modulating $S1P_{1R}$ and $S1P_{5R}$ on neural cells, which may confer neuroprotective benefits.
Objectives: Neuroprotection by ozanimod was investigated using animal models of demyelination and assessed with histological and functional readouts. Plasma neurofilament light chain (NF-L) was assessed as a potential biomarker of neurological damage. The direct activity of ozanimod on primary rodent astrocytes *in vitro* was explored for their potential role in neuroprotection.
Methods: To study neuroprotection *in vivo*, C57BL/6 mice were treated with cuprizone to demyelinate axons in the brain and concurrently treated with ozanimod (or an ozanimod surrogate RP-101074) for 6 weeks. Neuroprotection was assessed by axonal pathology in the corpus callosum (SMI-32 staining), functional assessment through kinematic gait analysis and the presence of plasma NF-L. Direct activity of ozanimod was examined on activated primary rodent astrocytes *in vitro*.
Results: Ozanimod and its surrogate RP-101074 are neuroprotective in the cuprizone-induced mouse model demonstrating a reduction in swollen and transected axons and improved functional assessment through kinematic gait analysis. Plasma NF-L was significantly elevated in cuprizone-treated mice over naïve controls and ozanimod or RP-101074 treatment significantly reduced elevated plasma NF-L. Ozanimod directly effects primary rodent astrocytes through activation of ERK and AKT signaling pathways and attenuated the release of pro-inflammatory cytokines, including IL-1β and TNFα, induced by LPS activation.
Conclusion: Ozanimod is potentially neuroprotective through direct CNS effects, as demonstrated by reduced axonal breaks and improved functional capabilities following cuprizone-induced demyelination. CNS tissue preservation of neurons by ozanimod

may be mediated in part by its direct activity on astrocytes, attenuating their inflammatory response to a perturbed environment and thus maintaining a more optimal milieu for neuronal survival. Furthermore, plasma NF-L served as a biomarker indicative of demyelination and was reduced upon ozanimod or RP-101074 treatment.

Neuropsychology and Cognition

P161

Screening for Cognitive Impairment and Depression in MS Patients: Current Practices, Perceptions, and Barriers in Selected United States MS Clinics

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Background: Leading international MS organizations recommend using validated tools to screen patients for cognitive impairment and depression. Studies are needed to assess neurologists' current screening practices, perceptions, and barriers.
Objectives: Assess (1) the extent to which validated tools are used to screen MS patients for cognitive impairment and clinical depression; (2) neurologists' perceptions of the clinical value of formal screening; and (3) barriers to using screening tools.
Methods: (1) Reviews of electronic medical records (EMRs) of MS patients (n = 300) in 2 large specialty clinics in the Southeastern U.S.; and (2) surveys administered to national leaders in MS research and treatment who practice in 10 academic medical centers across the U.S. (n = 11).
Results: EMR reviews indicated low rates of documented use of validated tools for assessing cognitive impairment (2%) and depression (3%), whereas a substantial proportion of patients were documented to have these disorders (36% and 44%, respectively) based on informal assessment. Rates of documented screening were similar across the 2 MS clinics. Referrals to neuropsychologists were made for 26% of patients with documented cognitive impairment. Referrals to psychiatrists were made for 64% of patients with documented depression. Among survey respondents, 45% and 36% reported using validated tools to assess cognitive impairment and depression, respectively. Specific screening tools varied across the 10 MS clinics. Respondents who reported not using validated tools cited lack of time to administer them and analyze the results, lack of evidence supporting their use, lack of compensation by insurers, and preference for assessing cognition and mood through loosely structured patient interviews.
Conclusion: In 2 U.S. specialty clinics for MS, only a small proportion of patient EMRs indicated documented use of validated tools for assessing cognitive impairment and depression. National leaders in MS research and treatment reported disparate practices and perceptions regarding the use and value of validated tools versus loosely structured patient interviews. Given the high prevalence of cognitive impairment and depression among MS patients and the negative impact of these comorbidities on quality of life, these findings have implications for addressing variations in the uptake of international recommendations to screen patients for cognitive impairment and clinical depression.

P162

Initiation of natalizumab is associated with improvements in cognitive function as measured by NeuroTrax

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Background: Cognitive impairment affects the majority of MS patients and is not commonly recognized or monitored. NeuroTrax (NT) is a computerized cognitive assessment administered in an office setting in ~45 minutes. NT provides an objective cognitive profile measure with a global cognitive score (GCS) and 7 individual domain scores (memory, executive function, attention, information processing speed, motor function, verbal function, and visual-spatial processing). A historical publication has described the use of NT in a MS cohort (N=1500) with ≤30 years of disease duration (Achiron, et al. PLoS One 2013;8:e71058). This cohort exhibited poorer cognitive performance than healthy subjects, especially in the executive function and information processing speed domains.
Objectives: To assess cognitive function as measured by NT in MS patients treated with natalizumab for ≥2 years.
Methods: This retrospective observational study included US patients aged 18–70 years with MS who had ≥2 cognitive test dates >10 months apart in the course of routine clinical care while on 300 mg intravenous natalizumab every 4 weeks for ≥2 years. Chart information was retrospectively reviewed to examine NT data assessed at baseline and yearly thereafter. This study measured change in GCS and the 7 individual domain scores from baseline to post >24 infusions of natalizumab. Change from baseline in global and individual domain scores at each year was analyzed using a generalized estimating equation model adjusted for baseline Expanded Disability Status Scale (EDSS) score and age.
Results: In the intent-to-treat population at baseline (N=52), 22 patients (42%) had disease duration of 0–5 years and 30 (58%) had disease duration ≥6 years. The mean (standard deviation [SD]) baseline EDSS score was 2.17 (1.74). Prior to initiating natalizumab, 12 patients (23%) were treatment naive and 40 (77%) were on another disease-modifying treatment (DMT). GCS score improved significantly from baseline (median [range]: 97.9 [63.2–115.4]; mean [SD]: 95.5 [12.9]) to year 2 (median [range]: 101.2 [61.4–116.3]; mean [SD]: 98.9 [13.2]; P=0.0029). Improvement was observed in all 7 cognitive domains from baseline through year 2.
Conclusion: Whether patients were treatment naive or previously treated with other DMTs, natalizumab significantly improved cognitive function, measured by NT global scores, over 2 years of treatment. Cognitive impairment can be reduced in MS patients with high-efficacy DMT use.

P163

Chronic Demyelination Induces Significant Changes in Hippocampal Structure and Function

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Background: Nearly 40 to 70% of multiple sclerosis (MS) patients experience cognitive impairment. The impact of inflammation on neuronal synaptic plasticity is well established in experimental autoimmune demyelination which showed deficits in hippocampal long-term potentiation (LTP) and cognitive memory tasks. These detrimental effects were thought to be due to activated microglia and inflammatory soluble mediators. However, the impact of chronic demyelination on hippocampal function, such as seen during progressive MS, is understudied.

Objectives: The role of hippocampus axon myelination/demyelination was investigated in the cuprizone (CPZ) diet model of MS. We hypothesize that chronic demyelination induces substantial changes in the function of hippocampal circuitry and synaptic transmission involved in learning and memory.

Methods: C57Bl/6 male mice were fed CPZ for 9 and 12 weeks. Immunohistochemistry, Western blotting, and Golgi Sholl analysis was performed. Additionally, functional synaptic electrophysiology was performed to assess CA3-CA1 glutamatergic transmission which is a widely studied example of synaptic plasticity. Synaptic transmission and plasticity was assessed by measuring field excitatory post-synaptic potentials (fEPSPs) from the dendrites of CA1 pyramidal cells in the stratum radiatum during LTP.

Results: Significant decreases in myelin protein staining, indicating demyelination, was observed in the hippocampus. Demyelination was accompanied with an increase in microglia and astrocytes. Significant alterations in synaptic proteins and a decrease in the dendritic arborizations of pyramidal neurons in the stratum radiatum was observed during demyelination. Chronic demyelination also increased stimulation intensity to reach fEPSP threshold and this increase in threshold persisted following remyelination. Interestingly, LTP in the CA3-CA1 circuitry was enhanced with 9 weeks of CPZ induced demyelination but 12 weeks CPZ and 3 weeks remyelination groups showed decreased evoked LTP amplitudes when compared to normal animals.

Conclusion: This data demonstrates that there are significant changes in myelin protein, inflammatory cells, and synaptic proteins that correlate with changes in long term potentiation in demyelinated animals. Understanding these complex changes in the hippocampal circuitry during demyelination will allow us to identify new therapeutic targets which may aid in treating this impairment in MS patients.

P164

Comparing Relationships between Demographic and MS Disease Factors, and Objective and Subjective Fatigue Metrics

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Background: Although much research has been devoted to characterizing fatigue in Multiple Sclerosis (MS), associations between fatigue, and demographic and disease factors have consistently eluded replication from one study to another. The present study examines the relationship between demographic and MS disease factors, and objective and subjective fatigue metrics. Findings may contribute to improved understanding of fatigue, as well as the identification of risk and potential protective factors.

Objectives: To determine the relationship between perceived and objective fatigue severity, and demographic and MS disease factors.

Methods: A retrospective chart review was conducted for patients with MS who had undergone neuropsychological testing. Perceived fatigue was measured using the Fatigue Severity Scale (FSS). Objective fatigue was measured using a previously validated method of modified scoring on the oral Symbol-Digit Modalities Test (SDMT) examining productivity change over the course of administration. Correlation and regression analyses were run between demographic and disease variables (i.e., age, race, gender, employment status, upper extremity function, lower extremity function, cognitive function, disease duration, depression) and objective and perceived fatigue severity.

Results: Combined, employment status and walking speed were significantly associated with objective cognitive fatigue. Gender, depression, disease duration, walking speed, and employment status were significantly associated with perceived fatigue. Objective and perceived fatigue were not significantly associated with each other.

Conclusion: Employment status and walking speed were significantly associated with both objective and perceived fatigue severity. Findings further our understanding of the relationship between objective and perceived fatigue, and their association with concomitant patient and disease factors.

P165

Cognitive Reserve and Cognitive Fatigue in MS

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Background: Fatigue is among the most prevalent and disabling centrally mediated symptoms in Multiple Sclerosis. The present study examines whether cognitive reserve is associated with objective and perceived fatigue severity in MS. Findings may contribute to improved understanding of cognitive fatigue, as well as the identification of risk and potential protective factors.

Objectives: To determine the relationship between cognitive reserve and fatigue in MS.

Methods: A retrospective chart review was conducted for patients with MS who had undergone neuropsychological testing. Cognitive reserve was measured via proxy of years of education and IQ. Perceived fatigue was measured using the Fatigue Severity Scale (FSS). Objective fatigue was measured using modified scoring on the oral Symbol-Digit Modalities Test (SDMT) examining productivity change over the course of administration. Correlation and regression analyses were run between reserve and fatigue variables.

Results: Neither educational attainment nor general intellectual functioning was significantly associated with objective cognitive fatigue or perceived fatigue severity.

Conclusion: Although current findings do not indicate the presence of a relationship between reserve and fatigue in MS, future study is warranted examining reserve and previously documented neurophysiological fatigue network activation patterns.

Pathogenesis - Immunology

P166

From T Cell Receptor to Antigen, Systems Approach to Discovering T Cell Antigen(s) in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

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Background: The role of T cells in Multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) is well established. However, long-standing quest in MS is to determine key T cell antigen(s), which drive the initial response.

Objectives: 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.

Methods: By using single cell paired TCR sequencing and mass spectrometry based cytometry (CyToF), we have analyzed both MS patients and in mice with EAE with respect to their overall immune system and the specific T cell types.

Results: We have analyzed the TCR repertoire of brain homing, activated CD4, CD8, and gd T cells from the blood of 18 recent onset untreated MS patients and found significant T cell clonal expansion which is not seen in healthy controls. Using yeast displayed peptide-HLA (p-HLA) library which contains ~ 5 X 10^8 peptide antigens, we have screened expanded CD4 TCRs from HLA-DR*1501 homozygous MS patients and found ligands which are not myelin. These peptides from yeast library, which resembles peptides from pathogen can activate CD4 T cell clones from MS patients. Similarly, in mice upon EAE induction there is co-mobilization and oligoclonal expansion of CD4, CD8, and gd T cells day 10 post-immunization both in blood and in the central nervous system (CNS) as determined by single cell paired TCR sequencing. Moreover, these expanded T cell clones are similar and shared between mice and tissue (blood and the CNS), indicating shared specificities. Many of the expanded CD4 and CD8 T cell clones do not respond to myelin indicating initiation of broad antigen specificities upon EAE immunization. We have determined antigen specificities for some of these expanded CD8 TCRs from EAE using yeast displayed mouse class I peptide-MHC (p-MHC) library. We show that CD8 specific peptides derived from yeast library can significantly abrogate MOG_{35-55} induced EAE. Moreover, CD8 T cells isolated from class I peptide immunized mice can suppress the proliferative capacity of MOG_{35-55} specific CD4 T cells *in vitro*.

Conclusion: Overall, our results suggest that there is coordinated and focused antigen specificity of the T cell responses involving all cell types, both in MS and in EAE. Moreover, we have developed a systematic approach in which one can employ single cell paired TCR sequencing and yeast displayed p-HLA/MHC to find disease triggers not in only MS but also in other neurological disorders.

P167

Characterization of MS Brain Lesions Using Flow Cytometry and Histochemistry

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Background: Detailed characterization of immune cells in brain lesions of persons living with multiple sclerosis (MS) is commonly performed by immunohistofluorescence (IHF). Since this technique only allows phenotyping of immune cells with 3-4 markers, the need for other techniques to further explore the profile of these infiltrating cells is high.

Objectives: To provide a method to assess both the phenotype of infiltrating immune cells (with flow cytometry) and the type of lesion (with histochemistry) within a single MS brain lesion.

Methods: MS brain tissue (n=1) with a short-postmortem delay is cut into slides. Demyelinated areas (lesions) or normal appearing tissue are cut out from grey and white matter (n=13). One third of the lesion/tissue piece is directly frozen for lesion characterization (pre-active, active, and chronic inactive lesions) by hematoxylin and eosin (H&E), luxol fast blue (LFB) and oil red O staining. The rest is processed for flow cytometric analysis. For this, each lesion is cut separately into very fine pieces and treated with Collagenase and DNase. Next, it is passed through a 100 μM and 70 μM membrane. The suspension is then loaded onto a 37% percoll for immune cells isolation. To further purify the cell suspension, red blood cells are removed by positive magnetic bead isolation. The obtained immune cells are then processed for flow cytometry.

Results: Preliminary results show that we can detect T cell subsets (CD3, CD4, CD8, CCR7, CD45RO), macrophages (CD14), dendritic cells (CD11c) and B cells subsets (CD19, CD27, CD138, IgD, IgA) in the separate lesions by flow cytometry. Furthermore, we could characterize their adhesion molecule profile (MCAM, α8 integrin, ALCAM, CD6, ICAM). This information is then combined with the data obtained from histochemistry to see in what lesion type these cells are present. Furthermore, the high CD4/CD8 T cells ratio typical for human peripheral blood is inverted in most of the lesions. In addition, the fraction of cells expressing cell adhesion molecules was overall higher in the lesions compared to the periphery. Interestingly, this seems to be the highest in pre-active lesions (n=2).

Conclusion: Our technique allows to characterize immune cells found in one specific MS lesion using both flow cytometry and histochemistry to define the type of immune cells (T, B and dendritic cells and macrophages) that are present within a specific lesion type (pre-active, active, chronic inactive).

P168

The Transcription Factor Bhlhe40 Sustains TH17 Cell Pathogenicity in EAE

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Background: Cytokine-producing T_H17 cells are implicated in MS disease pathogenesis. We have previously shown that mice deficient for the transcription factor Bhlhe40 are markedly resistant to EAE, an animal model of MS. Bhlhe40-deficient T_H cells produce low amounts of GM-CSF and increased amounts of IL-10. Following EAE induction, IL-1β secreted by myeloid cells promotes Bhlhe40 expression by T_H17 cells. Here, we use a combination of new mouse strains and techniques to explore the mechanisms whereby Bhlhe40 regulates T_H17 cell encephalitogenicity.
Objectives: To elucidate the role of Bhlhe40 in T_H17 cells during EAE.
Methods: Newly generated *Bhlhe40*$^{fl/fl}$ mice were crossed to a variety of Cre-deleter strains to allow cell type-specific deletion of Bhlhe40. EAE was induced by active immunization. Dual reporter mice were generated by crossing *Bhlhe40*^{GFP} mice to IL-17A fate-mapping mice. ChIP-Seq was performed for Bhlhe40 in T_H17 cells generated in vitro.
Results: Myeloid cell expression of Bhlhe40 was not required for EAE susceptibility. Deletion of Bhlhe40 in T cells (*Cd4*-Cre) resulted in an almost complete abrogation of EAE. *Il17a*-Cre x *Bhlhe40*$^{fl/fl}$ mice developed milder EAE than controls, with delayed onset and reduced severity. These mice largely recovered from clinical EAE, suggesting a requirement for continued Bhlhe40 expression in T_H17 cells for disease maintenance. In IL-17A fate-mapped T_H cells, those that expressed Bhlhe40 had a greater proportion of cells producing GM-CSF, with many IL-17A$^+$IFN-γ$^+$GM-CSF$^+$ triple-positive cells and many IL-17A$^-$IFN-γ$^+$GM-CSF$^+$ ex-T_H17 cells. Publicly available transcriptomic data suggest that within human T_H cell subsets, Bhlhe40 is expressed most highly in "$T_H1/17$" cells that share T_H1 and T_H17 cell properties and have been associated with autoimmunity. ChIP-Seq identified thousands of genomic loci bound by Bhlhe40 in murine T_H17 cells, and suggested new means by which this factor could regulate pathogenicity.
Conclusion: Bhlhe40 is intrinsically required for T_H17 cells to sustain EAE pathogenesis. Studies are underway to explore how the direct target genes of Bhlhe40 promote encephalitogenicity.

P169

Altered Expression of Signature Genes of Human IFN-γ-Secreting TH17 Cells in Relapse-Remitting Multiple Sclerosis

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Background: T_H17 cells are implicated in the pathogenesis of Multiple sclerosis (MS). In human autoimmune diseases, IFN-γ-secreting T_H17 ($T_H1/17$) cells are found in elevated numbers in inflamed tissues. We have previously reported a molecular signature of murine pathogenic T_H17 cells that induce experimental autoimmune encephalomyelitis (EAE) in animals.
Objectives: To investigate the degree to which this molecular signature of murine pathogenic T_H17 cells is observed in human $T_H1/17$ cells, and to determine whether the expression of signature genes of $T_H1/17$ cells is altered in MS.
Methods: We utilized a capture assay that separates live CD4$^+$ T subsets from peripheral blood based on differential secretion of IL-17 and IFN-γ to sort *ex vivo* $T_H1/17$, T_H17 (IFN-γ$^-$IL-17$^+$), T_H1 (IFN-γ$^+$IL-17$^-$) and DN (IFN-γ$^-$IL-17$^-$) cells from healthy donors and untreated patients with MS. Cells isolated from healthy controls were subjected to the nCounter gene expression assay and the similarity between human and murine gene signatures of T_H17 was integrated via comparative transcriptomic analysis to define a molecule signature of $T_H1/17$ cells. Expression of the deduced signature genes in MS was assessed with *qPCR* assay.
Results: $T_H1/17$ and T_H17 cells had distinct transcriptional profiles. Compared to T_H17 cells, $T_H1/17$ cells displayed gene signatures with marked similarity to mouse pathogenic T_H17 cells. *q*PCR analysis confirmed enhanced expression of signature genes *IFNG, CCL5, CCL4, CLL3, GZMB, IL3, CXCR3, RGS2* and *CSF2* in $T_H1/17$ cells. We assessed the expression of *IL10* in addition to these signature genes in untreated patients with relapse-remitting MS and found that $T_H1/17$ cells have elevated expression of *CXCR3* and reduced expression of *IFNG*, *CCL3*, *CLL4*, *GZMB* and *IL10* compared to healthy controls. In T_H17 cells, *GZMB* and *IL10* showed reduced expression in MS. The low expression of *IL10* in CXCR3^{hi} $T_H1/17$ cells in MS suggests these pro-inflammatory cells may more readily migrate to CNS since CXCL10 (IP-10), a ligand for CXCR3, is increased in the inflamed CNS in MS. Moreover, compared to clinically active patients, stable patients have higher *IL10* expression in T_H17 cells.
Conclusion: Our results identify signature genes of $T_H1/17$ cells that can be used to investigate the pathogenicity and response to treatment in T_H17 cells in human autoimmune diseases.

P170

Role of Mir-155 in Virus-Mediated Demyelinating Disease

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Background: MicroRNAs (miRNAs) are noncoding RNAs that modulate cellular gene expression, primarily at the post-transcriptional level. We previously reported that miR-155 mediates susceptibility to viral-induced demyelinating disease and is necessary for optimal T-cell accumulation, migration, and effector function. Compared to WT mice, *miR-155-/-* mice infected with a neurotropic strain of murine hepatitis virus (JHMV) exhibited increased mortality, as well as significantly exacerbated clinical disease concomitant with decreased CD4$^+$ and CD8$^+$ T cell infiltration into the CNS, decreased ability to clear virus, and impaired T-cell effector function.
Objectives: We sought to further characterize the mechanisms through which miR-155 affects clinical disease during viral-induced neuroinflammation, and to determine whether the primary role of miR-155 in mediating clinical demyelinating disease is to regulate T cell accumulation and function.

Methods: Wild type (WT) C57 BL/6 or *miR-155-/-* mice were infected with JHMV. Twenty-four hours post infection, half of the JHMV-infected *miR-155-/-* mice received $CD8^+$ T cells from previously immunized WT mice. Clinical scores were assessed for 21 days. Demyelination, virus titers, and T-cell infiltration into the CNS were assessed. In addition, *CD4-Cre-miR-155-/-* mice and miR-155fl/fl mice were infected with JHMV. Mortality and clinical scores were assessed for 21 days. Brains were assessed for immune-cell infiltration and viral titers, and spinal cords were assessed for demyelination.
Results: JHMV-infected *miR-155-/-* mice that received WT $CD8^+$ T cells demonstrated a rescued phenotype with regard to clinical scores, viral load, and $CD8^+$ T cell infiltration to the CNS. There were no significant differences in demyelination among groups. JHMV-infected *CD4-Cre-miR-155-/-* mice developed exacerbated disease and decreased T-cell infiltration to the CNS compared to control mice; however, the differences were not as dramatic as those seen between JHMV-infected *miR-155-/-* mice and WT mice, and there were no differences in mortality between the groups.
Conclusion: These findings suggest that regulation of T cells is likely the primary, but not sole, mechanism by which miR-155 mediates demyelinating disease in our model.

P171

CD70 Expression Defines a Subset of Pro-Inflammatory and Pathogenic T Cells That Are Implicated in Multiple Sclerosis

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Background: CD70, a cytokine that binds CD27, is upregulated on T cells after activation. CD70 could be associated with T_H1 and in T_H17 differentiation.
Objectives: 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.
Methods: Flow cytometry (FC) was used to characterize $CD70^+$ T cells in peripheral blood (PB), cerebrospinal fluid (CSF) and MS brain lesions. To identify the amount of soluble CD70 in serum and CSF an enzyme linked immunoassay was used. To quantify mRNA, we used RT-PCR. Immunohistochemistry (IHC) on frozen MS brain sections was used to detect CD70 in MS lesions.
Results: In the PB of healthy donors (HD) we confirmed that CD70 is present, albeit low, on *ex vivo* T cells. *Ex vivo* $CD70^+$ T cells express higher amounts of CCR6, CD161, CD11a, CD49d and MCAM then $CD70^-$ T cells. $CD70^+$ T cells produce significantly higher amounts of IL17 and IFNγ compared to $CD70^-$ T cells. In addition, *in vitro* activation of T cells with 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, 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 the PB of untreated MS patients, the percentage of *ex vivo* $CD70^+$ T cells 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 producing $CD70^+$ T cells in MS compared to HD. T_H1 and T_H17 cells from untreated MS patients show a higher expression of CD70 compared to HD. In the CSF of untreated MS patients, the percentage of $CD70^+$ T cells, together with the presence of soluble CD70 is significantly higher compared to the PB. In white matter and cortical lesions of MS brains, $CD70^{hi}$ T cells were found.
Conclusion: CD70 expression, upregulated by TGFβ, discriminates a highly active and pro-inflammatory subset of T cells. The expression and pro-inflammatory nature of CD70 in *ex vivo*, polarized or TGFβ stimulated T cells is higher in MS patients compared to HD.

P172

Functional Characterization of Myeloid Derived Suppressor Cells in Multiple Sclerosis

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Background: Myeloid-derived cells play important modulatory and effector roles in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells, composed of monocytic (MO) and polymorphonuclear (PMN) fractions, which can suppress T cell activities in EAE. The mechanisms by which MDSCs are sustained during relapsing and chronic neuroinflammation has not been well addressed. MicroRNAs (miRNAs) are a class of small, non-coding RNAs that are implicated in the pathogenesis of several diseases including MS. MiR-223 is highly expressed in myeloid cells and acts as an important modulator of their development and functions. MiRNAs represent potential therapeutic targets in human diseases.
Objectives: To study MDSC immune-modulatory functions in the context of MS.
Methods: MiR-223 qPCR analysis was performed on spinal cord autopsied MS tissues, 8 areas of normal appearing white matter (NAWM) and 7 active MS lesions. Whole blood samples were collected from 40 RRMS (24 untreated, 10 glatiramer acetate and 6 dimethyl fumarate) patients and 16 healthy subjects and evaluated for the MDSC markers: CD33, CD15, CD14 and HLA-DR using flow cytometry. MDSCs were sorted to perform in vitro T-cell suppression assays and qPCR. To assess whether human MDSCs might traffic to the CNS in MS, sections of thoracic spinal cord and lymph nodes from MS patients were analyzed by immunohistochemistry (IHC) with an anti-CD33 antibody.
Results: MiR-223 expression was higher in active MS lesions compared to NAWM. Significantly decreased numbers of circulating MDSCs and higher MDSC expression of microRNA

miR-223 were found in relapsing-remitting MS patients (RRMS) versus healthy subjects. MDSCs from RRMS patients also displayed decreased expression of a critical mediator of MDSC suppressive function, the signal transducer and activator of transcription 3 (STAT3), compared with healthy controls. STAT3 was demonstrated to be a miR-223 target gene. MDSCs isolated from control and MS subjects were able to inhibit autologous T cell proliferation in vitro. IHC for CD33 revealed the presence of MDSCs in the spinal cord meninges, close to an active MS lesion and in the lymph nodes.
Conclusion: These results support a critical role for miR-223 in modulating MDSC biology in MS and suggest potential novel therapeutic applications.

P173
Diet-Induced Obesity Enhances the Severity of Experimental Autoimmune Encephalomyelitis
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Background: Being overweight as an adolescent is a risk factor for the development of multiple sclerosis (MS). This effect is further amplified if the person is also a carrier of the human leukocyte antigen (HLA) MS risk allele *HLA-DRB1*15:01*, suggesting that the state of obesity may promote MS by activating pathogenic T helper cells through HLA-restricted antigen presentation.
Objectives: To investigate whether induction of an overweight state in mice through administration of an obesogenic diet will increase susceptibility to experimental autoimmune encephalomyelitis (EAE), a model of MS.
Methods: Female and male C57BL/6J mice were fed either a high-fat diet (HFD) or normal chow diet (NCD) for 3 weeks to induce an overweight state. EAE was induced with myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ in complete Freund's adjuvant. The frequency and cytokine production of MOG-specific T cells were examined. In non-immunized NCD and HFD mice, the levels of serum cytokines and adipokines were measured, and the functionality of immune cell populations was profiled.
Results: Upon induction of EAE, HFD mice developed more severe clinical symptoms compared to NCD controls. This correlated with increased myelin destruction in the spinal cord and an enhanced expansion and production of IFN-γ and IL-17 by MOG_{35-55}-specific T cells. To determine the cellular basis of this enhanced T helper (Th) response with HFD, we isolated spleens and lymph nodes from non-immunized HFD and NCD mice and examined the frequency of immune cells and the *in vitro* functioning of dendritic cells (DC), regulatory T cells (Treg), and $CD4^+$ T cells. We observed that while DC and Treg functioned normally, $CD4^+$ T cells from HFD mice produced higher levels of IL-17 upon anti-CD3 and anti-CD28 stimulation. Further examination of the naïve $CD4^+$ T cell population revealed higher IFN-γ production by HFD group compared to NCD counterparts, which correlated with higher IFN-γ-induced STAT1 phosphorylation. Serum profiling experiments showed that leptin was the only pro-inflammatory cytokine upregulated in the circulation of HFD mice. Studies in mice that were deficient in the leptin receptor in the $CD4^+$ T cell compartment demonstrated that increased leptin signaling with HFD was the driver of the pro-inflammatory T cell phenotype.
Conclusion: A diet-induced overweight state promotes a Th1/Th17 pro-inflammatory state through increased leptin production.

P174
Interleukin-26, a TH17-Associated Cytokine, Enhances BBB Integrity: Significance for MS
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Background: Pathogenic T helper (T_H)17 cells are importantly involved in multiple sclerosis (MS). Cytokines expressed by these cells, interleukin(IL)-17 and IL-22, have been shown to compromise the blood-brain-barrier (BBB). Disruption of the BBB is an important early event in MS, which allows recruitment and migration of peripheral cells into the central nervous system. Interleukin-26, which signals through its heterodimeric receptor IL-10R2 and IL-20R1, is another cytokine expressed by T_H17 cells. Therefore, it might be involved in BBB functionality and have important implications for MS.
Objectives: To investigate the presence of IL-26 in MS patients and to assess the effect of IL-26 on the integrity of the BBB.
Methods: Quantitative PCR and western blot were used to detect IL-26 in T_H1, T_H2, T_H17 differentiated cells and IL-26 receptor (IL-26R) in human primary BBB endothelial cell (hBEC) cultures. Immunohistochemical staining (IHC) for IL-26/CD4 and IL-26R was performed on brain tissue from MS patients and controls. Next, the effect of dimeric recombinant human IL-26 (rhIL-26) on hBEC cultures was studied *in vitro* in permeability and transendothelial electrical resistance assays. The effect of IL-26 on BBB integrity was also studied *in vivo*, in a mouse model for neuroinflammation, experimental autoimmune encephalomyelitis (EAE). Therefore, 5 days after EAE induction, mice were daily injected with rhIL-26 or HBSS. At different time points, IgG and fibrinogen extravasation in the spinal cord was assessed by IHC. Moreover, clinical disease score was determined.
Results: Our results showed that IL-26 is mainly expressed by T_H17 differentiated cells in HC and MS patients. Moreover, we found $CD4^+IL\text{-}26^+$ cells in perivascular infiltrates in MS brain tissue. Next, we showed that hBEC express the heterodimeric IL-26R. This receptor was also found on blood vessels in MS brain tissue. 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, reduced the 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 rhIL-26 treated group.
Conclusion: Although IL-26 is largely an T_H17 associated cytokine, it promotes BBB integrity *in vitro* and *in vivo* and reduces disease severity in EAE.

P175
Gr-1+ Leukocytes Facilitate Meningeal Localization of B Cells Involved in Antigen Presentation during EAE
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Background: The success of B cell depletion therapy for the treatment of multiple sclerosis (MS) raises important questions about the participation of B cells in autoimmunity targeting the central nervous system (CNS). We have utilized the animal model experimental autoimmune encephalomyelitis (EAE) to demonstrate the capacity for B cells to independently coordinate inflammatory events in EAE in an MHCII-dependent manner. Furthermore, we have established a new system in which B cell expression of MHCII is temporally regulated. Mice in which B cells are the only antigen presenting cell (APC) exhibit rapid onset of EAE when MHCII expression is induced three weeks following encephalitogenic CD4 T cell transfer. Rapid onset of EAE is coincident with the formation of large B cell clusters within the spinal cord meninges. Prior studies suggest granulocytes are important for leukocyte recruitment to the CNS during EAE.
Objectives: Define the mechanisms involved in B cell localization to the meninges during EAE. Specifically, determine whether Gr-1+ cells are required for B cell localization to the meninges during EAE mediated by B cell antigen presentation.
Methods: We employed a new murine system of Tamoxifen-induced MHCII expression by myelin oligodendrocyte glycoprotein (MOG)-specific B cells. Passive EAE was induced by transfer of MOG-specific CD4 T cells. MHCII expression was induced three weeks after T cell transfer. Gr-1+ cells were depleted in vivo around the time of Tamoxifen treatment using the anti-GR-1 antibody, RB-6. In vivo treatment with isotype control antibody served as a comparison.
Results: Rapid disease onset with meningeal B cell cluster formation was observed in mice treated with isotype control antibody. Delayed disease onset and reduced meningeal B cell cluster formation resulted from anti-Gr-1 antibody treatment.
Conclusion: B cell localization to the meninges during EAE is dependent upon Gr-1+ cells, suggesting that granulocytes may coordinate the early events required for B cell access to CNS antigens during autoimmune neuro-inflammation.

P176
Activation of Human Naïve T Regulatory Cells for MS Therapy By Stimulation with Antigen and Interleukin-4
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Background: A highly desirable goal for treatment of MS would be restoration of immune tolerance. A powerful mechanism of immune tolerance are antigen-specific T regulatory cells (Treg). Treg are a subpopulation of CD4+T cells that are CD25+CD127loFoxp3+. Naïve natural thymic Treg (tTreg) expanded ex vivo are being trialed in autoimmunity, however the numbers required are massive as they are required at a ratio of >1:1 to suppress effector T cells. In murine models, we have activated naïve Treg with antigen and IL-4 to induced antigen-specific Treg that express IL-5 receptor alpha, and are 10-1000 fold more potent at suppressing MBP induced EAE than naïve polyclonally expanded Treg.
Objectives: To extend our murine studies on antigen specific Treg to humans, and ultimately explore antigen-specific Treg in MS. As a first step, we activated antigen-specific human Treg by culture of tTreg with antigen and IL-4 to characterize their phenotype.
Methods: Peripheral blood was collected from healthy donors, Treg isolated as CD4+CD25+CD127lo cells using a Treg isolation kit, and cultured with IL-4 and antigen for 3-4 days. Their phenotypes were examined pre-and post-culture by multicolor flow cytometry using mouse anti-human antibodies, such as CD45RA to assess naïve and activated Treg, proliferation by CFSE assay and cytokine receptor expression by RT-PCR.
Results: Treg proliferation was enhanced in co-culture with both autoantigen and IL-4 (25.2%) compared to autoantigen (2.49%) or IL-4 alone (0.028%). On FACS analysis there was a marked increase in CD45RA-Foxp3hi population (23.2% vs 8.32%). There was also polyclonal activation of naïve CD25loCD45RA+ Treg as well (51.3% vs 53.0%). RT-PCR showed induction of IL-5Rα, the specific chain of IL-5 receptor, only in Treg cultured with IL-4 and antigen and not on other cells. Examination of chemokine receptor expression on PBMC showed increased expression of CCR6 and CXCR3 in CD45RA-Foxp3hi Treg population compared to CD45RA+Foxp3hi Treg, consistent with this population being activated Treg.
Conclusion: Human CD4+CD25+CD127loTreg can be activated in vitro to express the IL-5 receptor, mirroring results from murine models. Increased CD45RA-/CD45RO+ population is consistent with activation of antigen-specific Treg. This suggests culture with IL-4 as a potential pathway for activation of naïve Treg to produce potent antigen-specific Treg for MS therapy.

P177
Hyper-Activation of STAT3 in Myeloid Cells Leads to Atypical EAE By Neutrophil Priming and Induction of Reactive Oxygen Species
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Background: The JAK/STAT signaling pathway is critical for the initiation, regulation and termination of immune responses, and dysregulation of JAK/STAT signaling is associated with many

pathological conditions such as Multiple Sclerosis. Myeloid lineage–specific deletion of SOCS3, a negative regulator of STAT3, results in a severe, non-resolving atypical form of experimental autoimmune encephalomyelitis (EAE). LysMCre-SOCS3$^{fl/fl}$ mice with atypical EAE exhibit ataxia and tremors and are characterized by lesions, inflammatory infiltrates, elevated STAT3 activation, and increased cytokine and chemokine expression in the cerebellum. We previously demonstrated that greater numbers of infiltrating neutrophils were found in the cerebellum of LysMCre-SOCS3$^{fl/fl}$ mice. Depletion of neutrophils in LysMCre-SOCS3$^{fl/fl}$ mice prevents the atypical EAE phenotype, indicating their important role in the pathology of brain-targeted phenotype.

Objectives: This project is to determine the function of neutrophils in brain-targeted atypical EAE.

Methods: We characterized the phenotype of SOCS3-deficient neutrophils *in vivo* during atypical EAE. To neutralize reactive oxygen species (ROS), a ROS scavenger cocktail, a combination of reducing agents that neutralize ROS, was administered *in vivo*. We also characterized the phenotype of SOCS3-deficient neutrophils in response to G-CSF *in vitro*. In addition, RNA-seq analysis was performed to determine differential gene expression in SOCS3-deficient neutrophils in response to G-CSF.

Results: Neutrophils from LysMCre-SOCS3$^{fl/fl}$ mice show an overtly activated phenotype at the peak of EAE disease in the cerebellum with excessive production of ROS. Additionally, the frequency of ROS-producing neutrophils is significantly increased in LysMCre-SOCS3$^{fl/fl}$ mice at the peak of EAE. Administration of a ROS scavenger cocktail delayed disease onset and decreased the incidence of atypical EAE, indicating that increased oxidative burden from neutrophils contributes to the pathogenesis of atypical EAE. Mechanistically, SOCS3-deficient neutrophils exhibit hypersensitivity in response to G-CSF. RNA-seq analysis reveals a unique gene expression profile in SOCS3-deficient neutrophils in response to G-CSF, including elevated expression of a number of cytokine and chemokine genes.

Conclusion: Overall, this study demonstrates that SOCS3 deficiency in myeloid cells leads to atypical EAE by neutrophil hyperactivation and aberrant ROS production.

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Collaborative Role for Type-17 and CD8+ T Cell Immunity in Relapsing to Secondary Progressive EAE

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Background: Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) in which T cells recognize myelin self antigen and mediate an attack against neurons. Nearly half of MS patients present a relapsing-remitting (RR) disease course followed by chronically worsening secondary progressive (SP) symptoms. Both CD4$^+$ and CD8$^+$ T cells are important in the pathogenesis of MS. While CD4$^+$ T (Th) cells specific for myelin antigens are present in the blood of MS patients, CD8$^+$ cytolytic T (Tc) cells are found in great numbers in active progressive MS lesions. These findings suggest a combinatorial role of CD4$^+$ and CD8$^+$ T cells in progressive pathology. Experimental autoimmune encephalomyelitis (EAE) is an animal disease that recapitulates the immunopathogenic aspects of MS. Immunization of non-obese diabetic (NOD) mice with encephalitogenic myelin-derived peptide $MOG_{[35-55]}$, causes a biphasic disease course characterized by RR phase followed by SP disease. Here, we use a T cell receptor transgenic mouse (1C6) on the NOD background that possesses both CD4$^+$ and CD8$^+$ T cells specific for $MOG_{[35-55]}$ and thus enabling us to elucidate the role of both these T cells in CNS autoimmunity.

Objectives: We sought to determine whether CD4$^+$ and/or CD8$^+$ T cells could induce progressive forms of EAE.

Methods: 1C6 CD4$^+$ or CD8$^+$ T cells were purified from the spleens of 1C6 mice. These T cells were then stimulated *in vitro* with agonistic anti-CD3 and anti-CD28, with defined cytokine cocktails that lead to the differentiation into IFNγ^+ Th1/Tc1 cells, or IL-17$^+$ Th17/Tc17 subsets for 5 days and adoptively transferred i.v. to lymphocyte-deficient NOD.Scid recipients.

Results: 1C6 Th17 recipients developed initial EAE symptoms much more rapidly than Th1 recipients with mean day of onset 13.53d±1.183 (Th17) and 31.22d±3.857 (Th1). 1C6 Tc17 cells induced RR disease course which later became IL-17$^+$IFN-g$^+$ "double producers" in the CNS and Tc1 cells showed delayed disease that rapidly progressed upon onset. Interestingly, cotransfer of 1C6 Th1+Tc1 cells or Th17+Tc17 induced progressive lethal EAE with a mean maximal severity of 3.7±0.1225 (Th1+Tc1) and 3.667±0.1667 (Th17+Tc17). All Th17+Tc17 recipients developed RRSP EAE.

Conclusion: Activated 1C6 CD4$^+$ and CD8$^+$ T cells can invoke progressive CNS autoimmunity in recipient mice. Further work is needed to elucidate the cellular mechanisms by which 1C6 T cells elicit damage to CNS tissue in the progressive stage.

P179

Induction of GM-CSF By Cigarette Smoke in T Cells: A Potential Pathogenic Role of Smoking in Multiple Sclerosis

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Background: Cigarette smoke is an environmental factor that is associated with the incidence and progression of diseases characterized by chronic inflammation and T cell dysfunction; including Multiple Sclerosis (MS) and other autoimmune diseases. Over the last 10 years, multiple epidemiological studies show a significant association between cigarette smoking and both faster incidence, progression, disability and mortality. Current data suggest that granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-17 producing T cells are pathogenic cells and essential for the development of autoimmune inflammation.

Objectives: To study the immunological effects of cigarette smoke extract in healthy subjects and non-treated people with MS.

Methods: In this study, using intracellular cytokine staining (ICS) and relative quantification Real-Time Polymerase Chain Reaction (RT-PCR), we investigated the expression of GM-CSF, IFN-γ, IL-17, IL-21 and IL-22 by human $CD4^+$ and $CD8^+$ T cell fraction after culture of PBMCs with anti-CD3 and anti-CD28 derived from healthy volunteers and non-treated people with MS, in the presence or absence of freshly prepared cigarette smoke extract (CSE).
Results: We found that an in vitro non-toxic concentration (5%) of CSE significantly induces the expression of GM-CSF in both $CD4^+$ and $CD8^+$ T cells. In addition, the co-expression of IFN-γ and GM-CSF is significantly higher in $CD8^+$ T cells compared to $CD4^+$ T cells in both healthy controls and people with MS. However, the expression of IL-17, IL-21 and IL-22 was not significantly induced after CSE exposure. Further investigations are ongoing to assess the susceptibility of human T cells to cigarette smoke exposure and immunological pathways involved.
Conclusion: These findings link cigarette smoking to GM-CSF induction in healthy and MS individuals which will lead to new insights/ therapeutic approaches in the pathogenesis of MS.

P180

MS Disease-Relevant B Cell Subsets Impact Microglia/Macrophage Biology: Implication to the CNS Compartmentalized Inflammation of MS

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Background: B cells appear to contribute to MS relapses through antibody-independent mechanisms, including induction of pro-inflammatory T cell responses in the periphery. Compared to healthy controls (HC), MS patients harbor higher proportions of pro-inflammatory effector B cells (Beff) that also produce abnormally elevated IL-6, TNF and GM-CSF levels, while IL-10 producing B cells (Breg) are deficient. B cells also persist within the inflamed MS CNS including within meningeal immune collections that are described adjacent to the subpial cortical lesions. Of interest is whether soluble products from meningeal immune cells (including B cells) may contribute to the subpial cortical injury. These subpial lesions, now implicated in progressive MS, are notable for demyelination, neuronal loss and activation of microglia/macrophage. We have previously shown that MS patient B-cell secreted products are toxic to oligodendrocytes and neurons.
Objectives: Assess effects of secreted products from MS-implicated B cell subsets on human microglia/macrophage responses.
Methods: B cells were purified from the periphery of MS and matching HC donors, driven into either Beff or Breg subsets and supernatants were collected after 3-day culture. Human-derived microglia and macrophage were cultured with the B cell supernatants for 48h, then washed carefully, and their subsequent cytokine secretion, phenotype and phagocytic function were assessed using ELISA, flow cytometry and fluorescent microscopy, respectively.
Results: We first demonstrated that Beff supernatants substantially enhanced human microglia and macrophage pro-inflammatory (IL-12 and IL-6) cytokine responses, while down-regulating their IL-10 production. Beff supernatants also increased human microglia/macrophage expression of the T-cell co-stimulatory molecule CD80, while Breg supernatants enhanced microglia/macrophage expression of quiescence molecules including TREM-2. Finally, we demonstrated that Beff and Breg supernatants could reciprocally impact the capacity of microglia/macrophage to phagocyte myelin via soluble factors.
Conclusion: These results indicate that disease-relevant human B cell subsets, previously implicated in the periphery of MS patients, can impact the biology of both resident CNS microglia and infiltrating myeloid cells. We postulate that this may contribute to propagation of MS CNS-compartmentalized inflammation and subpial cortical injury associated with progressive disease biology.

P181

Pparδ Activity in T Cells Limits the Development of Th17-Mediated Inflammation during EAE

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Background: Multiple sclerosis (MS) is thought to be initiated by myelin-reactive T helper (Th) 1 and Th17 cells. Its prevalence has increased over the past 50 years implicating the involvement of changing environmental factors in disease risk. Therefore, finding new genes that are modulated by environmental cues and at the same time regulate the development of pathogenic T cells may lead to finding novel therapeutic targets. The nuclear receptor peroxisome proliferator-activated receptor delta (PPARδ) could be such a gene, given that it senses dietary fatty acids and has anti-inflammatory roles. We previously reported that mice with global deficiency in PPARδ ($PPAR\delta^{-/-}$) exhibit enhanced Th1/Th17 responses and more severe disease compared to control mice during experimental autoimmune encephalomyelitis (EAE), suggesting that PPARδ could be a negative regulator of Th1/17 inflammation; however, $PPAR\delta^{-/-}$ mice also exhibit defects in T cell development resulting in increased memory T cells in the periphery, thus complicating the interpretation of these studies.
Objectives: This study was designed to tease out the role of PPARδ in the mature T cell compartment in the regulation of neuroinflammation. To this end, we used mice with PPARδ-deficiency restricted to mature T cells ($PPAR\delta^{fl/fl}$Lck-Cre^{dis}), thus bypassing the T cell developmental defects.
Methods: We induced EAE in $PPAR\delta^{fl/fl}$Lck-Cre^{dis} and controls, followed mice for clinical signs, and examined the development of central nervous system (CNS) inflammation during the acute and post-acute phase using flow cytometry and immunohistochemistry.

We also measured cytokine production by peripheral myelin-reactive T cells in pre-symptomatic mice and evaluated the ability of naïve CD4+ T cells to differentiate into Th1 and Th17 cells.
Results: PPARδ$^{fl/fl}$Lck-Cre^{dis} mice developed more severe EAE than WT mice. This was accompanied by the presence of more IL-17-producing CD4+ T cells in the CNS during the acute phase and more CNS immune cell infiltration and demyelination at 30 days post-onset of EAE. Similarly, peripheral myelin-reactive T cells from PPARδ$^{fl/fl}$Lck-Cre^{dis} mice showed higher IL-17 production. We observed that naïve CD4+ T cells from PPARδ$^{fl/fl}$Lck-Cre^{dis} mice also produced more IL-17 upon stimulation and differentiated more efficiently towards the Th17 lineage under Th17-skewing conditions.
Conclusion: Our findings revealed that PPARδ is an important negative regulator of Th17 inflammation during EAE by selectively inhibiting Th17 differentiation.

P182

Leptomeningeal B Cell Aggregates Associate with Subpial Pathology in a Natural Model of Multiple Sclerosis

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Background: Multiple sclerosis (MS) is an idiopathic demyelinating disease in which meningeal immune cell infiltrates correlate with accelerated clinical disease progression. Interactions of distinct immune cell subsets and resident stromal/endothelial cells at sites of such chronic inflammation are therefore of considerable interest. The study of MS meningeal immunity has been limited due to constrained access to MS specimens, the long clinical course of the disease and the confounding factors of experimental models. Unlike models such as experimental autoimmune encephalomyelitis, naturally occurring models offer a unique opportunity to understand MS pathogenesis and provide a more compelling framework for translational research.
Objectives: We propose granulomatous meningoencephalomyelitis (GME), an idiopathic demyelinating disease of young dogs with a female bias, as a natural model to study neuropathological mechanisms of MS, particularly within the leptomeningeal compartment.
Methods: We determined the pathological changes occurring in GME brains (n=45) by MRI imaging and histo/immunofluorescent analysis.
Results: We predominantly found perivascular mononuclear cell infiltration in the cortex and white matter associated with moderate demyelination. The leptomeningeal space, which represents an important niche supporting immunological activity, displayed areas of focal and disseminated gadolinium enhancement that correlated with heavy lymphocytic infiltration. These leptomeningeal infiltrates had collections of proliferating (Ki67+) B cells, germinal center B cells, plasma cells and follicular dendritic cells contained in a specialized network of collagen fibers resembling conduit networks and associated with the expression of the lymphorganogenic chemokines CXCL13 and CCL21. T cells localized in the periphery of these B cell clusters were characterized by low frequencies of T regulatory cells. Although perivascular parenchymal infiltrates contained clusters of B cells, they lack the cellular and extracellular matrix signatures found in the meningeal compartment. Finally, the presence of leptomeningeal B cell clusters correlates with increased subpial demyelination, neuronal degeneration and axonal pathology.
Conclusion: Thus, our findings indicate that the leptomeningeal microenvironment sustains the development of organized immune cell aggregates during chronic neuroinflammation and suggest GME as a novel naturally occurring model to study leptomeningeal B cell driven inflammation and neuropathology.

P183

Extracellular Galectin-3 Is Involved in B Cell Cytokine Regulation: Implications for MS

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Background: Galectin-3 (Gal-3) belongs to the lectin protein family and plays a role in apoptosis, activation, proliferation, inflammation, and cell-cell adhesion. It is shown to be involved in autoimmune diseases including multiple sclerosis (MS). The involvement of B cells in MS has been substantiated by the effective treatment of relapsing MS by B cell depletion therapies. However, the exact role of Gal-3 on B cell physiology remains enigmatic, especially in relation to MS.
Objectives: To assess the presence of Gal-3 in the peripheral blood of healthy volunteers (HV) and MS patients, and to investigate the effect of extracellular Gal-3 on B cells in the context of MS pathogenesis.
Methods: Gal-3 levels were assessed in serum from HV (n=22) and MS patients (n=74), and in cerebrospinal fluid (CSF) from patients with other neurological diseases (OND, n=15) and MS (n=14), by Enzyme-Linked Immuno Sorbent Assay (ELISA). Whole blood samples from HV (n=12) and MS patients (n=22) were analyzed for Gal-3 expression on B cells by flow cytometry (FC). In addition, purified B cells from HV (n=6) activated with B cell receptor crosslinking and CD40 ligand were cultured with or without interleukin(IL)4 or Gal-3 (1, 10, 100nM) and IL4. Gal-3 on the surface of activated B cell (FC), Gal-3 secretion (ELISA) and B cell cytokine expression (FC) were assessed.
Results: Our data demonstrate that Gal-3 levels are increased in serum and CSF obtained from MS patients. Furthermore, surface Gal-3 on B cells was also up-regulated in whole blood of MS patients, as compared to controls. Upon activation, B cells secreted Gal-3, and Gal-3 was up-regulated on their surface. When activating B cells in the presence of IL4, more cells expressed Gal-3 on

their surface. Activated B cells with Gal-3 on their surface had a higher production of pro-inflammatory cytokines (GMCSF, IFNγ) compared to Gal-3 negative B cells. However, treatment of B cells with 100nM Gal-3 reduced the IL6, TNFα and IFNγ producing B cell fraction.

Conclusion: Gal-3 is increased in serum, CSF and on B cells of persons living with MS. IL4 not only led to the generation of effector B cells but also to an up-regulation of Gal-3 on their surface. These data support the concept that extracellular Gal-3 is a marker for inflammation. As *in vitro* treatment with Gal-3 resulted in an overall downregulation of proinflammatory cytokines by B cells, it also supports the concept that Gal-3 expression by B cells might be a regulatory mechanism to dampen inflammation.

P184

Nlrx1 Prevents the Development of Spontaneous Experimental Autoimmune Encephalomyelitis in Mice

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Background: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) associated with inflammation, demyelination, and neuronal damage. The current MS therapeutic agents are directed towards inhibition of T and B cell function. We, on the other hand, demonstrate endogenous molecules that inhibit innate immune response can be the potential therapeutic targets for MS. Nlrx1 is an inhibitory NOD-like receptor (NLR) that suppress intracellular inflammatory pathways. Nlrx1 inhibits the progression of experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. We hypothesized that Nlrx1 prevents the development of MS. We created a new mouse model of MS by crossing $Nlrx1^{-/-}$ mice to 2D2 mice that have high numbers of myelin-specific T cells. The resulting progeny develops EAE spontaneously (spEAE).

Objectives: We monitored the development of spEAE and characterized the CNS inflammation in $Nlrx1^{-/-}$ 2D2 mice.

Methods: The activation of macrophages and T cells were evaluated using flow cytometry. We quantified the expression of myelin basic protein using immunofluorescence. The activation of astrocytes and microglia were quantified using immunofluorescent staining of Iba1 and GFAP. We measured the inflammatory mediators in the CNS by ELISA. To study whether lack of Nlrx1 in innate immune cells potentiates the CNS inflammation, we transferred activated myelin-specific T cells into T- and B-cell deficient $RAG^{-/-}$ or $Nlrx1^{-/-}$ $RAG^{-/-}$ mice.

Results: $Nlrx1^{-/-}$ 2D2 mice developed spEAE at 7–17 weeks of age. The disease manifested in 62% of $Nlrx1^{-/-}$ 2D2 mice with complete paralysis of the hind limbs. We observed demyelination and massive infiltration of leukocytes including myelin-specific $V\beta11^{+}$ T cells in the spinal cord of spEAE mice. Moreover, the increased expression of Iba1 and GFAP as well as inflammatory mediators including TNFα, IL-1β, CCR5, IFNg and IL-9 were observed in the spinal cord of spEAE mice. Following the adoptive transfer of T cells, $Nlrx1^{-/-}$ $RAG^{-/-}$ mice developed paralysis while none of the $RAG^{-/-}$ mice became paralyzed. The spinal cords from $Nlrx1^{-/-}$ $RAG^{-/-}$ mice showed demyelination and increased expression of Iba1 and GFAP compared to $RAG^{-/-}$ mice.

Conclusion: This study demonstrates that Nlrx1 inhibits the CNS inflammation and prevents the development of EAE. Our findings suggest that Nlrx1 acts at the level of innate immune response and can be considered as a potential therapeutic target to suppress early phases of inflammation within the CNS.

P185

Phenotypic Analysis of T Regulatory Cells in Multiple Sclerosis Patients

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Background: T-regulatory cells (Treg) are thought to be protective in autoimmune diseases such as MS and are described as CD4+CD25+CD127loFOXP3+T cells, yet it is a heterogenous population. Naïve Treg express CD45RA and have low expression of FOXP3 and CD25, whereas activated Treg have low expression of CD45RA. Activated Treg have increased CD25 and FOXP3. It is now known that activated Treg can be induced to mimic effector cells of the Th1, Th2, Th17 subtypes and these cells respectively express the relevant chemokine receptor (CXCR3, CCR8, CCR6) to promote their migration to sites of inflammation. We have shown in a rat model that unlike naive Treg which supress at 1:1 ratios with effector T-cells, in vitro generated Th1-like Treg suppress at 1:100 in vivo and 1:1000 in vitro.

Objectives: To compare the frequency of three CD4+CD25+CD127loFOXP3+ Treg phenotypes, respectively CD45RA+, CD45RAlo FoxP3lo, and CD45RAlo FoxP3hi in healthy humans and MS patients. Our future studies will examine the effect of currently approved MS therapies on Treg on these three populations.

Methods: Blood from MS patients (n=31) and healthy donors (n=9) was compared. Peripheral blood mononuclear cells (PBMC) were isolated using standard Ficoll method and stained with a panel of Treg markers. The CD4+and Treg populations were analysed for CD45RA and Foxp3 expression. Chemokine receptor expression specific to Th1-like Treg (CXCR3), Th2-like Treg (CCR8), Th17-like Treg (CCR6) and naïve tTreg (CCR7) was examined.

Results: Analysis of CD45RA and FoxP3 expression within CD4+T-cells and Treg identified three populations: CD45RA+ Foxp3lo, CD45RAloFoxp3lo and a third CD45RAloFoxp3hi population of activated Treg. The CD45RAloFoxp3hi population was significantly increased in MS patients when gated on either CD4+T-cells (p=0.002) or Treg (CD4+CD25+CD127lo) (p=0.009). CCR6+Treg, but not CXCR3+ or CCR7+Treg, were lower within the CD45RA-Foxp3hi population in MS patients compared to healthy controls (p=0.056). This population is believed to contain activated antigen-specific Treg. These results suggest reduced numbers of Th17-like Treg that suppress Th17 responses. There was a relative increase in CD45RA+FoxP3lo cells in MS (p=0.058).

Conclusion: These findings suggest an increase in the proportion of activated Treg in MS. There was a lower relative proportion of CCR6+Treg, which suggests a relative deficiency of Th17-like Treg in MS.

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Oligodendrocyte Death in Culture Is Induced By Exosome-Enriched Fractions from Secretory Products of B Cells from Patients with Multiple Sclerosis

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Background: B cells are important in the pathogenesis of multiple sclerosis (MS), including B cell functions unrelated to production of immunoglobulins (Ig). Supernatants (Sup) obtained from cultures of blood B cells from MS patients were cytotoxic to rat oligodendrocytes (OL) *in vitro*; those from normal controls (NC) produced little to no toxicity (Lisak et al. 2012). We recently confirmed this effect on rat OL and on rat and human neurons (Neu). Killing was independent of complement, did not correlate with Sup levels of IgG, IgM or any single or combination of a large number of cytokines and other proteins. Death of OL and Neu involved apoptosis and was caused by one or more factors with a molecular weight greater than 300 kDa (Lisak et al. 2017).
Objectives: To further characterize the toxic factors for OL within the B cell Sup by investigating the effects of extracellular vesicles isolated from Sup of relapsing remitting MS (RRMS) patients compared to NC.
Methods: Sup were obtained from cultures of blood B cells of RRMS and NC, diluted 1:4 with OL culture medium and screened for toxic effects on OL as measured by trypan blue uptake. We obtained exosome (Ex) enriched (Ex-En) preparations from these screened Sup by two methods, either an Ex isolation kit or ultracentrifugation. OL were incubated with Ex-En preparations obtained with the kit from 4 MS and 4 NC Sup containing fetal calf serum, and OL death determined. Sup and Ex-En prepared by UC from serum free B cell cultures from 2 MS and 2 NC were tested for OL cytotoxicity. Proteomic analysis was performed on serum free B cell Sup.
Results: Incubation of OL with Sup, either with serum or serum free, from MS patients induced OL cell death; those from NC were not toxic. Ex-En preparations from MS Sup from both serum containing and serum free Sup induced OL death whereas preparations from NC did not. Cell debris was not toxic. Preliminary proteomic analysis of serum free Sup demonstrated the presence of proteins characteristic of Ex from B cells.
Conclusion: Much of the *in vitro* toxicity of Sup from B cells of patients with RRMS appears to be present in Ex-En fractions prepared by two different methods. Preliminary proteomic analysis of serum free Sup derived from B cells reveals proteins known to be present in Ex from B cells. Studies are currently underway to determine which components of Ex-En mediate the killing of OL.

P187

Regulation of Myeloid Cells Function By Nanoparticles in EAE

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Background: Antigen-presenting cells (APCs) make up a significant proportion of the cells found within lesions of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). These APCs have the ability to capture myelin debris and promote either an inflammatory or a tolerogenic response from effector lymphocytes. In MS patients and EAE animals, APCs typically induce an inflammatory response.
Objectives: The Miller laboratory have developed a novel carboxylated poly(lactic-co-glycolic) acid (PLGA) nanoparticle-based therapy that selectively targets myeloid cells, mitigating their inflammatory impact. Our goal was to understand by which mechanism these PLGA particles modulate the immune response in EAE.
Methods: Using fluorescent labeled PLGA particles, we were able to detect the location of the particles, the cells that uptake them, and evaluate the time frame of this process. Injection at onset and peak of EAE disease was used to observe the effects and mechanisms by which the particles were acting.
Results: We found that all $CD11b^+$ myeloid cells have the ability to take up PLGA particles, as early as 30 minutes following i.v. injection. Interestingly, microglia are unable to engulf particles *in vitro*. Moreover, immunofluorescence analysis shows that particles accumulate in the spleen 3h post-injection, but are largely undetectable after 24h. In EAE, we observe that PLGA particle injections delay the onset of the disease and more importantly attenuate active disease. We observe a reduction in immune cell infiltration into the CNS of PLGA particle-treated mice, most notably of myeloid cells and $CD4^+$ T lymphocytes. Moreover, we notice that PLGA-associated cells undergo sequestration into the spleen and increase their expression of caspase-3, pointing to an upregulation of apoptosis. In addition, MHC II, CD86 and PD-L1 expression are increased on myeloid cells within the spleen of these mice. $CD4^+$ T cells analysis shows an upregulation of IL-10, TGF-beta and CTLA-4 expression in animals injected with PLGA particles.
Conclusion: Collectively our data demonstrate that PLGA particles are captured by APCs, which subsequently induces their death in the spleen and/or a change in their phenotype, creating an environment in which APCs are able to skew the T cell response to induce a more pronounce anti-inflammatory response.

P188

Multiple Sclerosis Patients Have a Increased Cellular Response to Autoantigens Which Cross-React with Proteins from Epstein-Barr Virus

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Background: Epstein-Barr virus (EBV) is associated with multiple sclerosis (MS), but the role that EBV plays in MS is not clear. Our hypothesis is that the robust immune response to persistent EBV infection causes MS through molecular mimicry or cross-reactivity.

We previously demonstrated an increased antibody response to 3 EBV antigens in MS. We demonstrated that antibodies specific for these EBV proteins also bind to the cytoskeletal protein septin-9, the mitochondrial protein DLST, or the nuclear protein HNRNPL. The antibody response to septin-9 or DLST is increased in a subset of MS patients.
Objectives: To determine whether MS patients have an increased cellular response to the autoantigens septin-9, DLST, or HNRNPL.
Methods: We produced recombinant human proteins in E. coli and purified the hexahistidine-tagged proteins with nickel affinity chromatography. We obtained peripheral blood mononuclear cells (PBMC) from MS patients and controls. We stimulated PBMC with 10 micrograms/ml antigen, added radioactive thymidine on day 4, and harvested and counted the cells on day 5. Each experiment included controls to correct for possible residual bacterial contamination of the recombinant proteins.
Results: We tested the cellular response in 15 MS patients and 5 controls. Six MS had a proliferative response to septin-9, two to HNRNPL, and one to DLST. The maximum stimulation index for septin-9 was 4.8. No patient responded to more than one antigen. None of the controls had a proliferative response to any of the three antigens.
Conclusion: A subset of MS patients has a T cell proliferative response to the autoantigen septin-9. Further investigation with larger numbers of patients and controls is needed, along with determination of the cytokine profile and phenotype (CD4 vs. CD8) of the responding cells. This work suggests a unique mechanism for autoimmunity, whereby B cells producing an anti-EBV immunoglobulin which cross-reacts with a self antigen stimulate an autoreactive T cell response. If further work supports the pathogenic potential of the septin-9 reactive T cells, then induction of tolerance to this antigen would be an attractive approach to an effective, antigen-specific treatment with minimal toxicity.

P189
Serum Brain Derived Neurotrophic Factor Levels in Multiple Sclerosis and Neuro- Behçet's Disease
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Background: Brain derived neurotrophic factor (BDNF) is involved in neuronal and glial development and survival. Neurons and astrocytes are its main cellular sources in the central nervous system (CNS). BDNF is also expressed in immune cells and in lesions of multiple sclerosis (MS). Over the last few years, evidence from MS and experimental models of neuroinflammation has suggested that autoimmune responses could exert neuroprotective effects through the release of neurotrophins by autoreactive T cells.
Objectives: Specifically, the role of BDNF in facilitating brain tissue repair in neuroinflammation has been well recognized. Regulation of BDNF activity may have important implications in the control of various autoimmune or inflammatory conditions. MS and Neuro- Behçet's Disease (NBD) that have some clinical similarities and are important immune mediated diseases of CNS. The pathogenesis of these diseases remains unclear, with concerning the role of cytokines, chemokines, epigenetic regulators, neurotrophins, inflammasomes, semaphorine like inflammatory molecules and other peptide structures that control the balance of inflammation.
Methods: To clarify the role of BDNF in MS and NBD, we investigated their levels in the sera of patients by enzyme linked immunosorbent assay (ELISA) method.
Results: In present study, we detected low levels of BDNF in sera of patients with MS in relapses than remission, inactive phase of NBD and control groups.
Conclusion: Our results suggested that BDNF may play a role in the pathogenesis of MS and NBD especially at recovery stage after inflammation. BDNF should be studied in greater detail on the basis that reducing inflammation with in the CNS.

P190
Conventional Dendritic Cells Are Critical for the Initiation of Experimental Autoimmune Encephalomyelitis
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Background: Multiple sclerosis (MS) is a neuroinflammatory disorder characterized by infiltration of $CD4^+$ T cells into the central nervous system (CNS). Within the CNS, the T cells become re-activated by interaction with an MHC-II^+ antigen presenting cell (APC) and promote a pathologic inflammatory response.
Objectives: The aim of this study is to investigate the role of MHC-II^+ APC subsets in CNS autoimmunity using the animal model experimental autoimmune encephalomyelitis (EAE).
Methods: EAE was induced by adoptive transfer of myelin-primed $CD4^+$ T cells or by active immunization with myelin peptide. Cells were analyzed by flow cytometry and immunofluorescence. APC were sorted by FACS and co-cultured with myelin-specific T cells to assess antigen presentation. Dendritic cells were depleted by diphtheria toxin (DT) in mice with DC-specific expression of the DT receptor.
Results: At the peak of clinical disability in EAE, MHC-II is expressed by microglia, B cells, monocyte-derived dendritic cells (moDC), and conventional dendritic cells (cDC). moDC are thought to be the dominant APC in settings of inflammation such as EAE; however, the role of cDC is unclear. To assess the antigen presentation capacity of these subsets, we sorted cells from the CNS and spleen at the peak of EAE and co-cultured them with naïve T cells from 2D2 transgenic mice, which have a T cell receptor specific for myelin antigen. Contrary to expectation, B cells and cDC, but not moDC, displayed the capacity to activate myelin-specific T cells ex vivo.
We next investigated whether these subsets are present in the naïve CNS and may initiate the neuroinflammatory response. We identified MHC-II^+ cDC and B cells, but few activated microglia or moDC, in the naïve CNS. The cDC and B cells were particularly enriched in the meninges, and MHC-II^+ cells were identified adjacent to the meningeal vasculature by immunofluorescence.
B cell-deficient mice are susceptible to EAE, so we hypothesized that conventional dendritic cells are critical for disease initiation. To deplete conventional dendritic cells, we administered DT to mice with DC-specific expression of the DT receptor. DC depletion significantly reduced the incidence of disease, demonstrating

a critical role for the dendritic cell population in initiation of adoptive transfer EAE.
Conclusion: Conventional dendritic cells are present in the meninges in the naïve CNS and are critical for the initiation of adoptive transfer EAE.

P191
Gene Therapy: An In Vivo Approach to Induce Immune Tolerance, Inhibit Neuro-Inflammation and Disease, Regardless of Genetic Background
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Background: Multiple sclerosis (MS) is a complex autoimmune disease. Although the exact etiology is unknown, the disease is thought to result from peripheral activation of myelin-reactive $CD4^+$ effector T cells that have escaped immune-regulatory mechanisms. Active suppression by regulatory T cells (Tregs) plays a key role in the control of self-antigen-reactive T cells and the induction of peripheral tolerance *in vivo*. Unfortunately, reduction in the frequency or suppressive function of peripheral $CD4^+CD25^+FOXP3^+$ Tregs have been observed in various autoimmune diseases, including MS. An attractive therapeutic strategy for restoring self-tolerance and controlling disease is to selectively induce antigen-specific Tregs. Recently, we developed an efficient *in vivo* approach of inducing immune tolerance through ectopic expression of myelin oligodendrocyte glycoprotein (MOG) in the liver. Using an AAV vector containing the full DNA coding sequence for MOG, we demonstrate that hepatic gene therapy can prevent and reverse preexisting MOG_{35-55} induced EAE (*Keeler. et.al MolTher 2017*).
Objectives: The objective of this study was to demonstrate that AAV gene immunotherapy has the ability to prevent disease regardless of the genetic background of the animal or the epitope used to induce the disease.
Methods: Mice were given AAV.MOG or Null vector. Two weeks later EAE was induced in mice with different genetic backgrounds (C57BL/6 $\{H2^b\}$ and DBA/1 $\{H2^q\}$) using combinations of strain-specific immunogenic epitopes of MOG (C57BL/6: $MOG_{119-132}$, MOG_{35-55} & $MOG_{119-132}$ and full-length protein MOG_{1-125}; DBA/1: MOG_{79-96}) emulsified adjuvant. Animals were monitored for clinical signs of EAE and scored accordingly.
Results: Following EAE induction, Null mice began developing clinical signs of severe ascending paralysis, while AAV.MOG treated mice remained virtually symptom free (mean peak scores for Null vs AAV.MOG as mean±SEM for each epitope combination) [C57BL/6: 3.3±0.8 vs 0±0; 3.7±0.2 vs 0.25±0.3, and DBA/1: 3.5±0.4 vs 0±0]. Null mice also had substantial inflammation compared to AAV.MOG mice.
Conclusion: In contrast to approaches using *ex vivo* engineering or expansion of Ag-specific Tregs, we have demonstrated that AAV8.MOG gene therapy can dynamically induce immune tolerance *in vivo* to multiple immunogenic epitopes of MOG which inhibits neuroinflammation and disease, regardless of genetic background. Eliminating the need to identify HLA/MHC specific epitopes, makes this approach universally applicable as an effective therapy.

P192
A Cohort Study of the Use of Plasma Exchange in Acute Central Nervous System Demyelinating Events in Pediatric Patients
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Background: Plasma exchange (PLEX) can improve recovery of acute central nervous system (CNS) demyelinating events related to multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), transverse myelitis (TM) and acute disseminated encephalomyelitis (ADEM) if recovery with pulse steroids (PS) is incomplete. Although there is a single randomized controlled trial in adults, there are limited case series in pediatric patients.
Objectives: We aim to describe the effectiveness and safety of PLEX in pediatric patients with acute events of MS, NMOSD, TM and ADEM with limited improvement after PS.
Methods: This is a retrospective cohort study of pediatric patients with acute CNS demyelinating events seen at a single tertiary referral center who received PLEX as a second- or third-line therapy between 2006 and 2017. Through chart review, presence of clinical improvement by physician assessment was noted pre- and post-PS and pre- and post-PLEX. Expanded Disability Status Scale (EDSS) scores were noted pre- and post-PLEX. Clinical improvement and EDSS scores were collected from chart review using clinical notes before and after each treatment.
Results: 23 patients followed at the Pediatric MS Center at the University of California, San Francisco received PLEX for acute events of MS (n=15), NMOSD (n=6), TM (n=1), and ADEM (n=1). At time of PLEX initiation, median age was 14 years (range 3-17; n=23); median time between the acute event and PLEX initiation was 19 days (range 3-90; n=15); median number of sessions of PLEX per patient was 5 (range 3-7; n=22). 9 of 19 patients had no clinical improvement after PS, while 10 improved. Of those with no improvement after PS (n=9), 8 improved after PLEX, 1 of which started PLEX while already on PS. Of those who improved after PS (n=10), 8 had additional improvement after PLEX, 1 of which started PLEX while already on PS. Of the 4 patients with no available physician assessment after PS, all improved after PLEX. 12 of 23 patients had pre- and post-PLEX EDSS scores available. Median pre-PLEX EDSS score was 4.25 (range 3-7.5; n=12), and median post-PLEX EDSS score was 3.75 (range 3-7.5; n=12). 4 patients had improved EDSS scores by 1 or more points. Side effects during PLEX included hypotension (n=2), nausea (n=2), thrombocytopenia (n=1), and gastrointestinal discomfort (n=1).
Conclusion: PLEX is an overall well-tolerated second-line treatment option for pediatric patients with acute CNS demyelinating events with limited response to PS.

P193
Hypothesis: Early Neutralization of the Meningeal Tertiary Lymphoid Organs By CXCL13 Blockage Could Prevent Progression of Multiple Sclerosis
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Background: multiple sclerosis (MS) is an autoimmune disease with a progressive course. Disease modifying therapy has accomplished a reduction in the traffic of pro-inflammatory cells through the blood brain barrier and modulation within the central nervous system but has not prevented disease progression.
Objectives: intrathecal activity of the immune system in MS seems to be dependent on the meningeal tertiary lymphoid organs (mTLO). We hypothesize a possible therapeutic route that could prevent disease progression based on the role of homeostatic B-cell attracting chemokine CXCL13.
Methods: PubMed review (2001–2017) entering keywords meaning TLO, lymphogenesis, CXCL13, MS.
Results: 1) the TLO originates *de novo* in non-lymphoid tissue by lymphoid neogenesis becoming the determinant key in the pathogenesis of autoimmune diseases; 2) infection and/or immunization trigger the formation of transient germinal centers (GC) which resolve after antigen clearance; 3) the GC are localized within the follicles of the lymph nodes and other secondary lymphoid organs (SLO) and do have prominent lymphocytic mitosis; 4) the secondary GC are critical in the development of B-cell immune response providing necessary infrastructure for the capture and storage of antigens which drive-in cell division and maturation, B-cell selection with high affinity for immunoglobulin receptors and differentiation of B-cells and plasma cells; 5) ectopic GC perpetuate autoimmune disease by maintaining antibody diversity, isotype switching, B-cell differentiation, oligoclonal expansion and production of auto-reactive plasma cells at the local site of inflammation; 6) the chemokines CXCL13 and CXCL12 play a key role in the process of lymphoid organogenesis which is shared by SLO and TLO; 7) CXCL13 is produced within the SLO in dendritic follicular cells and macrophages; 8) when the mTLO are established in the time span of MS is still unknown; 9) high levels of CXCL13 are present in the CSF of patients with the clinically isolated syndrome who convert to clinically definitive MS within two years; 10) complementary intrathecal therapy could be necessary for the deactivation of the mTLO to arrest disease progression; 11) a novel therapeutic monoclonal antibody targeting CXCL13 has shown therapeutic effect in the Th17-mediated murine model of MS.
Conclusion: complementary early treatment of MS, using CXCL13 blockage, could neutralize the formation of the mTLO reducing risk of disease progression.

Pathogenesis - Neurodegeneration

P194

Selective Deletion of AMPA Receptors on Oligodendrocytes Prevents Demyelination and Axonal Injury in Autoimmune Demyelination

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Background: Although current treatments for multiple sclerosis (MS) reduce disease symptoms and relapses by modulating the immune system, CNS inflammation and disease progression persist. This emphasizes the need for neuroprotective therapies in MS. One promising pathological mechanism to target is excitotoxicity, as neurons and oligodendrocytes (OLs) are vulnerable to damage via excess glutamate, and MS patients have elevated levels of glutamate in the brain as measured by MRI. We previously demonstrated that glutamate release from the system x_c^- transporter is an important mechanism in demyelination during experimental autoimmune encephalomyelitis (EAE) in mice. However, how glutamate specifically affects OLs during EAE, and whether protecting myelin prevents neurodegeneration, is unclear.
Objectives: The aim of this study is to determine whether deletion of the target for excitotoxic glutamate selectively in OLs, the AMPA receptor (AMPAR), prevents myelin and axonal damage in EAE.
Methods: The GluA4 AMPAR subunit was selectively deleted from OLs in mice as a result of Cre expression under one of two OL-specific promoters: Olig2 or Plp1. Deletion was confirmed with immunohistochemistry, and functional reduction of AMPARs was determined using Ca_i^{2+} imaging of *ex vivo* optic nerves. Mice were subjected to MOG_{35-55}-induced EAE. To rule out potential effects on the immune system as a result of GluA4 deletion in OLs, $CD4^+$ T cell numbers and phenotypes in spinal cords, and proliferation in spleens, were analyzed with FACS analysis at peak of disease. Extent of demyelination, axonal damage, and reactive gliosis was determined by immunohistochemistry 30 days post-EAE induction using 3D confocal imaging.
Results: Deletion of GluA4 in OLs resulted in reduced Ca_i^{2+} after treatment with glutamate, indicating a functional reduction in AMPAR activity. Mice subjected to EAE and deficient in GluA4 selectively on OLs had improved clinical scores and reduced myelin damage in spinal cords. Furthermore, axonal damage in conditional knockout mice was abrogated. No alterations in numbers or phenotypes of CNS-infiltrating $CD4^+$ T cells or proliferation in spleens was observed.
Conclusion: These data support that conditional deletion of the target for excitotoxic glutamate on myelin confers CNS protection that is independent of modulating the immune system. This suggests the importance of maintaining myelin integrity to promote axonal health and prevent neurodegeneration in MS.

P195

Autoimmunity to the RNA Binding Protein hnRNP A1 Contributes to Neurodegeneration in MS

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Background: Heterogeneous nuclear ribonuclear protein A1 ('A1') is an RNA binding protein (RBP) that has been shown to play major roles in neurological disorders, such as amyotrophic lateral sclerosis. Pathologic features of neurodegeneration in these disorders include the formation of pathogenic stress granules (SGs) and mislocalization of A1 from the nucleus to the cytoplasm in neurons. MS patients, in contrast to healthy controls, make antibodies to 'M9', A1's nuclear localization sequence.

Objectives: We hypothesized that the *in vitro* application of cytokines and A1-M9 antibodies would induce SG formation and A1 mislocalization in neurons. We further hypothesized that in an *in vivo* model of MS, A1-M9 antibodies might exhibit pathogenic features in neurons similar to those observed in other neurologic conditions.
Methods: SKNSH cells were treated for 72 hours with T_H1 or T_h17 associated cytokines or A1-M9 antibodies, which recognize the identical immunodominant epitope of A1 as MS patients. Cells were immunostained for A1 and SGs. Experimental autoimmune encephalomyelitis (EAE) was induced in female C57BL/6J mice via immunization with MOG_{35-55}. At the first sign of disease, mice were injected with either PBS, IgG2b isotype control or A1-M9 antibodies.
Results: Cells exposed to T_H1 or T_H17 cytokines and A1-M9 antibodies showed increased formation of cytoplasmic SGs and a redistribution of A1 from nucleus to cytoplasm compared to isotype control antibodies and untouched controls ($p<0.005$). Furthermore, cells treated with A1-M9 antibodies showed significantly more SGs than those treated with cytokines alone ($p<0.005$). In EAE, animals treated with the A1-M9 antibodies were sicker and exhibited a spastic rather than flaccid phenotype, which was observed in controls ($p<0.05$). Significantly, mice injected with A1-M9 antibodies showed mislocalization of A1 protein from the nucleus to the cytoplasm in spinal cord ventral horn neurons compared to either PBS or IgG2b isotype control mice.
Conclusion: These data indicate that cytokines and A1-M9 antibodies contribute to neuronal cell damage via SG formation and A1 redistribution, phenomena not previously reported in MS and which may play a role in neurodegeneration in MS.

P196
Thalamic MRI and Histopathologic Correlations in Advanced Multiple Sclerosis
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Background: Thalamic atrophy occurs early in MS and is associated with cognitive impairment and fatigue. We sought to determine characteristics of extra-thalamic injury that may lead to thalamic atrophy.
Objectives: To examine MRI characteristics predictive of thalamic atrophy and investigate pathological correlates.
Methods: We used a rapid autopsy program with *in situ* postmortem MRI followed by brain fixation. Thalami were excised from fixed coronal slices and 30μm free floating sections were stained for myelin, neurons, activated microglia, and axons/dendrites. We acquired T1 MPRAGE, T2, and FLAIR. A semi-automated technique was to calculate volumes: T1 and T2 lesion (T1LV, T2LV), brain parenchymal fraction (BPF), total grey matter fraction (GMF), and thalamic (TV). Thalamic pathology was recorded for subjects with the most and least TV loss by MRI. In a separate *in vivo* cohort, we evaluated the relationship between volumes of thalamic nuclei and other deep grey matter structures to cortical grey matter volume, BPF, and T1LV/T2LV.
Results: Ninety-five subjects with MS had MRI and tissue available and 25 (26%) had grossly apparent thalamic lesions. Mean TV was 13.5 mL ± 2.7. MRI thalamic lesion burden did not correlate with thalamic atrophy [Spearman rho (ρ) -0.15, $p = 0.15$] but did correlate with BPF ($\rho = 0.61$, $p < 0.001$), T2LV ($\rho = -0.65$, $p < 0.001$), and T1LV ($\rho = -0.48$, $p < 0.001$). T2LV strongly correlated with T1LV ($\rho = 0.76$) and with TV ($\rho = -0.65$) more than total grey matter fraction (GMF; $\rho = 0.44$) or BPF ($\rho = -0.54$); all $p < 0.001$. Most had progressive courses: 74 (72%) secondary progressive, 14 (15%) primary progressive, and 7 (7%) relapsing. The mean disease duration was 25 ± 11.8 years and mean age at death was 59 ± 12 years.
Histologically, neuronal density was reduced, and neurons were less polygonal in demyelinated lesions compared to normal appearing grey matter. Activated microglia were present in normal appearing thalamic tissue but were increased in lesions and lesional borders. Axonal density was decreased in perilesional and lesional areas. Histopathologic data for TV extremes as well as MRI metrics for an in vivo cohort will also be presented.
Conclusion: Although thalamic lesions exhibit neuronal, axonal, and glial pathology, thalamic atrophy correlates with extra-thalamic metrics. These findings suggest that thalamic atrophy in MS results more from Wallerian or transsynaptic degeneration than from intra-thalamic lesions and reflects global white matter disease burden.

P197
Complement Dependent Synapse Loss in a Mouse Model of Multiple Sclerosis
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Background: Multiple sclerosis (MS) is an inflammatory, neurodegenerative disease of the CNS characterized by both grey and white matter injury. However, cognitive impairments and progressive neurologic decline correlate best with degeneration of brain grey matter. Microglial activation and a reduction in synaptic density are key features of grey matter pathology that can be modeled with experimental autoimmune encephalomyelitis (EAE) in which mice have significant cortical and hippocampal synapse loss and microgliosis. Complement deposition on synapses followed by microglial engulfment has been shown during normal development and in disease as a mechanism for pruning synapses that potentially are still functional. Thus, we tested whether complement dependent synapse loss is a primary source of injury in EAE.
Objectives: To determine if there is excess complement production and activation in the EAE hippocampus and whether preventing complement activation via genetic knockout of C1qa protects synapses during EAE.
Methods: EAE was induced in wild-type (WT) and C1qa knockout mice by immunizing with $MOG_{35-55.}$ Brain slices and hippocampal lysates were probed for the complement factors, C1q and C3, and synaptic and microglial markers via immunohistochemistry and immunoblot.
Results: C1q protein levels were significantly increased in the hippocampus of EAE mice compared to sham-immunized controls. C1q often localized with synapses (identified by the postsynaptic marker PSD95). EAE mice also had increased levels of

C3 activation products pointing to engagement of the early complement pathway. WT mice with EAE displayed a significant decrease compared to sham controls in the number of synapses in the CA1 striatum radiatum region of the hippocampus. C1qa knock out prevents this EAE-induced synapse loss in the hippocampus but does not improve the EAE clinical score which is largely a phenotype of white matter spinal cord disease.
Conclusion: Pathologic expression and activation of the early classical complement pathway mediates synapse elimination in the EAE hippocampus but does not influence the EAE clinical score. Thus, loss of complement component C1qa is specifically neuroprotective in the EAE grey matter.

P198
Identification of Multiple Sclerosis Related Pathways through Genome-Proteome Correlations
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Background: Multiple sclerosis (MS) is an immune-mediated, inflammatory, demyelinating and neurodegenerative disease of the central nervous system with complex inheritance and pathophysiological mechanisms.
Objectives: The objective of this study is to explore underlying disease mechanisms in an MS cohort, using genomic data obtained by a genome-wide association study (GWAS) and cerebrospinal fluid (CSF) proteomic data. This data was used for pathway enrichment analyses and clustering of the pathways in order to reveal affected pathways.
Methods: Proteome data were previously obtained through 2D-gel electrophoresis and mass spectrophotometry analyses using 179 MS patients and 42 non-MS controls. Among the study group, 11 unrelated MS patients and 60 healthy controls were subjected to SNP genotyping on the Illumina HumanCytoSNP-12 BeadChip. Pathway enrichment analyses of differentially expressed proteins and MS-associated SNPs were conducted using the functional enrichment tool PANOGA. The resulting enriched pathways for GWAS and proteomics were then merged using Fisher's method. In order to establish representative pathways among highly similar groups of enriched pathways, clustering was performed, and the most significantly altered representative pathways in MS were identified.
Results: Top 20 representative pathways had P values ranging from 6.96E-30 to 2.20E-09. Immunological pathways such as complement and coagulation cascades (hsa04610, P=6.96E-30), Toll-like receptor signaling (hsa04620, P=8.96E-13), and neurological pathways such as Notch signaling (hsa04330, P=1.24E-13), Prion diseases (hsa05020, P=5.13E-13) were identified. In addition, other pathways known to be important in neural network, and immune cell proliferation and migration were observed: Regulation of actin cytoskeleton (hsa04810, P=9.64E-27), Adherens junctions (hsa04520, P=6.64E-25), Calcium signaling pathway (hsa04020, P=1.15E-18), ECM-receptor interaction (hsa04512, P=1.24E-14), SNARE interactions in vesicular transport (hsa04130, P=4.03E-12), Cell cycle (hsa04110, P=3.87E-11).
Conclusion: In this study, genomic and proteomic data of the same MS cohort were used, and affected pathways were identified through bioinformatic analyses. We found a number of representative pathways related to immunological and neurological mechanisms of which complement and coagulation cascades, actin cytoskeleton regulation, and cell-cell adherens junctions seem to be of the highest importance in MS pathophysiology.

Pathogenesis - Role of glia

P199
Cell-Specific and Region-Specific Transcriptomics in the MS Model: Focus on Astrocytes
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Background: Changes in gene expression that occur across the CNS during disease do not address the heterogeneity of cell types from one CNS region to another. Molecular mechanisms underlying distinct disabilities may differ based on the neuroanatomic pathway involved. MS is multifocal neuroanatomically and is characterized by distinct disabilities affecting walking, vision, cognition and fatigue. We hypothesize that neuroprotective treatments tailored for each disability may be more effective than treatments aiming to reduce a composite of many disabilities in clinical trials.
Objectives: A cell-specific and region-specific transcriptomics approach was used to determine gene expression changes in astrocytes in the MS model, EAE.
Methods: Astrocyte specific RNAs from various neuroanatomic regions were attained from EAE and healthy control mice using RiboTag technology. Sequencing and bioinformatics analyses were used to determine EAE induced gene expression changes in astrocytes in each CNS region. RNA sequencing and bioinformatics analyses of human autopsy tissues were used to determine whether gene expression changes identified in EAE also occurred in MS.
Results: Twice as many gene differences were observed during EAE in spinal cord astrocytes than in spinal cord all cells, demonstrating the importance of the cell-specific transcriptomics approach. EAE induced gene expression changes in astrocytes differed between neuroanatomic regions when comparing astrocytes from spinal cord, cerebellum, cerebral cortex and hippocampus, demonstrating the importance of the region-specific transcriptomics approach. The top gene pathways that were changed in astrocytes from spinal cord during chronic EAE involved decreased expression of cholesterol synthesis genes, while immune pathway gene expression was increased. Optic nerve from EAE and optic chiasm from MS both showed decreased cholesterol synthesis gene expression.
Conclusion: Together, this provides proof-of-concept that a cell-specific and region-specific gene expression approach can identify potential treatment targets in distinct neuroanatomic regions during multifocal neurological disease. Here, decreased cholesterol synthesis gene expression in astrocytes in spinal cord and

optic nerve was identified as a potential treatment target relevant to walking and visual disabilities, respectively. This disability specific approach represents a novel strategy for discovering tailored neuroprotective treatments for MS.

P200

Astrocyte Specific Transcriptomics Reveal an A1 Profile and Complement Activation in Optic Nerve during EAE

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Background: Multiple sclerosis (MS) is characterized by immune cell infiltration, glia reactivity and damage to different cell types in the central nervous system (CNS). Optic neuritis is common in MS and its model experimental autoimmune encephalomyelitis (EAE). Astrocytes are known to be important in both MS and EAE, but gene expression profiles within astrocytes during disease remain unknown.
Objectives: To determine gene expression profiles in astrocytes of the optic nerve in EAE using RiboTag Technology.
Methods: RiboTag mice expressing hemagglutinin (HA)-tagged ribosomal RNA specifically in astrocytes were created by crossing RiboTag mice with mGFAP -Cre mice line 73.12 (*GFAP-Cre 73.12 RiboTag*). Chronic active MOG_{35-55}-EAE was induced. Healthy mice were used as controls. At EAE day 50, mice were sacrificed, and optic nerves were collected. Astrocyte enriched RNA was immunoprecipitated, isolated and processed for RNA sequencing and bioinformatics analyses. Validation of the genes of interests was performed by qPCR and immunohistochemistry.
Results: RNA seq data showed that optic nerve astrocytes display a phenotype characterized by lipocalin2 (LCN2) as the top most significantly up-regulated gene during EAE. Further, these astrocytes acquire an A1 profile, with complement component C3 and SerpinG being among the most induced genes. Pathway analysis revealed the complement cascade as one of the most enriched pathways. This was accompanied by overexpression of C3a receptor (C3aR) by microglia/macrophages, suggesting crosstalk between microglia/macrophages and astrocytes during disease. This expression profile was not observed in either retinal astrocytes or optic nerve head astrocytes, underscoring the heterogeneity of astrocytes across regions during disease.
Conclusion: Here the RiboTag approach was used for the first time in the optic nerve in an animal model of MS. This cell-specific approach can offer therapeutically relevant insights into molecular mechanisms underlying visual disability in MS.

P201

The Interplay between Cellular Metabolism and Myelin Phagocytosis By Human Myeloid Cells in 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). The molecular control of this myelin clearance by myeloid cells (MDMs and microglia) is largely unknown. The metabolic state of myeloid cells (defined by oxidative phosphorylation; OXPHOS and glycolysis) has a major impact on cellular function.
Objectives: The aim of this study is to understand how myelin uptake can impact cellular metabolism in MS patient and healthy control donor MDMs. To explore how certain metabolic pathways can control the ability of human myeloid cells to phagocytose myelin.
Methods: Macrophages (MDMs) were cultured $CD14^+$ selected monocytes taken from whole venous blood samples of control donors and untreated MS patients. Myelin phagocytosis was measured using pHrodo-labeled myelin in a flow cytometry assay. The 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.

P202

Microglia Depletion Results in Axonal Protection in a Viral Model of Multiple Sclerosis

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Background: Intracranial (i.c.) inoculation of C57Bl/6 mice with the neuroadapted JHM strain of murine hepatitis virus (JHMV) causes encephalomyelitis and demyelination. JHMV is a well-accepted preclinical model of the human demyelinating disease multiple sclerosis (MS). Here, we demonstrate that depletion of microglia results in enhanced viral replication within the central nervous system (CNS) and decreased survival and axonal damage.
Objectives: Our research objectives are to better understand the functional contributions of microglia in both host defense and neuropathology in a model of viral-induced neurologic disease.
Methods: Seven days prior to i.c. infection with 600 PFU JHMV, 5-to-8-week old Thy1-YFP C57Bl/6 mice [medium-to-heavy caliber axons express yellow fluorescent protein (YFP)] were fed chow formulated with colony-stimulating factor-1 receptor inhibitor PLX3397 or PLX5622 which deplete microglia or the same chow without inhibitors as a control (kindly provided by

Plexxikon, Inc., Berkeley, CA) for the duration of the experiment. Animals were sacrificed at defined days post-infection (dpi) to evaluate CNS viral titers and immune cell infiltration via flow cytometry. In addition, axonal damage was determined by live two-photon imaging of YFP-axons.

Results: At 5dpi, flow cytometry for $CD11b^{+}CD45^{int}$ cells/g microglia from brains revealed a 53% decrease in PLX3397-fed animals and 91% decrease ($p<0.005$) in PLX5622-fed animals; however, $CD4^{+}$ and $CD8^{+}$ T cell and macrophage infiltration into the brain was unchanged, highlighting the specificity of microglia depletion. PLX-treated animals had a significant increase in axons lacking signs of focal axonal degeneration compared to animals fed control chow ($p<0.05$). At 5dpi, viral titers were increased in the brains of PLX3397 ($p=0.06$) and PLX5662-fed mice ($p<0.05$) compared to control animals. The impaired ability to control JHMV replication within the CNS of animals fed PLX3397 was correlated with diminished survival by 14dpi (33% survival) when compared to control mice (89% survival) ($p<0.05$).

Conclusion: Depletion of microglia prior to JHMV infection of the CNS resulted in increased mortality and impaired control of viral replication, highlighting an important role for microglia in host defense. Moreover, depletion of microglia resulted in muted axonopathy when compared to control animals arguing that early axonal damage in response to JHMV infection is mediated, in part, by microglia.

P203

Histone Deacetylase SIRT1 Mediates C5b-9-Induced Cell Cycle in Oligodendrocytes

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Background: Oligodendrocytes (OLG) 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 multiple sclerosis (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.

Methods: OLG progenitor cells (OPC) purified from the brain of rat pups were differentiated in vitro. As a source of sublytic C5b-9 we used normal human serum and assembled C5b-9 from purified complement components. To investigate the pathway specificity of C5b-9 modulation of SIRT1 expression, we treated OLG with c-jun antisense oligonucleotide and a protein kinase C (PKC) inhibitor (H7). The levels of SIRT1 and myelin basic protein (MBP) mRNA were measured using real-time PCR and SIRT1 phosphorylated at Ser27 (pSIRT1), total SIRT1, MBP, cyclin D1 and H3K9me3 protein expression were measured using western blotting.

Results: Our data show a significant decrease of pSIRT and SIRT1 during OPC differentiation associated with a decrease of H3K9me3, an increase of cyclin D1 expression in the first 24 hours and a sustained increase of MBP. Stimulation of OLG with sublytic C5b-9 for 3 hours resulted in an increase in SIRT1 mRNA and protein levels. pSIRT1 levels remained increased up to 18 hours after exposure to C5b-9. C5b-9-stimulated SIRT1 mRNA induction was abolished after c-jun antisense oligonucleotide and H7 pretreatments. H3K9me3 levels also gradually increased after stimulation with C5b-9 as compared to unstimulated, as did cyclin D1 expression, indicating cell cycle activation. In addition, MBP mRNA and protein were significantly reduced after exposure to C5b-9.

Conclusion: Our data suggest that C5b-9 induces cell cycle activation by increasing SIRT1 levels through a c-jun and PKC dependent manner. SIRT1 regulates the levels of repressive methylation of H3K9, thus possibly modulating the levels of cyclin D1 and MBP. C5b-9-mediated MBP reduction may play an important role in inflammatory demyelination by affecting the OLG ability to express myelin proteins.

Pathogenesis - the blood-brain-barrier

P204

Mcam on the BBB Contributes to Neuroinflammation By Promoting the Recruitment of Encephalitogenic T Lymphocytes into the Central Nervous System

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Background: Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) driven by the migration of immune cells across the blood-brain barrier (BBB). To cross the BBB, inflammatory leukocytes use cell adhesion molecules. We have recently identified melanoma cell adhesion molecule (MCAM) as an adhesion molecule expressed by effector T cells and used by them to migrate into the CNS in both MS and its animal model, experimental autoimmune encephalomyelitis (EAE) (Larochelle *et al*. 2012, 2015). In parallel, we also detected MCAM expression on endothelial cells of the BBB (BBB-ECs) in lesions of both MS and EAE, but its function there remains ambiguous.

Objectives: To define the role of MCAM on BBB-ECs in mediating immune recruitment into the CNS in MS and EAE.

Methods: To decipher the precise function of MCAM on BBB-ECs, we generated an MCAM knockout (KO) mouse model on

the C57BL/6 background, and conducted *in vitro* adhesion and migration assays using MCAM KO versus wildtype (WT) primary BBB-ECs. To evaluate whether MCAM on BBB-ECs contributes to the development of neuroinflammation, we conducted experiments of passive EAE by adoptively transferring encephalitogenic T cells into MCAM KO versus WT mice. Lastly, we investigated *in situ* whether the expression of MCAM on the BBB correlates with increased inflammation in MS lesions.

Results: *In vitro*, the absence of MCAM on the BBB-ECs (i.e. MCAM KO BBB-ECs) resulted in reduced adhesion of inflammatory T cells to the endothelial monolayer and decreased migration across it. *In vivo*, EAE clinical severity and CNS immune infiltration were diminished in MCAM KO recipient mice as compared to WT recipients. *In situ,* we observed that the expression MCAM is preferentially upregulated in active MS lesions.

Conclusion: Our results demonstrate that MCAM on the BBB contributes to neuroinflammation by promoting the migration of inflammatory T cells into the CNS. Our goal is to establish MCAM as a promising therapeutic target to treat MS without impairing CNS immunosurveillance.

P205

Spatiotemporal Distribution of Fibrinogen in Marmoset EAE and Human MS Inflammatory Demyelinating Lesions

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Background: MS is an inflammatory demyelinating disease of the central nervous system, and despite its prevalence, the proximate trigger of the immune response is unknown. Experimental autoimmune encephalomyelitis (EAE) in the common marmoset recapitulates many radiological and pathological features of focal MS lesions in the cerebral white matter, unlike traditional EAE in rodents. Thus, marmoset EAE provides an opportunity to investigate how lesions form, as well as the relative timing of factors involved in lesion pathogenesis, especially during early stages of the disease.

Objectives: The objective of the study was to investigate the involvement of the plasma protein fibrinogen (a marker for blood-brain barrier (BBB) leakage also linked to a pathogenic role in inflammatory demyelinating lesion development), in marmoset EAE lesion pathogenesis, as well as sustained inflammation in human MS lesions.

Methods: We used MRI to track EAE lesions *in-vivo* to determine their age, stages of development, location, and histopathology for cellular composition. We focused on fibrinogen, inflammatory cells, and glia including microglia, astrocytes, and peripheral lymphocytes.

Results: We found that fibrinogen, not other markers of BBB leakage (albumin, dysferlin), is deposited around the central vein in early EAE lesions that are <6 weeks old, preceding demyelination and visible gadolinium enhancement on MRI; thus, fibrinogen deposition is one of the earliest detectable events in lesion pathogenesis. In slightly older lesions, fibrinogen is found inside microglia, suggesting rapid clearance. Quantification demonstrates positive correlation of fibrinogen deposition with accumulation of inflammatory cells, including microglia, macrophages, and T-cells. The peak of fibrinogen deposition coincides with the onset of demyelination and axonal loss. In samples from human MS tissue, fibrinogen was only found at the edge of chronic active lesions, which have ongoing demyelination and inflammation, but not in chronic inactive lesions; thus, fibrinogen may play a role in sustained inflammation even in the chronic setting.

Conclusion: Our data support the notion that fibrinogen is a key player in the early pathogenesis, as well as sustained inflammation, of inflammatory demyelinating lesions.

P206

Rapid Improvement of Symptoms after Fibrinolysis in a Patient with Multiple Sclerosis Exacerbation

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Background: To describe a unique case of rapid improvement in multiple sclerosis (MS) exacerbation following fibrinolytic therapy.

Objectives: Most demyelinating lesions in MS emerge around deep cerebral venules and are associated with fibrin deposition. Fibrin depletion ameliorates clinical symptoms in a mouse model for MS. We and others reported acute demyelinating lesions with restricted diffusion (ADLRD) seen on brain and spinal cord MRI in selected MS patients during clinical relapse. The pathogenesis of restricted diffusion is not clear, but an ischemic process is possible.

Methods: The patient is a 38-year-old woman with relapsing-remitting MS treated with fingolimod. Her baseline neurological exam was significant for mild right hemisensory deficit to touch and right hemiparesis. The patient developed acute onset of flaccid right-sided weakness and hypoesthesia involving the face, arm and leg. Due to rapid and fulminant onset of neurological deficit, she was suspected to have a stroke and received intravenous recombinant tissue plasminogen activator (rtPA, 0.9 mg/kg) at 227 minutes after symptom onset. The patient was followed with serial neurological exams and MRI.

Results: Prior to rtPA treatment, her NIH Stroke Scale score was 9. The patient's deficit rapidly improved in 5.4 hours after intravenous rtPA administration (NIH Stroke Scale score was 1, right upper limb drift). Brain MRI at 20 hours after symptom onset revealed a large (2.8x2.4cm) symptomatic, contrast-enhancing ADLRD in the left centrum semiovale. However, the patient's deficits deteriorated again by 21 hours from initial symptom onset with flaccid hemiplegia of the right side and NIH Stroke Scale score of 12. After a 5-day course of IV methylprednisolone

followed by 5 sessions of plasmapheresis, she partially regained motor strength. NIH Stroke scale score on day 15 was 7. Hypercoagulability tests were negative.
Conclusion: Rapid transient clinical improvement after a single infusion of rtPA during acute MS relapse suggests that fibrin is a potential therapeutic target in acute MS exacerbation.

P207
Immunomodulatory Role of Adiponectin in Experimental Models of Multiple Sclerosis
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Background: Multiple sclerosis (MS) can be mimicked by the animal model experimental autoimmune encephalomyelitis (EAE). In both MS and EAE, activation of immune cells against CNS antigens occurs in the periphery as self-reactive lymphocytes are detectable in the blood and gain access to the CNS by crossing the blood brain barrier (BBB) via mechanisms that are still being elucidated. Several recent studies showed that obesity during childhood/young adulthood confers increased risk of developing MS. Adipose tissue is an active source of cytokines, named adipokines, that regulate metabolic pathways, immune and inflammatory responses. Adiponectin is an adipokine with multiple anti-inflammatory effects which is increased upon calorie restriction, and decreased with obesity. Recent evidence suggests that the BBB is activated as a result of metabolic and inflammatory changes that occur in response to obesity. Adiponectin has been reported to have a variety of protective effects on endothelial function and therefore changes in its serum levels can potentially impact the BBB.
Objectives: To study the immunomodulatory role of adiponectin in the context of MS.
Methods: EAE induction: mice were immunized with MOG $_{35-55}$ to induce EAE. Clinical scoring was performed daily under blinded conditions. BBB *in vitro* model: human cerebral microvascular endothelial cells (HCMEC) were co-cultured with primary human astrocytes in a transwell system. The *in vitro* barrier integrity was assessed by measurements of trans-endothelial resistance (TEER) or by diffusion of fluorescein-dextran. Sodium Fluorescein Assay for BBB Permeability *in vivo*: mice were injected i.p. with fluorescein, brain regions of interest were collected and analyzed for fluorescein content.
Results: Administration of the globular or of the full-length adiponectin protein during EAE inhibited the disease. Furthermore, mice with genetic targeted deletion of adiponectin developed more severe EAE. Adiponectin treatment resulted in down-regulation in the spinal cord of vascular adhesion molecules (ICAM-1 and VCAM-1) associated to the BBB. Using *in vitro* approaches, we observed that endothelial cells and astrocytes (constituents of the BBB) express adiponectin receptor 2 and exposure of an *in vitro* human BBB model to adiponectin improved barrier integrity and reduced solute diffusion.
Conclusion: Based on these preliminary findings, we believe that adiponectin exerts neuroprotective effects that control leukocyte entry into the CNS via regulation of BBB permeability.

Prognostic Factors

P208
Prognostic Factors of Disability and Depression in Patients with Multiple Sclerosis: A Longitudinal Analysis of Electronic Health Records
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Background: Predicting the accrual of neurological deficits from multiple sclerosis (MS) is challenging. Most prior research has focused on the Expanded Disability Status Scale (EDSS), a modestly reliable tool heavily weighted by ambulation. Far fewer studies have investigated other outcomes, much less multiple outcomes in the same population.
Objectives: To identify prognostic factors of Timed 25-Foot Walk (T25FW; a robust measure of lower limb disability), Patient Health Questionnaire 9 (PHQ-9; a depression tool), and Performance Scales Sum (PSS-8, a measure of global disability) in relapsing remitting (RR) MS.
Methods: Electronic health records (EHRs) for 2,083 RRMS patients at The Mellen Center for MS, Cleveland Clinic, with a clinical visit between 1/1/2010-5/29/2012, and at least one additional visit within the ensuing 3 yrs were included in this retrospective cohort study (16,538 visits). T25FW, PHQ9, information for PSS-8, demographics, smoking status, body mass index (BMI), and insurance payer were extracted from the EHRs. Appropriate models were adjusted for vascular comorbidities, disease duration, disease-modifying therapies, median income of patient's ZIP code, marital status, walking aid use, and time between clinical visits. Gender- and race-specific differences were examined.
Results: T25FW speed: Older age, longer disease duration, higher BMI, lower median income, and a higher PHQ-9 scores predicted slower speeds. Walking speeds were slower in females than males, black patients than white patients, current/former smokers than never smokers, and Medicaid/Medicare beneficiaries than the privately insured.
PHQ9 score: Younger age, higher BMI, lower median income, and Medicaid beneficiaries predicted higher depressive scores. Current smoking predicted a 2 point increase in PHQ9 scores compared to never smokers. The effect of age and BMI were restricted to females and white patients, respectively.
PSS-8: Older age, higher BMI, lower median income, and higher PHQ-9 scores predicted accelerated disability. Faster disability accrual was evident among former/current smokers than never smokers, and Medicaid/Medicare beneficiaries than the privately insured. The effect of age was 2-fold greater in males than females.
Conclusion: We conducted a comprehensive longitudinal analysis of disability accrual. We identified multiple predictors of adverse outcomes; smoking, higher BMI, and lower socioeconomic status predicted worse outcomes for all measures.

P209

Vitamin D Levels and MS Measures in Progressive Multiple Sclerosis

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Background: 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 clinical and MRI features in progressive multiple sclerosis subjects (Primary: PPMS, Secondary: SPMS) from the ibudilast phase II clinical trial (NN102/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 mean difference between PPMS and SPMS was found on both 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 including T25FW, 9HPT, EDSS and SDMT. Associations between vitamin D3 level and WB MTR remained significant (p=0.02) in multivariate analysis with consideration of age, gender, disease duration, time of serum obtained and latitude of study site, every 1 ng/ml increasing in vitamin D3 resulted 2.1 percent unit increasing in WB MTR.
Conclusion: 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.

P210

Long-Term Predictors of Relapse or Disability Progression in Patients with Multiple Sclerosis in the Transforms and Freedoms/Freedoms II Studies

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Background: Disease and treatment histories can be useful predictors of long-term clinical outcomes in patients with multiple sclerosis (MS).
Objectives: To assess the utility of variables at baseline and over the first year of the phase 3 FREEDOMS/FREEDOMS II and TRANSFORMS studies and their extensions in predicting long-term clinical outcomes.
Methods: This *post hoc* analysis used pooled data from the fingolimod and placebo groups of the FREEDOMS/FREEDOMS II studies, and from the fingolimod and intramuscular interferon β-1a groups of TRANSFORMS. In the extensions, all patients received fingolimod. Multiple logistic regression analysis was used to assess which patient's disease characteristics at baseline or from baseline to month (M) 12 predicted M3 and M6 confirmed disability progression or relapses (3MCDP/R, 6MCDP/R) during M12–48. Variables at baseline (M0) and for M0–12 included sex, age, duration since diagnosis, previous treatment, percentage brain volume change (PBVC), lesion count, volume and activity (defined as ≥1 Gd+ or ≥2 new T2 lesions), Expanded Disability Status Scale (EDSS) score and relapse rate.
Results: In total, 1118 and 1103 patients were included in the FREEDOMS analysis sets for 3MCDP/R and 6MCDP/R, respectively, and 769 patients were analyzed for both outcomes in TRANSFORMS. In the FREEDOMS study, predictors of both 3MCDP/R and 6MCDP/R (odds ratio [95% CI]), respectively, were MS duration since diagnosis (1.036 [1.008–1.064], p=0.0102; 1.04 [1.011–1.069], p=0.0059), EDSS score at M0 (1.233 [1.103–1.379], p=0.0002; 1.229 [1.097–1.378], p=0.0004), number of relapses in M0–M12 (2.741 [1.900–3.953], p<0.0001; 2.788 [1.931–4.025], p<0.0001), lesion activity in M0–M12 (1.946 [1.214–3.120], p=0.0057; 1.638 [1.012–2.651], p=0.0444), and PBVC from M0–M12 (0.868 [0.758–0.994], p=0.0404; 0.869 [0.756–0.999], p=0.0486). In TRANSFORMS, predictors of 3MCDP/R and 6MCDP/R, respectively, were EDSS score at M0 (1.221 [1.078–1.382], p=0.0017; 1.228 [1.081–1.395], p=0.0016) and number of relapses in M0–M12 (1.655 [1.199–2.285], p=0.0022; 1.774 [1.279–2.460], p=0.0006); previous MS treatment (1.613 [1.135–2.292], p=0.0077) was a predictor of 6MCDP/R.
Conclusion: Baseline EDSS score and number of relapses during the first year were the most consistent predictors of disability worsening or relapses over 4 years in the phase 3 fingolimod trials. These findings support early review of treatment regimens to help to prevent worsening disability.

P211

Association of Vitamin D Status and Clinical and Radiological Outcomes of Relapsing Remitting Multiple Sclerosis

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Background: Recent studies suggest that low serum vitamin D levels are important environmental factor in MS. Vitamin D deficiency is a recognized risk factor for relapsing remitting multiple sclerosis (RRMS) and is associated with increased disease activity. It has also been proposed that the lower the vitamin D levels are correlated with disability. It has also been proposed that the lower the vitamin D levels are correlated with magnetic resonance imaging (MRI) activity.
Objectives: The aim of this study was to compare the serum levels of vitamin D in patients with RRMS patients and to determine its association with clinical and radiological findings.
Methods: 250 RRMS patients, 181 female, mean age 40.31 years of whom 25-(OH)-D serum concentrations and 3 T brain and cervical MRI were obtained included in the study. All clinical data including relapse at visit and expanded disability status scale were recorded in a standardized manner by a multiple sclerosis experienced neurologist.
Results: The largest group (68.8%) showed significant vitamin D deficiency (<20 ng/ml), 18.4 % showed the suboptimal level of vitamin D (20-30 ng/ml). The normal level of 25(OH)D (>30 ng/ml) was observed in 12.8 % of the patients. Statistically significant correlation was observed between the vitamin D status and frequency of relapses and disability. Overall, there was a negative correlation between vitamin D level and EDSS score (P = 0.001). Statistically significant correlation was observed between the vitamin D status and T2 lesion load and cervical lesions. P = 0.001) There was no statistically significant correlation in the association of vitamin D and contrast-enhancing T1 lesions (p=0.843).
Conclusion: Our findings confirm that deficiency of vitamin D in patients with MS is correlated with clinical course and radiological findings. Future studies should investigate whether vitamin D supplementation in MS patients may decrease clinical and MRI activity.

P212

Tumefactive Sclerosis and Leptomeningeal Gadolinium Enhacement: Case Report

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Background: Tumefactive lesions are a rare presentation of central nervous system idiopathic inflammatory demyelinating disease, characterized by lesions that can mimic tumors in magnetic resonance imaging (MRI): more than 2cm in size and with associated mass effect, perilesional edema and ring gadolinium enhancement. It has been stablished a correlation between meningeal inflammation and subpial cortical demyelinating lesions, with documented B cells follicles in meninges, indicating disease activity and representing a marker of gray matter damage and disease progression. The leptomeningeal enhancement is being studied as a predictor of Multiple Sclerosis (MS) development in asymptomatic patients with high risk factors as well as in those who already have the disease, as a predictor of new MS lesions.
Objectives: To describe a case of aggressive tumefactive variant of MS preceded by important leptomeningeal enhancement, emphasizing the important predictive value of this entity.
Methods: Case report. A 41 years old female with diagnosis of MS since 2011, treated with IFNβ-1[a], with an Expanded Disability Status Scale (EDSS) of 1.5. Annual control MRI showed important leptomeningeal enhancement and presented worsening in the next MRI control 3 months later. After a few weeks she presented disexecutive syndrome, homonymous left hemianopsia, left pyramidal, hemisensitive and hemicerebellar syndromes, rising EDSS up to 6.0. MRI showed tumefactive lesions affecting right parietal lobe and splenium, with intense gadolinium enhancement. Biopsy was performed searching for tumoral lesion, resulting only in important inflammatory process. We concluded tumefactive sclerosis.
Results: The patient started therapy with high doses of corticosteroids followed by Rituximab. She had partial recovery with an EDSS of 3.0 that correlated with volume decrease in MRI lesions.
Conclusion: Leptomeningeal enhancement is considered an important predictor of development, activity, relapse, disability and progression of the disease, also in MS variants like tumefactive ones.

PROs and QOL

P213

Observations of a Multiple Sclerosis Patient-Centered Specialty Practice: Analysis of Depression Patterns

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Background: Patient-centered care models require practices to organize care around patients and actively engage them in planning and managing their treatment and conditions. The Multiple Sclerosis (MS) and Neuroimmunology Center at Georgetown University is undergoing transformation to become a patient-centered specialty practice (PCSP) and aims to become the first MS PCSP recognized by the National Committee for Quality Assurance (NCQA). To determine the impact of transformation on patient experience and outcomes, a cohort of patients treated by the Center will be followed for 3 years in the MS-Advance Study.
Objectives: Since depression is a major MS comorbidity that could be aided by early identification and intervention, we examined baseline target variables and demographics of study participants to determine the prevalence of depression and whether degree of disability, cognitive status, or time since diagnosis predicted its occurrence.
Methods: Patients with relapsing-remitting or secondary progressive MS were enrolled in the Study by the Center (n=520). Patient-reported outcomes were collected through a novel online platform. Patient Health Questionnaire 9 (PHQ-9) scores were analyzed to identify patterns of depression. A multivariate linear regression analysis was run to correlate PHQ-9 scores with demographics and 3 target variables: Expanded Disability Status Scale (EDSS) score, Symbol Digit Modalities Test (SDMT) score, and time since MS diagnosis.

Results: 23% of participants reported depression in their past and 22% screened positive for moderate, moderately severe, or severe depression on their baseline PHQ-9. The degree of disability, cognitive status, or time since diagnosis did not appear predictive of depression. Income was the only variable with a statistically significant relationship with occurrence of depression. For those with an income between $100,000 and $149,000/year and income greater than $150,000/year (compared to those with an income of less than $15,000/year), there was a corresponding 5.4 and 7.7 unit decrease in PHQ-9 score, respectively, holding gender, race, marital status, living situation, EDSS score, SDMT score, and time since diagnosis constant.
Conclusion: Given the surprising result that we cannot readily predict risk of depression, an effective MS PCSP would integrate a mental health professional as part of the care team and yearly depression screening for all patients to meet patients care needs.

P214

Voice of the Patient: Effect of Neuroperformance Deficits on Interference with Daily Activities

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Background: As we refine the assessment of MS-related disability, it is essential that we include direct input from Persons with MS (PwMS) concerning the clinical meaningfulness of measures and what are the meaningful transitions in levels of functional status.
Objectives: The purpose of this study was to gain input from PwMS about the meaningfulness of four neuro-performance measures (NPM) in relation to their daily activities.
Methods: 62 PwMS were assessed with NPM measuring impairment in mobility (MOB), upper extremity (UE), visual (VIS), and cognitive (COG) function. After each test, participants were presented with 5 examples of everyday activities that are dependent upon each of the domains assessed and were asked to indicate, using a 0-10 scale, the impact that impairment in each of the 4 NPM has on each of those 5 daily activities.
Results: Participants reported a range of interference in daily activities in the MOB domain (median range for each of the five (Mr): 4-9; median total (Mt): 29). In contrast, the UE (Mr = 0-3; Mt= 10) and processing speed (Mr = 0-4; Mt= 12) domains showed a smaller range with less reported interference. The least amount of interference was for the VIS domain (Mr = 0-1; Mt= 3.5). Correlation analysis between NPM scores and interference scores showed positive and significant correlations for MOB (Spearman r = 0.59 to 0.68 for individual activities, for total score, r = 0.73, p<0.001) and UE (individual: r = 0.44 to 0.59, total: r = 0.61, p<0.001); in contrast, for both VIS and COG, correlations were non-significant and negative (VIS: r<-0.3; COG: r<-0.3). Interference scores for participants stratified by high and low disability levels in each domain were significantly different in the MOB (median = 38 vs. 19, p<.001) and UE domains (median = 21 vs. 3, p<.001), but not for VIS (6 vs. 2, p = 0.07) or COG domains (15.5 vs. 9, p = 0.34). Through regression analysis with modeling, a quantitative relationship between the NP and interference scores was identified for the mobility and UE measures, but not VIS or COG domains.
Conclusion: Strong correlations between NP and interference scores were found in the MOB and UE domains, such that a quantitative relationship was estimated; however, a similar relationship was not found in the VIS or COG domains. The VIS and COG NPM deficits may represent sub-clinical findings or indicate that the NPM tasks were difficult for participants to relate to regular activities.

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Successes and Challenges in Capturing Web-Based Patient-Reported Outcomes from Multiple Sclerosis Patients to Meet Patient-Centered Care Goals

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Background: The chronic, complex nature of multiple sclerosis (MS) requires continuous specialized care. The National Committee for Quality Assurance (NCQA) Patient-Centered Specialty Practice (PCSP) model is optimal to deliver such care, but NCQA has yet to recognize a MS practice as a PCSP. Use of a web-based platform to capture patient reported outcomes (PROs) may help MS practices meet NCQA PCSP standards and achieve MS care goals (e.g., reduce relapses). Notably, the PCSP model and clinical trials (CTs) share potential benefits such as improved care processes and analysis of at-risk patients. The use of a web-based system to capture PROs may help achieve shared PCSP and CT goals for MS care.
Objectives: To assess the advantages and disadvantages of capturing PROs online to meet PCSP standards and achieve MS care goals.
Methods: Participants in the Georgetown University MS-Advance Study completed web-based PROs (Neuro-QoL; Modified Fatigue Impact Scale; Patient Health Questionnaire, 9 item; Work Productivity and Activity Improvement Questionnaire; Treatment Satisfaction Questionnaire for Medication; Clinician and Group Consumer Assessment of Healthcare Providers and Systems) and journals. Responses were analyzed for reported treatment use, MS symptoms, and relapses. Responses from any patient who completed ≥1 PRO or journal from January-August 2017 were analyzed.
Results: 518 patients enrolled in the MS-Advance Study. 310 patients completed ≥1 PRO or journal entry. 191 patients reported using a disease modifying agent. Of the 259 patients who reported MS symptoms, 212 patients reported ≥3 MS symptoms daily. The top 3 daily symptoms reported by these patients (n=259) were poor balance (n=122), numbness or tingling (n=123), and leg or foot weakness (n=128). 257 patients reported a relapse in the last year.
Conclusion: Continuous collection of PROs via a web-based platform can help identify patients with active disease outside of the clinic setting. Some patients provided responses with prompt (e.g. email reminder), while others completed entries without

prompt; these behaviors warrant further study to determine how to elicit more complete and timely reports from patients. These results show that continuous collection of PROs can equip care teams with vital information to address PCSP goals, such as improved care management.

P216

Differences in Symptoms, Functioning and Quality of Life between People with Relapsing Versus Progressive Forms of Multiple Sclerosis

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Background: iConquerMS™ is a multiple sclerosis (MS) people-powered research network established in 2014, funded by the Patient-Centered Outcomes Research Institute. To date, more than 4,000 people with MS have joined iConquerMS™ and consented to provide data for research purposes. Four baseline surveys on the iConquerms.org portal are: Demographics; MS characteristics; Neuro-QoL Adult Short Form (Neuro-QoL) survey; and, PROMIS® Global Health Survey (PROMIS®). In June 2017, a de-identified dataset from the baseline surveys for more than 2,000 respondents was analyzed to assess differences between symptoms, functioning and quality of life for people with MS self-reporting relapsing-remitting ("relapsing") versus secondary+primary progressive ("progressive") forms of MS.
Objectives: 1) Create graphical comparisons of the characteristics of those respondents self-reporting relapsing versus progressive forms of MS. 2) Undertake statistical comparisons of the characteristics of the respondents self-reporting relapsing versus progressive forms of MS. 3) Reveal differences between relapsing and progressive forms of MS in the relative ranking of symptoms, functioning and quality of life.
Methods: Likert Scale questionnaire answers were converted to integer value raw scores. Total scores for each Neurol-QoL and PROMIS® domain were rank ordered for relapsing and for progressive forms of MS. Pairwise comparisons of the scores for each Neuro-QoL and PROMIS® domain for relapsing versus progressive forms of MS were performed using Chi-squared statistics or Fisher's Exact Test. Cohen's d was calculated for differences between the total scores for each Neuro-QoL and PROMIS® domain for relapsing versus progressive forms of MS and were rank ordered.
Results: For relapsing forms of MS, the 5 most affected of 12 Neuro-QoL domains were (in descending order of severity): fatigue, satisfaction with social roles and activities ("satisfaction"), sleep disturbance, cognitive function and anxiety. Whereas, for progressive forms of MS the top 5 most affected domains were: satisfaction, fatigue, lower extremity function, ability to participate in social roles and activities and sleep disturbance. The largest Cohen's d for the difference between relapsing and progressive forms of MS was for lower extremity function with a value of 1.4.
Conclusion: This characterization of the iConquerMS™ network highlights the quality of life areas that affect people with different forms of MS the most and provides an excellent basis for future research.

P217

Voice of the Patient: Impact of MS Symptoms on Daily Activities

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Background: As the assessment of MS-related disability is refined, it is essential to include direct input from Persons with MS (PwMS) concerning the clinical meaningfulness of measures and the impact MS symptoms have on their everyday functioning.
Objectives: To obtain the perspectives of PwMS concerning the impact that MS impairment has on areas of everyday function.
Methods: 62 PwMS were asked to think about any MS symptoms which interfere with their daily activities, other than walking speed, manual dexterity, vision, and speed of information processing. They were then presented with 5 common symptoms, one by one, and asked if they were affected by each symptom. For those that were endorsed, they were asked to identify an activity that is affected by that symptom. They were then asked to describe up to 5 additional MS symptoms that interfere with their daily activities, and identify an associated activity for each.
Results: A majority of respondents endorsed the impact of the 5 symptoms presented: fatigue (90.3%), incoordination (88.7%), spasticity (75.6%), bladder dysfunction (69.4%) and pain (54.8%). Fourteen additional symptoms were spontaneously mentioned as affecting daily activities at frequencies ranging from 22.6% (parasthesias) to 3.2% (Lhermitte's sign). Participants identified 31 daily activities associated with these symptoms. Many different activities were identified as being affected by more than one symptom (mean 2.1, range 1-7). For example, walking was noted to be affected by 7 different symptoms and sleeping was affected by 4. Most symptoms affected more than one activity (mean 3.2, range 0-11). For example, spasticity was noted to affect 11 different activities and pain affected 8.
Conclusion: In this study, participants used many different words to describe various symptoms. These symptoms converged to impact functionality in distinct disability dimensions. The importance of symptom management in MS care is evidenced by the number of daily activities that are affected by each symptom. Likewise, the complexity of addressing impairments in daily activities is increased by the number of symptoms that may be related to each impairment. Measures of specific performance dimensions (walking, upper extremity function) are clinically relevant because of the relationship to symptoms and daily activities.

P218

Relationships between Sleep, Fatigue and Depression Differ in Pediatric Multiple Sclerosis and Monophasic Demyelinating Disorders

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Background: Decreased sleep quality is associated with fatigue and depression in adults with multiple sclerosis (MS) and otherwise healthy children. The prevalence of sleep problems in pediatric MS and their relationship with fatigue and depression is not well studied.
Objectives: (1) To determine the prevalence of sleep abnormalities in MS youth. (2) To examine the relationship between sleep, fatigue and depression in this group.
Methods: Youth with MS or monophasic demyelination (mono-ADS) were recruited consecutively from the Neuroinflammatory Clinic at SickKids (SK), Toronto, Canada. Participants completed questionnaires: Children's Sleep Habits Questionnaire (CSHQ), Child Behavior Checklist Sleep Composite (CBCL), Pediatric Multidimensional Fatigue Scale (PedsQL) and Center for Epidemiological Studies Depression Scale (CES-DC). The CSHQ contains 8 subscales (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, daytime sleepiness). Mann-Whitney U tests were used to analyze differences between scores in the groups and Spearman's correlations to examine relationships between sleep, fatigue and depression. SK ethics approval was obtained.
Results: 77 participants (aged 5-17) were included (MS=30, mono-ADS=47). 57% of the MS and 55% of the mono-ADS group reported at least one sleep problem (p=0.91). 24% of the MS and 25% of the mono-ADS group met the threshold for a potential sleep disorder (p=0.77). Total sleep scores were not different between the MS and mono-ADS groups (p=0.68). Higher fatigue (Median(IQR): 22.5(12.5) vs. 12.0(10.0); p=0.004) and depression (10.5(9.3) vs. 5.0(6.0); p=0.008) were seen in the MS group than mono-ADS. Total sleep scores positively correlated with both fatigue (R=0.66, p<0.001) and depression (R=0.73, p<0.001) in the mono-ADS, but not the MS group. In the mono-ADS group, 7 CSHQ subscales positively correlated with fatigue and depression. However, only sleep duration positively correlated with fatigue and depression in the MS group.
Conclusion: Self-reported levels of overall sleep problems were associated with increased fatigue and depression in mono-ADS, but not MS. Reasons for this are unclear, but reinforce the role that ongoing disease activity may play in fatigue and depression in MS youth. Objective measures of sleep may provide further insight into the nature of the relationship between sleep, fatigue and depression in youth with demyelination.

P219

Patient Feedback on MS Mosaic Study's App Design

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Background: How multiple sclerosis (MS) lesions develop, what determines their extent or location, what symptoms are imposed, and how severe these symptoms are, depend on complex interplays between genetics, environmental conditions, biorhythms, medications, and even emotional states. Collecting data that represents this complexity, and developing the right predictive models for its analysis, will be absolutely crucial if we are to understand MS and provide personalized care.
Objectives: We have developed a novel mobile application that captures a great deal of this data, but its utility relies on the ability to keep research subjects engaged in data entry. In this work, we presented potential users with a demo version of our app and gathered feedback on its utility and design.
Methods: MS Mosaic is a Research Kit-based app designed to capture data on subjects' MS symptoms, medications, activity levels, sleep patterns, and iPhone-based task performance. This data can be viewed by the user via a graphical dashboard and textual reports, one of which is aimed at informing their provider. Subjects watched an 11-minute video demonstration of our mobile application's design and features. They then completed an open-ended survey that captures their impressions about the application's consent process, survey instruments, tasks, data visualizations, and resources. Responses were analyzed by the statisticians involved in this study.
Results: Seventeen subjects provided their input on app design, 14 (82%) of which were MS patients. More than 70% of responses were generally favorable within each section of the application. Favorable responses were seen in the Journal section (100%, p=0.00005), Dashboard (88%, p=0.0003), Weekly Reports (82%, p=0.008), Activities section layout (82%, p=0.008), Activities section tasks (76%, p=0.026), and Learn Section (71%, p=0.072).
Conclusion: The "Learn" section rated most poorly because of a desire for more features, like a user forum, comparative metrics between to all users, links to other active research studies, and general tips on MS management. Comments on the best received section (Journal) suggested offering an open field for general comments about the day by the primary user or their caregiver. Several subject suggestions are already built into the application, but were not highlighted in the brief demonstration video. Only one respondent disliked the user interface and app behavior overall.

P220

The Patient Derived Ambulation Scale (PDAS): A Single-Item, Patient-Reported Outcome Measure of Ambulation in Multiple Sclerosis Patients

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Background: Quantification of ambulation in clinical practice is desirable, but the 500 meter walk is not practical. We developed the Patient Derived Ambulation Scale (PDAS) as a patient reported outcome measure (PROM), with connection to the Expanded Disability Status Scale Ambulation Score.
Objectives: Determine the feasibility and validity of a single-item PROM of ambulation, the PDAS.
Methods: The PDAS will be compared to a number of other ambulation and lower extremity function tests. These will include the Walking Speed Test, Multiple Sclerosis Walking Scale 12, the NeuroQOL Lower Extremity subscale, and the Patient Determined Disease Steps.
Results: The PDAS was feasible to implement into clinical practice, requiring seconds of clinician time to review and interpret. Full analyses will be presented at the meeting with comparisons to other validated ambulation measures.
Conclusion: The PDAS is a single-item, patient reported outcome measure that is easy to implement into routine clinical practice and provides quantifiable information regarding a patient's ambulatory abilities. The PDAS may prove useful for tracking disease worsening, response to therapy, and identifying patients with progressive MS.

P221

Patient Perspectives on the Clinical Definitions and Impact of Multiple Sclerosis Progression

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Background: In the disease course of multiple sclerosis (MS), patients may transition from an initial isolated event (clinically isolated syndrome), through relapsing–remitting MS (RRMS) to secondary progressive MS (SPMS). There is growing recognition of the need to understand patient perspectives on MS progression; however, this understanding is lacking.

Objectives: To obtain personalized insights into patient attitudes towards MS progression, understanding of clinical definitions and impact to help improve discussions between healthcare professionals (HCPs) and patients with MS.

Methods: In-depth, qualitative telephone interviews about MS progression were conducted with a focused group of patient authors: KF (RRMS for 1 year), JB (RRMS for 18 years) and KM (SPMS for 6 years).

Results: Patients reported differing levels of MS progression awareness. KF understood the importance of lesion activity and relapses but was unsure what 'MS progression' meant, commenting: "I understand it in terms of how the disease will affect me in the future – how it may limit what I can do". JB and KM knew about 'progression to SPMS' but were reluctant to discuss it with their physicians, with JB aware that it would raise difficult questions about disease management.

MS is classified into four distinct forms: primary progressive MS, progressive–relapsing MS, RRMS and SPMS (Lublin et al. *Neurology* 1996;46:907–11). These classes are widely accepted by HCPs and play an essential role in treatment. However, patients may not understand or relate to the terminology. JB remarked that the different definitions make patients feel "compartmentalized", a point echoed by KM, who stated that terms were "confusing" and "frustrating". JB commented: "Putting a label on disease progression may do more harm than good. For example, will I still be able to get my treatment?". KM observed that while physicians may want to group patients, many people struggle to relate these terms to their daily lives, saying that "the classifications do not help me live with the reality of having MS".

Conclusion: Patients with MS may not fully understand 'disease progression' or the different clinical classifications used by HCPs, and those with RRMS may fear being labeled as having SPMS. There is a clear need for more patient-friendly language to describe MS progression and to facilitate HCP–patient discussions about the disease. It may be more appropriate to describe MS progression in terms of a disease spectrum.

P222

Current Correlations between Disease Modifiers and Symptom Experiences from the MS Mosaic Study

Dr. Fletcher L Hartsell, MD MPH[1] and Prof. Katherine Heller, PhD[2]

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Background: Nearly every person with multiple sclerosis suffers from persistent symptoms, but very little is known about whether these symptoms correlate with their current disease modifier.

Objectives: To evaluate whether membership within MS populations defined by common symptom experiences is predictive of current disease modifier use.

Methods: MS Mosaic is a longitudinal study (NCT02845635) that combines data from a mobile platform with existing biomarkers and then utilizes machine learning methods to help reveal a more comprehensive picture of MS. Continuously collected data from participants' daily symptom surveys and medication diaries is analyzed through a Bayesian generative hierarchical model that uses a Dirichlet process at a higher level and then represents the observed data at a lower level, providing a particular patient's "symptom-based sub-group" membership and attempts to predict their current disease modifier use (if any).

Results: Disease subtypes can be discovered by combining the symptom/medication diaries from the MS Mosaic app and machine learning clustering methodology.

Conclusion: The ability of these identified "symptom-based subgroups" to predict a given patient's current disease modifier is described.

P223

Current Correlations between Disease Modifiers and Physiologic Measurements from the MS Mosaic Study

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Background: Many people with multiple sclerosis suffer from mobility impairments or sleep disturbance, but very little is known about whether these symptoms correlate with their current disease modifier.

Objectives: To evaluate whether physiologic measurements of sleep and activity are predictive of current disease modifier use.

Methods: MS Mosaic is a longitudinal study (NCT02845635) that combines data from a mobile platform with existing biomarkers and then utilizes machine learning methods to help reveal a more comprehensive picture of MS. Continuously collected data from participants' daily symptom surveys, medication diaries, and mobile sensors is analyzed through a Bayesian generative hierarchical model that uses a Dirichlet process at a higher level and then represents the observed data at a lower level, providing a particular patient's "physiometry sub-group" membership and attempts to predict their current disease modifier use (if any).

Results: Disease subtypes can be discovered by combining the symptom/medications diaries and sensor-based physiometry measurements from the MS Mosaic app with machine learning clustering methodology.

Conclusion: The ability of these identified "physiometry subgroups" to predict a given patient's current disease modifier is described.

Rehabilitation and Comprehensive Care

P224

Moving Stronger: Preliminary Results of a 12-Week Group Exercise Program on Patient-Reported Outcomes

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Background: Despite the recent expansion of its therapeutic arsenal, multiple sclerosis (MS) remains a leading cause of disability. Exercise has proven to be an effective non-pharmacological approach to manage deficits, and improve quality of life in people with MS. Yet, engagement in physical activity remains limited in the MS community due in part to lack of access to adaptive exercise programs.
Objectives: To assess the safety and impact on patient-reported outcomes of the Moving Stronger program, a 12-week small group based exercise program offered at the YMCA, and designed specifically for people with MS of all ability levels.
Methods: Moving Stronger is a 12-week, multimodal (yoga, aquatics, resistance and aerobic training) exercise program comprised of twice-weekly supervised sessions led by YMCA instructors, and available at no cost to participants. Instructors are trained to understand the needs and limitations of people with MS to provide a safe environment. Each session is outlined with modifications to adapt to each participant's level of ability. 11 participants with clinically definite MS (EDSS= 2.5-6.5), enrolled in the Moving Stronger program, participated in the present study. Patient-reported outcome measures included MS Impact Scale 29 (MSIS-29), MS Fatigue Scale (MFIS) and MS walking scale (MSWS-12).
Results: All outcome measures improved significantly after the exercise intervention: MSIS-29 (76.18 to 59.18, p=0.002), MFIS (39.90 to 26.09, p=0.0004) and MSWS (41.38 to 36.60, p=0.026). No severe adverse events were reported.
Conclusion: Our preliminary results suggest that the Moving Stronger program is safe and may improve participants' perception of their mobility, fatigue, and symptoms. This Moving Stronger program is uniquely scalable and has the potential to become an integral component of the MS care paradigm.

P225

The Advanced Practice Provider (APP) Workforce and MS Patient Care

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Background: Recent research suggests that shortages among neurologists who provide care for individuals with multiple sclerosis (MS) may worsen over the next decade. Integrating advanced practice providers (APPs, i.e., Nurse Practitioners [NPs] and Physician Assistants [PAs]) in collaborative multidisciplinary teams to support MS patient disease management may address neurologist shortages and ensure that patients continue to receive high-quality comprehensive care. However, little is known about the role of APPs in MS care.
Objectives: This presentation details the roles APPs currently play in MS patient care, the reasons for and barriers to focusing on MS care experienced by APPs, and their career satisfaction.
Methods: From November 2016-April 2017, the study team administered 2 web-based surveys, one for NPs and one for PAs. Recruitment occurred via professional society listservs/email blasts and via direct email using a proprietary database. A total of 215 NPs and 395 PAs completed the surveys.
Results: The survey assessed whether APPs provide persons with MS with any of 11 clinical services, including direct care services (obtaining histories and performing exams, performing diagnostic studies, diagnosing conditions, providing therapeutics), supportive services (managing symptomatic care, providing social support to patients and families, counseling/educating patients and families), and care coordination (making referrals, coordinating care, addressing unmet needs). Among NPs and PAs who see or manage care for individuals with MS, 92.5% and 77.8%, respectively, provide at least 9 of the 11 services. The most common reason specified for focusing on MS care was working with a unique and challenging population (91% of NPs, 80% PAs). Barriers to providing MS care included lack of knowledge and patient comorbidities. APPs report high satisfaction with relationship with patients (90.2% NPs 85.8% PAs are very or extremely satisfied), colleagues (80.3% NPs, 78.5% PAs), clinical focus (79.9% NPs, 75.8% PAs), and careers (78.3% NPs, 80.1% PAs).
Conclusion: APPs already provide a comprehensive range of services to individuals with MS and can complement the MS physician workforce. These practitioners express high levels of satisfaction with multiple aspects of their careers, which suggests that provision of MS care is a fulfilling career goal. These findings suggest that the APP workforce will be critical to addressing MS physician shortages. This study was supported by the National MS Society.

P226

Differences in MS Care By Practice Site

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Background: Individuals with multiple sclerosis (MS) receive medical care in different practice settings, including MS centers, neurology practice, and primary care practices. However, little information is available on differences in characteristics of patient populations receiving care at each of these setting or the types of care received.
Objectives: This study examined differences in characteristics and quality of care for individuals with MS seen at MS centers, neurology practices, or primary care practices.
Methods: We analyzed data from the *Sonya Slifka Longitudinal Multiple Sclerosis Study* (funded by the National MS Society) to examine differences in sociodemographic and clinical characteristics, symptoms, and care received among individuals with MS at

MS center, neurology practices, and primary care practices. The study included 376 individuals who indicated that they receive MS care at MS centers, 552 at neurology practices, and 55 at primary care practices. Bivariate and multivariable analyses were performed in SAS.

Results: Comparing individuals receiving care at MS centers vs. neurology practices, there were no significant differences in sex, age, race/ethnicity, education, or income. Those seen at MS centers were significantly less likely to have private insurance or Medicare coverage vs. Medicaid coverage or being uninsured (86% at MS centers vs. 91% at neurology practices, $p<0.01$). There were no significant differences in clinical characteristics or resource utilization rates; however, those receiving care at MS center were significantly more likely to receive disease modifying therapies (DMTs, 84% vs. 79% at neurology practices, $p<0.05$). Compared with those treated at MS centers, individuals receiving MS care at primary care practices had lower socioeconomic status, lower rates of private insurance, greater duration of illness, and were more likely to report MS symptoms or poor health. They were also less likely to receive DMTs (51% vs. 84% at MS centers).

Conclusion: Individuals receiving care at MS centers and outpatient neurology practices had similar characteristics and rates of care, although those at MS centers were less likely to have private insurance, which may result in lower reimbursement for MS care. Greater rates of MS symptoms and decreased use of DMTs among individuals treated in primary care practices suggests opportunities for outreach to primary care physicians, to provide consultations for MS patients they follow. This study was funded by the National MS Society.

P227

Development of a Web-Based Fall Prevention Program for People with Multiple Sclerosis

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Background: More than half of people with multiple sclerosis (PwMS) report falling at least once every 3-6 months and over one-third report multiple falls in this time frame (1, 2). Currently there is no accepted standard of care for fall prevention in PwMS. Several approaches are used and have been studied including physical therapy, group exercise, and fall prevention education (3,4), but all of these have limitations in efficacy and implementation. Free From Falls (FFF), is a group based exercise and education fall prevention program for PwMS, developed by the National MS Society (NMSS). FFF consists of eight 2-hour instructor-led group sessions. Each session is comprised of about an hour of didactics and discussion, with accompanying power point slides and a handbook, and about an hour of exercise. Although FFF has shown promise, with suggestions of improvements in mobility, balance and balance confidence (5), access to the FFF program is limited to those who can attend a class at a given time and location and by the cost and availability of trained facilitators. We therefore developed a web-based version of FFF to improve access to this comprehensive MS fall prevention program.

Methods: We developed Free From Falls Online by adapting the original FFF program into a web-based format using Wix. We presented educational material as webinars with supplementary, downloadable reading material. The exercise component was adapted into a narrated video with persons of varying levels of disability demonstrating the exercises. The exercises are designed to improve balance and postural control. To address MS-specific barriers to internet use, such as low contrast, small font, cluttering of content and poor navigational design, we ensured the content was clearly displayed with an adapted layout that included accessibility features to help participants navigate the site.

Results: The web-based FFF program consists of eight narrated 30-minute webinars and one hour-long exercise video. The program is hosted on the NMSS website and is freely available to the public. We are evaluating its adoption, adherence, and efficacy for fall prevention in a pilot randomized controlled trial.

Conclusion: Comprehensive fall prevention programs can be delivered online to address limitations in access. Web-based delivery has the potential to increase access to these programs at relatively low cost to a much wider audience. The adoption, adherence, efficacy and effectiveness of online delivery require further study.

P228

Engaging Multiple Stakeholder Groups in the Development of Standards for Multiple Sclerosis Care: A Modified Delphi Process

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Background: Recommendations for improving multiple sclerosis (MS) care were presented in the widely endorsed report *Brain health: time matters in multiple sclerosis*.[1]

Objectives: We aim to engage multiple stakeholder groups in defining standards for MS care, derived from the report. The standards will address the timing of key steps in the MS care pathway and could inform the content of tools to help established and developing MS services in different countries strive for the highest level of care.

Methods: A Delphi process is a structured technique for gaining consensus among experts. An international Delphi Consensus Panel of MS neurologists is taking part in online surveys to agree and define the MS care standards. In addition, a 31-member Reviewing Group of MS nurses, people with MS and allied healthcare professionals is reviewing summaries of the Delphi Panel responses and providing feedback to 4 Chairs.

Consensus will be reached if at least 66% of round 1 Delphi Panel participants take part in the final round and reach 75% agreement or higher.

Results: In round 1, the Delphi Panel (n = 27) reviewed 21 principles. Over 75% agreed that each principle was an appropriate and accurate description of a good standard when considering brain health in people with MS; those who disagreed provided explanations. Three principles gained 100% (27/27) agreement: 'Evaluation of suitability/eligibility for treatment shortly after MS diagnosis', 'Early discussion with patient about the aims of

treatment' and 'Regular review of the aims of treatment'. The Reviewing Group reviewed these responses and commented. The Chairs then defined variables based on the principles and feedback received.

In subsequent rounds, neurologists assigned 'core', 'achievable' and 'aspirational' time frames (to reflect a minimum, good and high standard of care, respectively) to the variables. In the final round, neurologists have been asked if they agree with standards based on these results. The Reviewing Group will be asked if these standards are ambitious enough. The Delphi process is due to finish in September 2017.

Conclusion: A modified Delphi process has engaged MS neurologists, MS nurses, allied healthcare professionals and people with MS in the development of international standards for MS care. The final standards will form the basis of tools for potential use by multiple stakeholders to improve care in MS.

P229

Dynamic Stability during Long Walks in People with Multiple Sclerosis

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Background: Approximately 70-90% of people with multiple sclerosis (PwMS) experience difficulties in initiating and sustaining physical activities (motor fatigue) during daily life. Importantly, motor fatigue can act as an intrinsic risk factor for falls in PwMS by adversely affecting dynamic stability during walking. The effects of motor fatigue on dynamic stability during long walks haven't been investigated in PwMS.

Objectives: To investigate the impact of motor fatigue on dynamic stability in PwMS.

Methods: 17 PwMS and 8 healthy controls (HC) participated in a fast six-minute walk test (6MWT) wearing six-wireless inertial sensors. The prevalence of motor fatigue was documented by the distance walked index (DWI_{6-1}), calculated as a percentage change in distance from minute (min) 1 to 6 (DWI_{6-1}). The local dynamic stability was quantified by maximum finite-time Lyapunov exponents (λ_S) where larger λ_S indicates less stable dynamics. λ_S values were calculated for each min of walking and the percent change in λ_S from min 1 to 6 was calculated (Dynamic Stability Index, DSI_{6-1}). Between-group differences in DWI_{6-1} and DSI_{6-1} were assessed using independent t-tests. Pearson correlation coefficients compared the association between DWI_{6-1} and DSI_{6-1}. Post-hoc comparisons examined how λ_S changed over time across groups using t-tests corrected for multiple comparisons.

Results: PwMS demonstrated greater decline in distance during the 6MWT than HC (DWI_{6-1}=-4.9±1.6 vs. -0.3±1.7; p=0.01). Similarly, DSI_{6-1} was different across two groups (PwMS=6.4±4.0, HC=-14.9±2.7; p=0.001). DWI_{6-1} and DSI_{6-1} were significantly correlated in MS (r=-0.54), where greater decline in walking distance (motor fatigue) was associated with increases in λ_S (decline in stability). PwMS did not have different stability than HC until min 4 (p=0.004), and differences persisted at min 6 (p=0.03).

Conclusion: PwMS decelerated more than HC, demonstrating higher motor fatigue during the 6MWT. Similarly, DSI_{6-1} was larger in MS and this change in stability was negatively related to DWI_{6-1}. Combined, these results illustrate that with increased motor fatigue, there was decreased dynamic stability in PwMS. Future intervention studies targeting motor fatigue should focus on improving dynamic stability during physical activities. Finally, the differences in stability were only apparent after 4 min of walking. This presents strong rationale for the use of longer walks in PwMS as shorter walking tests are unlikely to capture changes in dynamic stability.

P230

Adherence Facilitates Outcomes in Patients on Interferon Beta-1b

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Background: Patients with multiple sclerosis (MS) may be treated with any one of many first-line disease modifying therapies (DMTs) until disease severity necessitates a switch to second-line treatment. No evidence of disease activity (NEDA) status, an outcome defined by the absence of relapses, disability progression, and MRI activity, can be considered a treatment goal across lines of therapy but also may affect the decision to switch to second line. While NEDA is difficult to achieve in a clinical study, it can be reached in individual patients.

Objectives: To describe the incidence of NEDA in a cohort of patients with MS treated with first-line interferon beta-1b

Methods: Patients with MS treated by a single provider (RB) from the Keck School of Medicine of USC who received treatment with interferon beta-1b for ≥1 year were retrospectively assessed for outcomes, adherence, and DMT choices. Interferon beta-1b had been prescribed for these patients based on specific criteria: all patients had ≥1 spinal lesion in addition to brain lesions at baseline (suggestive of expansive inflammatory disease), but patients with symptoms of major depressive disorder, a past suicide attempt, or comorbid autoimmune conditions were excluded. The importance of good adherence was reinforced on a regular basis by asking patients how many injections they had missed and reviewing imaging findings with patients.

Results: 41 patients were included, all of whom incidentally were currently employed, had completed higher education, and had sufficient family support. At the time of the analysis, 31 patients (75.6%) were undergoing treatment with interferon beta-1b (mean [SD] time on treatment: 7.3 [4.4] years) and 90.2% were considered adherent with therapy (defined as missing <10% of prescribed injections). Thirty-seven patients (90.2%) were relapse-free at the time of the analysis. Only 1 patient (2.4%) developed new spinal cord lesions, while 12 patients (29.3%) had spinal lesions that either decreased in size or were undetectable at last follow up. Median EDSS was 2.0 (mean [SD] change in EDSS score from baseline, -0.82 [1.0]). Thirty-six patients (87.8%) had NEDA.

Conclusion: The results of this retrospective analysis indicated that patients who were motivated to remain adherent with therapy had generally favorable outcomes while on interferon beta-1b treatment, including low rates of relapse, little or no change in disability, favorable MRI outcomes, and high rates of NEDA.

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Medication Management Strategies for Patients with Multiple Sclerosis-Related Cognitive Symptoms

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Background: Cognitive symptoms are experienced by approximately 43%-65% of people living with Multiple Sclerosis (MS). These symptoms can include memory difficulties, executive functioning and problem-solving deficits, and other areas of cognition, and can affect any area of daily life and functioning including driving, meal preparation, home management, and self-care. Medication management is an important Instrumental Activity of Daily Living (IADL) skill that occupational therapists (OTs) address in clinical treatment, and is an important functional daily activity, particularly for those living with MS. Poor medication timing, incorrect doses, medication disorganization, and under- or over-medication are some of the problems that can result due to cognitive deficits, and that have the potential to influence the patient's treatment plan and long-term course of disease.
Objectives: Describe OT intervention strategies for improved medication management in patients with MS, and provide a descriptive case study with clinical outcomes to demonstrate how some of these strategies can be applied clinically.
Methods: OT interventions that can be utilized to improve an individual's ability to engage in the IADL of medication management include compensatory cognitive strategies, safety assessment, adaptive equipment assessment and training, schedule development, environmental cues, and organization skill development. The descriptive case study will highlight the use of compensatory cognitive strategies, environmental cues, organization skill development, time management tools, and adaptive equipment based interventions with an individual living with MS who demonstrated cognitive deficits that challenged the ability to adhere to a medication regimen. Outcome measures utilized were the Canadian Occupational Performance Measure (COPM), Multiple Sclerosis Quality of Life Inventory (MSQLI), RAND Short Form-36 (RAND SF-36), and the Montreal Cognitive Assessment (MOCA).
Results: Pre-intervention outcome measures have been collected for the case study patient, and post-intervention outcome measures will be collected upon re-assessment and discharge from OT services, and reported at the conference.
Conclusion: This case study highlights the methodology and strategies OTs can utilize to address medication management IADL routines with individuals living with MS who experience cognitive symptoms and deficits, and demonstrates the benefits of OT interventions in improving adherence to a medication regimen.

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Integrative Evaluation of Mexican People with Multiple Sclerosis

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Background: Multiple Sclerosis (MS) prevalence has increased in México in the last 50 years, from 1.6 to 15 cases per 100,000 habitants. Still, there is only scarce information concerning this patient.
Objectives: Realize an integrative evaluation of Mexican people with MS.
Methods: For psycho-social factors World Health Organization Quality of Life Questionnaire (WHOQOL), Beck Depression Inventory II (BDI), Beck Anxiety Inventory (BAI) and other tests were applied. Cognitive impairment (CI) was assessed using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Chemistry panel and complete blood count were performed. Serum vitamin D (VD), interleukins (IL) 1β and 17 were assessed by enzyme-linked immunosorbent assay (ELISA). Bone mineral density (BMD) was assessed by a DXA equipment.
Results: 24 patients were evaluated. We obtained a mean relapse rate of 0.88 per year, which correlate with triglycerides ($p=0.000$), very low density lipoprotein (VLDL) ($p=0.000$) and neutrophils ($p=0.005$). Anxiety and depression symptoms were observed in 19 and 9 patients, respectively; both correlate with WHOQOL and MoCA domains. CI was observed in 2 and 21 patients according to MMSE and MoCA, respectively. MMSE correlate significantly with glucose ($p=0.03$), urea ($p=0.015$) and IL17 ($p=0.044$). MoCA significantly with quality of life (QoL), BAI ($p=0.035$), IL1β ($p=0.038$), low density lipoprotein ($p=0.036$) (LDL) and cholesterol ($p=0.039$). 12 participants presented osteoporosis, 3 osteopenia and 9 were healthy. Femur regions BMD correlate with evolution time. VD deficiency (<30ng/ml) was found in 100% of participants. VD concentration is explained, in an ordinary least squares regression ($R2=0.727$, $p=0.0001$): by femur diagnosis ($\beta=0.706$; $p=0.002$), femur neck diagnosis ($\beta=-0.451$; $p=0.027$), physical health ($\beta=0.327$; $p=0.023$), monocytes ($\beta=-0.425$; $p=0.023$) and MoCA's denomination domain ($\beta=0.341$; $p=0.025$). IL17 concentration is explained ($R2=0.845$, $p=0.0001$) by uric acid ($\beta=0.777$; $p=0.0001$) and MoCA orientation ($\beta=-0.260$; $p=0.012$). For an increase of a pg in IL17 uric acid rises 0.55 mg/dl.
Conclusion: We observed important correlations between evaluated variables in our population. It is important to propose an interdisciplinary evaluation of MS patients which will provide the necessary tools for the patient to confront adequately the diagnosis and MS evolution, improving their QoL.

Remyelination

P233

Targeting Innate Immunity in Multiple Sclerosis: Inducing TLR2 Tolerance Both Enhances Remyelination and Inhibits Immune-Mediated Inflammation in MS

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Background: Multiple sclerosis (MS) is a central nervous system (CNS) autoimmune disease characterized by both inflammatory demyelination and impaired remyelination. The remyelination defect in MS remains poorly understood and generally unamenable to treatment. Recent studies indicate that toll-like receptor 2 (TLR2) contributes to both the inflammatory component and the defective remyelination in MS. While most MS therapeutic modalities target the adaptive immune system, we recently reported that inducing TLR2 tolerance in the innate immune system by administering low dose TLR ligands attenuates adoptively transferred EAE. These findings, together with previous evidence that TLR2 signaling plays a role in inhibiting myelin repair, now suggest that inducing systemic TLR2 tolerance may represent a novel approach for both attenuating the inflammatory component and improving remyelination in MS.
Objectives: To assess the effect of TLR2 tolerance induction on CNS myelin repair.
Methods: Chow containing 0.2% cuprizone was fed to C57BL/6 mice for 5 weeks to induce demyelination. During the 2 week period of remyelination following discontinuation of cuprizone, systemic TLR2 tolerance was induced by administering very low dose TLR2 ligands. Controls were treated with vehicle control (VC). After the 2 week remyelination period, evaluation of remyelination included Black-Gold staining and electron microscopy (EM) measurements of myelinated fiber frequency and g-ratios.
Results: The induction of TLR2 tolerance during the period of remyelination significantly enhanced myelin recovery, restoring myelinated axon frequency to baseline levels (30% unmyelinated) compared to VC (60% unmyelinated; $p<0.0001$). Moreover, myelin thickness measurements demonstrated that TLR2 tolerance induction also significantly improved remyelination, restoring g-ratios to baseline levels (0.71) compared to VC (0.76; $p<0.001$).
Conclusion: Our results indicate that inducing TLR2 tolerance significantly enhances myelin repair in addition to attenuating the inflammatory component of MS. Questions presently being addressed include whether the enhancement in remyelination is mediated through the innate immune system and/or directly through an effect on oligodendrocyte maturation. The novel therapeutic approach of inducing TLR2 tolerance via administration of very low dose TLR2 ligands may represent a two-pronged approach for treating both the inflammatory and myelin repair components of MS.

P234

Increase in Chemokine CXCL1 with Therapeutic Erβ Ligand Treatment Leads to an Increase in Axon Myelination in a Mouse Model of Multiple Sclerosis

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Background: Estrogen receptor β (ERβ) ligands have been shown to induce remyelination in different mouse models of multiple sclerosis (MS). Recent work using chronic myelin oligodendrocyte glycoprotein experimental autoimmune encephalomyelitis (MOG-EAE), has shown that different ERβ ligands (diarylpropionitrile (DPN), Chloroindazole (IndCl), WAY 202041 (WAY)) all demonstrate remyelination, but show differential immune effects in the periphery during late stage EAE.
Objectives: Here, we wanted to investigate a potential common immunomodulatory link during peak disease that could explain the neuroprotective effect of ERβ ligands
Methods: Peripheral cytokine analysis, flow cytometry, and immunohistochemistry were performed on vehicle-treated, prophylactic 17β-estradiol (E2) treated and therapeutic ERβ ligand (Ind-Cl, and WAY 202041 and DPN) age matched female C57BL/6 MOG-EAE mice.
Results: Therapeutic ERβ ligand treatment, although had no significant effect early in EAE disease (before day 21 post induction), was protective later in disease (after day 21 post induction). IndCl treatment showed the greatest reduction on oligodendrocyte (OL) toxic interferon gamma (IFNγ) and enhanced chemokine C-X-C motif ligand 1 (CXCL1) intensity on astrocytes in thoracic spinal cord white matter tracts. CXCL1 has been shown to stimulate OPC migration, proliferation, and differentiation, suggesting a potential mechanism of action for IndCl mediated remyelination in the CNS. In addition, immunohistochemistry revealed that all tested ERβ ligands studied promoted remyelination in the CNS of EAE mice despite massive CNS immune cell accumulation.
Conclusion: The present study indicates an intricate interplay between the peripheral and central immune systems that seems to be responsible for the remyelinating effects of ERβ ligand treatment during peak EAE disease. The results offer new possibilities for combination therapy to achieve functional recovery from MS disease. More studies including conditional gene knockouts will be needed to address the relationship between immune modulation and neuroprotection by ERβ ligands.

P235

Novel Estrogen Receptor-B Ligands Induce Oligodendrocyte Survival, Differentiation, and Remyelination in Mouse Models of Multiple Sclerosis

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Background: Current therapeutics reduce relapse rates in multiple sclerosis (MS) patients, but fail to reverse or prevent neurodegeneration or initiate repair/remyelination. We have been investigating the clinical potential of estrogens in different mouse models of MS and have recently shown the superior therapeutic effects of a highly selective estrogen receptor ligand β (ERβ), chloroindazole (Ind-Cl) in promoting axon remyelination. Therapeutic administration of Ind-Cl during peak disease induced a reversal in motor deficit and ameliorated clinical scores. In addition, there was substantial improvement in callosal conduction accompanied by improved callosal and optic nerve myelination and an increase in mature oligodendrocytes (OL). Furthermore, Ind-Cl also included a decrease in peripheral Th1 cytokines and T cell numbers in the CNS of experimental autoimmune encephalomyelitis (EAE) mice.

Objectives: These promising results with Ind-Cl prompted us to develop novel analogues of (STW1 and STW2 Ind-Cl derivatives) Ind-Cl for pre-clinical development.
Methods: Primary oligodendrocyte (OL) progenitor (OPC) cultures were used to screen for OPC proliferation and OL differentiation effects. Two superior analogues that induced increased OPC proliferation and differentiation were further tested in EAE mice groups (8-week-old female C57Bl/6) and compared with vehicle-treated and normal mice. Rotarod behavior, callosal conduction recordings, cytokine/chemokine analysis, and immunohistochemistry was performed.
Results: Two Ind-Cl analogues (STW1 and STW2 Ind-Cl derivatives) increased proliferation of OL progenitors (OPC) in primary cell culture, decreased EAE clinical disease, improved rotarod performance, and improved callosal axon conduction similar to Ind-Cl. Cytokine and chemokine analysis showed a significant increase in KC (CXCL1) chemokine levels in all ERβ ligands tested. KC stimulates OPC proliferation, migration arrest and OL differentiation.
Conclusion: These data suggest that ERβ ligands, including Ind-Cl and analogues, induce increases in various chemokines and growth factors and may be responsible for survival of OLS and the remyelinating effects seen during EAE. Our future goals are to study the effects of these analogues longitudinally and proceed with toxicity studies for use in future MS clinical trials.

P236

A Novel In Vivo Screen for Oligodendrocyte Differentiation and Myelination

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Background: Repair of demyelinated axons is a major goal of current multiple sclerosis research, and diverse approaches to identifying remyelinative therapies are being developed. Zebrafish (*Danio rerio*) is very useful for drug screening, as its genome, pharmacology and drug metabolism are well conserved relative to humans. It is ideal for rapid analysis of the impact of different signaling pathways on myelination, given its transparent embryos and rapid ex utero development. We have studied the Akt/mTOR pathway as an important driver of oligodendrocyte differentiation and myelination, and when zebrafish are exposed to modulators of the mTOR or other pathways that can induce myelination, many elements of myelination can be rapidly quantified, including cell number, cell migration, cell proliferation, myelin internode number, or internode length.
Objectives: One approach to identify targets to enhance myelination is high throughput screening of small molecule libraries, where a large number of potential drugs that can be screened. However, structure-activity relationship analysis often suggests the need to modify hits from such screens for optimal activity and/or delivery to the brain. We have developed a medium throughput screen to identify putative remyelinating drugs in an *in vivo* context, using a transgenic zebrafish model, where a targeted library or a library of chemically modified derivatives of lead compounds from a high throughput screen can be rapidly screened.
Methods: The zebrafish myelin protein zero (*mpz*) promoter, which is sensitive to many of the classically identified myelination inducers, was used to drive expression of membrane-bound enhanced green fluorescent (EGFP) protein. Imaging allowed quantification of oligodendrocyte cell number, differentiation, and length and number of myelin internodes. Given that the EGFP is membrane bound, this line allows quantification of altered promoter activity and altered membrane accumulation. Using live zebrafish allows immediate assessment of toxicity in the whole animal.
Results: GC1, a thyroid hormone receptor agonist, significantly increased *mpz* promoter activity. Transgenic zebrafish are well suited to establish the details of the drug's pro-myelinating effects, and our studies demonstrate that GC1 increases myelin internode length and number and myelin RNA levels.
Conclusion: This novel in vivo zebrafish screen is currently in use, screening pathway-specific libraries for new drugs to enhance myelination.

P237

Role of 5-Lipoxygenase Activity in Primary Myelination

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Background: Remyelination failure in multiple sclerosis (MS) is associated with severe disability and disease progression. The mechanisms governing myelination, and remyelination are multiple and not all have been identified. Here, we propose a novel and previously unrecognized mechanism mediated by 5-lipoxygenase (5-LO) activity within the central nervous system (CNS). 5-LO is the rate-limiting enzyme for the synthesis of leukotrienes (LTs), a group of lipid mediators currently known for their potent immune modulating functions. Our data suggest that 5-LO is also active within the normal CNS and that LT-evoked mechanisms control myelination.
Objectives: To define the effect of 5-LO activity on primary myelination in normal CNS.
Methods: mRNA and protein levels of 5-LO pathway members were determined in the developing adult mouse CNS by qPCR and Western blot, respectively. 5-LO cellular localization was visualized by immunohistochemistry (IHC). LT levels in tissues were determined by liquid chromatography-mass spectrometry (LC-MS/MS) and in oligodendrocyte lineage cell (OLC) cultures by a commercially available leukotriene detection kit (Cayman Chemicals). Myelination patterns were identified by examining CNS tissues of 5-LO knockout (5-LOKO) and wildtype (WT) mice by transmission electron microscopy (TEM).
Results: mRNA of genes encoding for 5-LO pathway associated proteins were present both in the developing and adult CNS. Protein levels paralleled mRNA results. 5-LO immunoreactivity was detected prominently in CC1+ oligodendrocytes and infrequently in other glial cells and neurons in the normal CNS. Moreover, we detected LT production in the normal CNS and in purified OLC cultures. TEM analysis showed that the CNS of 5-LOKO mice exhibited earlier myelination and thicker myelin sheaths as compared to WT controls.

Conclusion: Our data suggests there is a functional association between 5-LO activity and myelination. Detection of 5-LO in oligodendrocytes implies that 5-LO exerts its effects in a cell specific manner. Our findings suggest that 5-LO activity may be a promising target for future therapies that promote remyelination in demyelinating diseases.

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Ensheathment of Synthetic Nanofibers By Postnatal Rat Oligodendrocyte Precursor Cells Is Enhanced By RNS60

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Background: RNS60 is an experimental therapeutic that contains charge stabilized oxygen nanobubbles generated using the modified Taylor-Couette-Poiseuille flow under elevated oxygen pressure. It is currently in early stages of clinical trials for the treatment of multiple sclerosis (MS). Although RNS60 is known for its immunomodulatory activity (Khasnavis, 2012 and Mondal, 2012), this product has also been shown to have direct effects on the cells of the central nervous system (CNS). RNS60 enhances transmission at giant squid synapse by increasing ATP synthesis (Choi 2014). Further, our earlier work using rat postnatal brain derived oligodendrocytes (OLs) has shown RNS60 to increase spare glycolytic capacity and spare respiratory capacity under optimal and metabolic stress conditions respectively (Rao, 2016). Our current study aims to assess the effect of RNS60 on ensheathment of nanofibers by OLs.
Objectives: To quantify the effects of RNS60 on the ensheathment of nanofibers by rat postnatal OL precursor cells (OPCs)
Methods: Rat postnatal brain derived OLs were collected following a standard shake-off procedure from mixed glial cultures (McCarthy and de Vellis, 1980). Cells were plated in laminin coated nanofibers chamber slides (Sigma - Z694576) and grown in DMEM-F12 medium supplemented with N1. 10% (v/v) RNS60 was applied once on the third day after the culture initiation. Cells were fixed and immunostained for O4 and myelin basic protein (MBP) on the seventh day for imaging.
Results: We detected an increase in the proportion of O4+ ensheathing cells out of the total number of O4 expressing cells in the RNS60 treatment condition compared to controls. In addition, RNS60 substantially increased the number of ensheathing processes per cell. At the time point we analyzed, MBP expression was mostly restricted to cell body; in more prolonged cultures, MBP was expressed in cell processes.
Conclusion: The observation that RNS60 promotes the ensheathment of nanofibers by rat postnatal OPCs is an initial step in defining its capacity to promote remyelination in MS.

P239

Targeting EAE-Induced Demyelination and Axonal Pathology By Transplanting Haematopoietic Stem Cells That Overexpress Ngr(310)Ecto-Fc Fusion Protein

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Background: Haematopoietic stem cell (HSC) transplantation is currently being trialed to treat multiple sclerosis (MS) as a means of modulating autoimmune-mediated inflammation and neurological disability. As MS is an immune-mediated neurodegenerative disorder, immunomodulation may not be effective for progressive neurodegeneration. Nogo receptor 1 (NgR1) is a high affinity receptor for myelin-associated inhibitory factors (MAIFs) that block for neurite outgrowth and may potentiate axonal degeneration in an animal model of progressive multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE).
Objectives: HSCs can be utilised as carriers of the therapeutic protein for specific delivery into EAE lesions and can potentiate neurological recovery.
Methods: As MS and EAE exhibit large numbers of inflammatory cell infiltrates within central nervous system (CNS) lesions, we utilized transplantable HSCs as a cellular delivery method of the NgR(310)ecto-Fc fusion protein.
Results: We have shown that we can deliver the specific NgR(310) ecto-Fc fusion protein through the transplantation of lentivirus (LV)-transduced HSCs that encode the NgR-Fc protein to sites of EAE pathology. We exclusively identified macrophages that were positive for the myc-tag (NgR-Fc-positive) occupying significant areas of inflammation and demyelination ($2.0 \times 10^3 \pm 0.5 \times 10^3$ cells/mm^2, $p<0.0001$), signifying the engulfment of NgR-Fc protein-MAIF complex by activated macrophages, which may increase the phagocytic activity of these populations and enhance repair. Importantly, n=3 animals transplantated with therapeutic NgR(310)ecto-Fc overexpressing HSCs, were rescued from symptoms associated with EAE.
Conclusion: Our results suggest that HSCs can be utilised as carriers of the therapeutic protein for specific delivery into EAE lesions and can potentiate neurological recovery.

Symptom Management

P240

Relationship between Caffeine Intake, EDSS and Fatigue Scale in Patients with Multiple Sclerosis

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Background: Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disorder of the central nervous system (CNS). Due to the variable clinical course of MS, it is classified into relapsing and progressive phases and three phenotypes of relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Caffeine is a

central nervous system stimulant of the methylxanthine class. It is the world´s most widely consumed psychoactive drug. Recent scientific evidences showed that caffeine intake could be associated with decreased mortality from cardiovascular and neurological diseases, diabetes type II, as well as from endometrial and liver cancer. Previous studies on consumption of caffeine and (MS) have yielded inconclusive results.

Objectives: We aimed to investigate whether consumption of caffeine is associated with disability of MS.

Methods: 126 patients with diagnosis of MS (42 RRMS, 42 PPMS and 42 SPMS) with MRI assessment of brain and spinal cord were recruited from multiple sclerosis clinic in Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran included in the present study. A 168-item semi-quantitative food frequency questionnaire (FFQ) was used for assessment of dietary intake of caffeine. Medical history questionnaire, EDSS and Fatigue questionnaire recorded from all participants.

Results: Mean ± SD of EDSS and fatigue scale in SPMS and PPMS groups was significantly higher than RRMS group. Dietary intakes of caffeine in RRMS was higher that two other subgroups but not significantly. There was a negative significant association between caffeine intake and EDSS in RRMS subgroup (r=-0.556, p=0.031). In addition, there was a significant negative correlation between caffeine intake and Fatigue scale in all participants (r=-0.312, p=0.028). Other correlations were not significant. Age, gender, energy intake and blood pressure were not confounder variables.

Conclusion: Our study demonstrated that there is a negative significant correlation between intakes of caffeine with fatigue scale in all participants. In addition, dietary intakes of caffeine can decrease EDSS in RRMS patients and caffeine consumption may exert a protective role against multiple sclerosis. The concern of high caffeine intake is dehydration induced caffeine. Further studies with larger sample sizes and other population needed to prove this correlation.

P241

Relationship between Fatigue and Routine Biochemical Parameters in Patients with Multiple Sclerosis

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Background: Fatigue is one of the most common symptoms seen in approximately 80% of patients with Multiple Sclerosis (MS). A lot of biochemical factors play a role in the mechanism of fatigue. Especially, identification of biochemical factors that associated with fatigue and analyzed by available laboratory tests, may provide better insight into the causes of fatigue in MS patients.

Objectives: The purpose of this study was to examine the relationship between the routine biochemical parameters and fatigue in patients with MS.

Methods: Thirty-six ambulatory patients with MS (Age:36.17± 9.02 years, EDSS: 1.58±1.04) participated in the study. Fatigue was assessed using the self-report Fatigue Severity Scale (FSS). Then, fasting venous blood from participants were collected to measure biochemical parameters, including glucose, creatinine, calcium, sodium, potassium, magnesium, phosphorus, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglyceride, ferritin, vitamin B12, vitamin D, folate, thyroid stimulating hormone, triiodothyronine, thyroxine. Biochemical parameters were assessed using routine laboratory techniques. Spearman correlation analysis was used to determine relationships between the routine biochemical parameters and fatigue.

Results: In patients with MS, the fatigue severity was associated with glucose level (r: 0.332, p:0.048), sodium level (r:- 0.529, p:0.001), high-density lipoprotein cholesterol level (r:- 0.449, p:0.006), folate level (r:- 0.341, p:0.042), triiodothyronine level (r:- 0.446, p:0.006), and thyroxine level (r:- 0.371, p:0.026).

Conclusion: This study showed that the fatigue severity in patients with MS is negatively correlated with sodium, high-density lipoprotein cholesterol, folate, triiodothyronine, thyroxine levels but is positively correlated with glucose levels. Checking regularly the routine biochemical parameters may help us better understand the cause of fatigue and so manage the fatigue in patients with MS.