Abstracts from the 24th Annual Meeting of the Consortium of Multiple Sclerosis Centers

Multiple Sclerosis: Sustaining Care, Seeking a Cure

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Multiple Sclerosis: Sustaining Care, Seeking a Cure

We are pleased to present this electronic supplement to the International Journal of MS Care (IJMSC) containing the abstracts from the 2010 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC), held from 2 to 5 June 2010 in San Antonio, Texas. These abstracts include platform, poster, Whitaker Research Track, “works in progress,” and National Multiple Sclerosis Society Tykeson Fellows presentations delivered at the meeting. If you were not able to attend the conference, this is a wonderful opportunity for you to appreciate the diversity and depth of this outstanding group of presentations. This PDF document can be searched using key words to identify abstracts on topics of individual interest. In addition to being distributed at the meeting and mailed with the Summer 2010 issue of IJMSC, this electronic supplement is available on the CMSC website at www.mscare.org.

We are very grateful to Bayer HealthCare Pharmaceuticals, Inc., for an educational grant that allowed us to make these abstracts available.

We hope that this material will assist you in your care of MS patients and stimulate your interest in furthering research and care in MS.

—Lael A. Stone, MD

Editor in Chief
Twenty-three patients with relapsing-remitting multiple sclerosis (MS) are currently being researched, as visual loss is one of the most common and disabling physical symptoms in multiple sclerosis (MS). Low-contrast letter acuity charts are currently being researched, utility in tracking disease progression and the process of neurodegeneration in MS. However, little if any research has been conducted on the potential utility of low-contrast visual acuity as a means of examining cognition in MS. 

**Objectives:**

The primary objective is to determine whether there are any relationships of low-contrast visual acuity and near visual acuity with cognitive performance within a comprehensive neuropsychological battery.

**Methods:**

Fifty-two patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) were administered a comprehensive neuropsychological evaluation assessing emotional functioning, memory, executive functioning, processing speed, attention, visuospatial abilities, motor skills, and verbal fluency. Visual examination included an assessment of low-contrast visual acuity (5%, 2.5%, and 1.25% illuminated charts), near visual acuity, and visual acuity. 

**Results:**

Sloan translucent low-contrast letter charts (SLCLC) and the reduced logarithmic near visual acuity chart (NVAC) exhibited correlations with cognitive and physical performance independent of age. This relationship was strongest among tests of motor functioning and processing speed. For example, SLCLC was significantly correlated with performance on the Nine-Hole Peg Test ($r = 0.49, P < 0.001$), Multiple Sclerosis Functional Composite Test ($r = 0.48, P < 0.001$), and Symbol Digit Modalities Test ($r = 0.48, P < 0.001$). NVAC was also significantly correlated with performance on the Nine-Hole Peg Test ($r = 0.50, P < 0.001$), SDMT ($r = 0.43, P < 0.01$), and Paced Auditory Serial Addition Test ($r = 0.42, P < 0.01$).

**Conclusions:**

Contrast sensitivity and near visual acuity play important roles in everyday life. It has been suggested that a measure of visual function should be strongly considered for addition to the Multiple Sclerosis Functional Composite Test. Low-contrast and near visual acuity may be promising tools for detecting physical and cognitive changes in patients with RRMS and SPMS and should be examined more closely in larger, longitudinal studies.

**Disclosure:** Nothing to disclose

**Keywords:** Psychological issues and MS

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**RESULTS**

Within a comprehensive neuropsychological evaluation assessing emotional functioning, memory, executive functioning, processing speed, attention, visuospatial abilities, motor skills, and verbal fluency, visual examination included an assessment of low-contrast visual acuity (5%, 2.5%, and 1.25% illuminated charts), near visual acuity, and visual acuity. Sloan translucent low-contrast letter charts (SLCLC) and the reduced logarithmic near visual acuity chart (NVAC) exhibited correlations with cognitive and physical performance independent of age. This relationship was strongest among tests of motor functioning and processing speed. For example, SLCLC was significantly correlated with performance on the Nine-Hole Peg Test ($r = 0.49, P < 0.001$), Multiple Sclerosis Functional Composite Test ($r = 0.48, P < 0.001$), and Symbol Digit Modalities Test ($r = 0.48, P < 0.001$). NVAC was also significantly correlated with performance on the Nine-Hole Peg Test ($r = 0.50, P < 0.001$), SDMT ($r = 0.43, P < 0.01$), and Paced Auditory Serial Addition Test ($r = 0.42, P < 0.01$).

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**Disclosure:** Nothing to disclose

**Keywords:** Psychological issues and MS
emotional functioning, memory, executive functioning, processing speed, attention, and visuospatial abilities. Serum 25-hydroxyvitamin D levels were obtained through laboratory work prior to the neuropsychological evaluation. Results: Lower vitamin D levels were associated with worse performance on a test of verbal learning (r = 0.49, P < .05). Detailed examination of learning trials demonstrated that this effect was particularly pronounced for single trial learning (r = 0.65, P < .001). No significant association was found between serum vitamin D and later learning trials. Conclusions: MS patients frequently experience memory difficulties. Our results suggest that low serum vitamin D is associated with poor list learning performance, and specifically with poor initial trial learning. These findings suggest the importance of determining vitamin D levels in order to maximize cognitive potential among MS patients. Future randomized trials should examine whether vitamin D supplementation may improve learning in MS.

Supported by: MidAmerica Neuroscience Institute
Disclosure: Nothing to disclose
Keywords: Psychological issues and MS

(P04) A MOTIVATIONAL “MERCY MOMENT”: STORY OF MULTIPLE SCLEROSIS

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Background: Hearing someone’s patient story firsthand or in a videotape is an incredibly powerful tool in motivating health-care workers to serve by responding with compassion to the needs of others. Objectives: This presentation will discuss a project, “Mercy Moments,” and show a 7-minute DVD to foster empathy in multiple sclerosis (MS) health-care professionals, especially nursing and rehabilitation specialists. Methods: As a professional MS nurse and patient, I shared my “Mercy Moment” MS story, “Chicken Soup: Living with MS,” on videotape and live as a speaker. This videotape was developed as a part of a “Healing Environment” Retreat program initiated in 2007 at St. John’s Mercy Medical Center. Throughout the year, St. John’s Mercy sponsors retreats in which groups of coworkers brainstorm opportunities to make our environment more conducive to healing. The top ten initiatives from each retreat are identified, and teams are formed to work on them. One healing environment program outcome from a 2009 team of coworkers (of which I was a member) was titled “Mercy Moments.” Our program goal was to create a forum for our coworkers who have been patients to speak out and share their stories or those of their family members to foster compassion, empathy, inspiration, and advocacy. Diverse strategies to connect using stories on all levels were developed using an intranet “Storybook,” videotape, and speaker series. Results: Compassion, empathy, and inspiration were fostered in coworkers at St. John’s Mercy Healthcare. Conclusions: MS health-care professionals will be inspired and their hearts will feel warmed by this presentation. They will be motivated to serve their patients with compassionate care.

Disclosure: Nothing to disclose
Keywords: Comprehensive care and MS, Service delivery in MS

(P05) MULTIPLE SCLEROSIS: TYSABRI-SPECIFIC EFFECTS ON COGNITIVE FUNCTION

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Background: The cognitive effects of natalizumab treatment compared with those of other disease-modifying therapies (DMTs) are not well described. Objectives: Evaluate cognitive function with natalizumab compared with other DMTs. Methods: Forty-six natalizumab patients (mean ± SD age, 43.2 ± 9.1 years; mean education, 15.1 ± 2.5 years; 76% female; mean intertest interval, 14.9 ± 3.9 months; mean Expanded Disability Status Scale [EDSS] score, 3.8 ± 2.2; disease duration: <5 years, 9%; 5–10 years, 50%; >10 years, 41%) were tested with a 30- to 60-minute computerized cognitive assessment battery for mild impairment (Mindstreams, NeuroTrax Corp, NJ) once prior to or early in treatment (0–3 infusions) and again after extended treatment (>9 infusions). Thirty-seven comparison patients (mean age, 45.8 ± 10.8 years; mean education, 14.9 ± 3.6 years; 78% female; mean intertest interval, 18.3 ± 5.0 months; mean EDSS score, 2.8 ± 1.8; disease duration: <5 years, 32%; 5–10 years, 43%; >10 years, 24%) were stable: Avonex (n = 10), Betaseron (n = 5), Rebif (n = 5), CombiRx (n = 5), Copaxone (n = 4), or no treatment (n = 8). Repeated-measures analysis of variance (ANOVA) was used to evaluate improvements: EDSS, age- and education-adjusted cognitive domain scores, and raw outcome parameters from individual tests. Cohen’s d was computed as a measure of effect size. Given the directional hypothesis of improvement with treatment, P < .05 (1-tailed) was considered significant. Mixed-model ANOVA controlling for EDSS was used to evaluate the interaction between change over time and group. Results: Improvement was found in the natalizumab group (P = .04, d = 0.21) but not the comparison group (P = .15, d = 0.11) for memory domain, driven by verbal memory (natalizumab: .001 < P < .004; 0.43 < d < 0.55; comparison: .18 < P < .62; 0.02 < d < 0.14). Improvement was found in the natalizumab group (P = .005, d = 0.41) but not the comparison group (P = .31, d = 0.07) in verbal function, both for matching (natalizumab: P = .01, d = 0.38; comparison: P = .17, d = 0.20) and rhyming (natalizumab: P = .01, d = 0.45; comparison: P = .94, d = 0.01). A similar pattern was found for EDSS score improvement (natalizumab: P = .03, d = 0.11; comparison: P = .26, d = 0.05). For the cognitive measures above, interactions controlling for EDSS were near significant, except memory domain scores and delayed verbal memory accuracy. Conclusions: Natalizumab-specific treatment effects relate to improved language processing, including retrieval of newly learned verbal material.


Keywords: Disease-modifying treatment in MS, CNS repair, Symptomatic treatment of MS
Impairments related to multiple sclerosis (MS) can limit the ability of patients to perform typical daily functions or activities. MS therapies may improve patients’ ability to perform such activities. The PRIMUS Activities scale, a patient-reported outcome measure of activity limitation, queries patients about their ability to perform approximately 20 daily activities without aids or assistance. Objectives: To report data from the phase 3 TRANSFORMS trial in relapsing-remitting MS on the effects of oral fingolimod (FTY720) versus intramuscular (IM) interferon beta-1a (IFNβ-1a; an approved standard MS therapy) on PRIMUS score.

Methods: TRANSFORMS was a randomized, double-blind, double-dummy, parallel-group study. Patients (aged 18–55 years) with relapsing-remitting MS (revised McDonald criteria) were randomized to receive daily oral fingolimod, 0.5 mg or 1.25 mg, or weekly IM IFNβ-1a, 30 µg, for 12 months. PRIMUS Activities scores were recorded at baseline, month 6, and month 12 for patients in countries where PRIMUS was available. The treatments were compared in terms of improvement or worsening in PRIMUS Activities scores (defined as a change of ≥2 points). Results: PRIMUS Activities scores at baseline were similar for all treatment groups. Change from baseline in PRIMUS Activities scores at month 12 was lower with fingolimod 1.25 mg (0.12; n = 260) and 0.5 mg (0.08; n = 280) compared with IM IFNβ-1a (0.43; n = 270; P < .05 for both comparisons). At month 12, 17.5% to 19.6% of fingolimod-treated patients experienced improvements in PRIMUS Activities scores from baseline, compared with 14.1% of IM IFNβ-1a-treated patients. Odds ratios for the proportions of patients with improving or worsening PRIMUS Activities scores indicated a benefit of both fingolimod doses over IM IFNβ-1a.

Conclusions: Patients treated with oral fingolimod for 12 months experienced less deterioration in their ability to independently perform daily activities than those treated with IM IFNβ-1a.

Supported by: Novartis Pharmaceuticals Corporation

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(P08) MAXIMIZING THE MYELINOGENIC POTENTIAL OF OLIGODENDROCYTES FOR REPAIR

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Background: Current efforts have focused on identifying global determinants (transcription and growth factors) that promote differentiation of oligodendrocyte precursor cells into myelinating oligodendrocytes during development. Based on this view, myelination is an all-or-none event that is controlled in part by the transcriptional program responsible for differentiation. However, it is evident that the central nervous system (CNS) is composed of heterogeneous microenvironments that shape the unique architecture and relationship between neurons and glia. As an alternative approach, myelination can also be viewed as a graded process, and maximizing the capacity of an oligodendrocyte to form numerous myelin segments with varying internode lengths (myelogenic potential) may offer an effective strategy for future therapies.

Objectives: The objective of our work is to ascertain the nature of this myelogenic potential and identify the molecular cues that promote the formation of myelin internodes. Methods: Generation of a transgenic mouse line with sparsely labeled oligodendrocytes (0.1–0.5%) and biochemically and genetically manipulating the microenvironment of the oligodendrocyte lineage may offer an effective strategy for future therapies.

Results: We show that activation of Ras-GTP through loss of Nf1 results in failure to myelinate large-diameter axons in adult mouse corpus callosum, which is mimicked by cell autonomous transgenic expression of constitutively active CNI-HaRasV12 or loss of Nf1 specifically in oligodendrocytes. This myelination defect is specific to large-caliber, not small- or medium-caliber, axons. Electron microscopic analysis of all three mouse models showed frequent splitting of lamellae within the myelin. The PLP-Cre; Nf1 fl/fl model mimics MRI abnormalities found in patients with MS and neurofibromatosis type 1. After cuprizone injury, remyelination is accelerated in Nf1 mutant, but demyelination and remyelination are delayed in CNI-HaRasV12 mutants.

Conclusions: Results from this study indicate an important role for the Nf1-Ras signaling pathways in control of oligodendrocyte myelination and may be relevant to aspects of brain dysfunction in patients with MS, neurofibromatosis, and Costello syndrome.

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Disclosure: Nothing to disclose

Keywords: Glial biology, CNS repair

(P10) QUALITY INDICATORS FOR MULTIPLE SCLEROSIS

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Background: Determining whether individuals with multiple sclerosis (MS) receive appropriate, comprehensive health care requires tools for measuring quality. Indicators of qual-
ity of health care have been published for many medical conditions, but not for MS. **Objectives:** To develop quality indicators for the care of people with MS. **Methods:** We used a modified version of the RAND/UCLA Appropriateness Method in a two-stage process to identify relevant MS care domains and to assess the validity of indicators within high-ranking care domains. Based on a literature review, interviews with 10 individuals with MS, and discussions with MS providers, 25 MS symptom domains and 14 general health domains of MS care were identified. A multidisciplinary panel of 15 stakeholders in MS care, including 4 people with MS, rated these 39 domains in a two-round modified Delphi process. The research team performed an expanded literature review for the 28 most highly ranked domains to draft 86 MS care indicators. Through another two-round modified Delphi process, a second panel of 18 stakeholders rated the validity of these preliminary indicators using a 9-point response scale. Indicators with a median rating in the highest tertile were considered valid. **Results:** Among the most highly rated MS care domains were appropriateness and timeliness of the diagnostic work-up, bladder dysfunction, cognition dysfunction, depression, disease-modifying agent use, fatigue, and spasticity. Of the 86 preliminary indicators, 76 were rated highly enough to meet predetermined thresholds for validity. Because measurement programs have limited resources and need to select a subset for implementation, we further categorized the final set of 76 valid indicators according to four criteria that may be pertinent to a measurement program: the strength of the panel rating for an indicator, the expected frequency with which an indicator would be triggered, level of evidence supporting the indicator, and ability to implement an indicator using administrative databases. **Conclusions:** Following a widely accepted methodology, we developed a comprehensive set of quality indicators for MS care that can be used to assess quality of care and guide the design of interventions to improve care among people with MS.

**Supported by:** National Multiple Sclerosis Society  
**Keywords:** Comprehensive care and MS, Service delivery in MS

(P11) LABORATORY USE OF CMS CONSENSUS STATEMENT STANDARDS FOR OLIGOCLONAL BAND ANALYSIS

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**Background:** Laboratory standards for cerebrospinal fluid (CSF) analysis of oligoclonal bands (OCBs) were published in a 2005 Consensus Statement by a Consortium of Multiple Sclerosis Centers (CMSC) study group. The extent to which clinical laboratories practice these standards has not been evaluated. **Objectives:** To determine the prevalence among clinical laboratories of the following two major Consensus Statement standards to improve the diagnosis of multiple sclerosis (MS): 1) the use of isoelectric focusing with immunodetection (IEF/ID) methods, and 2) the direct comparison of paired serum and CSF samples. **Methods:** Together with the College of American Pathologists (CAP), we conducted a cross-sectional survey in 2009 of laboratories that evaluate CSF specimens. The questionnaire included items about demographic characteristics as well as institutional practices. We asked laboratorians that analyzed OCBs whether they used IEF/ID methods and whether they assessed paired serum and CSF samples for OCBs. **Results:** Of 228 identified clinical laboratories that analyzed CSF for OCBs, 225 reported whether they used IEF/ID methods or not. Sixty-two (27.6%) of these 225 laboratories classified themselves as community hospital laboratories, 55 (24.4%) as university laboratories, 44 (19.6%) as county/city hospital laboratories, 28 (12.4%) as commercial reference laboratories, 14 (6.2%) as Veterans Administration laboratories, and the remaining 22 (9.8%) as other types. Eighty-six (38.2%) of the 225 laboratories used IEF/ID methods, while 139 (61.8%) of laboratories required paired serum and CSF samples for testing. Only 61 (27.1%) of the 225 laboratories, however, followed two major CMSC Consensus Statement standards for the analysis of OCBs: 1) the use of IEF/ID, methods, and 2) the direct comparison of paired serum and CSF samples. **Conclusions:** Because two of the principal laboratory standards of the Consensus Statement for the analysis of OCBs are not widely implemented, physicians who use CSF analysis to evaluate patients with suspected MS should be aware of the methodology used by their clinical laboratories.

**Supported by:** Consortium of Multiple Sclerosis Centers  
**Disclosure:** Nothing to disclose  
**Keywords:** Immunology and MS

(P12) CLINICAL USEFULNESS OF THE PHYSICAL FUNCTIONING MEASURES IN AMBULATORY PEOPLE WITH MULTIPLE SCLEROSIS

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**Background:** Multiple sclerosis (MS) has a major impact on physical function, employment, and quality of life. It is important to identify early decline, using responsive measures, in order to plan interventions to maintain functioning. **Objectives:** The main aim of this study was to examine the psychometric properties and clinical usefulness of physical functioning measures in ambulatory people with MS using the International Classification of Functioning, Disability and Health (ICF) as a framework. **Methods:** Participants were obtained from a population-based cohort of people with MS (n = 277) living in central Finland in 2000. The physical functioning measures along with self-reported performance were used in a 2-year prospective longitudinal study in ambulatory people with MS (n = 120). The predictors of self-reported performance were identified using multinomial logistic regression. A combination of anchor- and distribution-based approaches were used to determine the responsiveness of physical functioning measures. **Results:** The most significant predictors of perceived difficulties or dependence in performance included lower scores on the Box and Block test; lower Berg Balance Scale scores; greater velocity moment when standing with eyes open; slower 10-m walk test times.

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**Keywords:** Immunology and MS

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and shorter stride length; and shorter distance in the 6-minute walk test. During the 2-year follow-up, 51% of people with MS reported deterioration, compared with 26% rated as deteriorated by the clinician. The measures most responsive to deterioration were the Functional Status Questionnaire self-care, mobility, and domestic life items; distance and change in heart rate during the 6-minute walk test; the 10-m walk test velocities, stride length, and cadence; repetitive squatting; and the Box and Block test. **Conclusions:** The results revealed the value of the clinical outcome measures in detecting minor decrements in functioning that precede and often predict the onset of detectable dependence in performance. By using responsive measures it is possible to identify early decline. Continuing disability prevention should focus on the early stages of disability, thereby enabling people with MS to enhance their functioning, performance, working ability, and independent living in society. In particular, the finding that the clinical measures in the ICF activities component predicted poor performance is important for health-care professionals.

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**Disclosure:** Biogen Idec (consulting fee)

**Keywords:** Rehabilitation strategies and therapy and MS, Management of activities of daily living in MS

### PSYCHOSOCIAL ISSUES

#### (P13) MEASURING SELF-EFFICACY IN MULTIPLE SCLEROSIS: A NEWLY DEVELOPED SCALE AND SHORT FORMS

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**Background:** Managing one’s health can be demanding for people with multiple sclerosis (MS) given the complexities of the disease and array of symptoms experienced. Those who develop confidence in disease management often have better health outcomes and quality of life. Few scales exist to measure self-efficacy (SE) in rehabilitation populations.

**Objectives:** The objective of our study was to develop an SE scale to measure an individual’s confidence in his or her ability to manage MS and its impact on emotional well-being and quality of life. Few scales exist to measure self-efficacy (SE) in rehabilitation populations.

**Methods:** Items were developed to assess respondents’ confidence to meet commonly reported challenges in MS. Data were collected via surveys of community-dwelling individuals with MS (n = 473) enrolled in an ongoing longitudinal survey study. Items were administered three times within 12 months to the same sample. Dimensionality was examined using factor analyses. Item Response Theory (IRT) analyses were used to examine psychometric properties of the scale. Short forms were created by balancing item content and IRT parameters (difficulty and discrimination). Scoring tables were created for the full scale and short forms. **Results:** The final full scale consists of 18 scored items and 2 additional unscored items for clinical purposes only. Factor analytic results indicated that the scale is sufficiently unidimensional to meet the assumptions of IRT. All 18 final items fit the Graded Response Model. A six-item and a ten-item short form correlated >0.96 with the full 18-item scale. Individuals with greater SE had statistically significantly (all P < .001) greater SF8 physical and mental scores and less pain interference, fatigue, depression, anxiety, perceived stress, interference with participation in valued activities, and sleep problems. **Conclusions:** The new SE scale is psychometrically sound and includes items relevant for measuring SE of people with MS.

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**Disclosure:** Nothing to disclose

**Keywords:** Management of activities of daily living in MS

#### (P14) SYMPTOMS THAT PREDICT PARTICIPATION IN PEOPLE WITH MULTIPLE SCLEROSIS

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**Background:** People with multiple sclerosis (MS) often experience an array of symptoms, the accumulation of which can greatly affect participation in valued activities. **Objectives:** This study identified symptoms that predict community participation in a sample of 1271 individuals with MS.

**Methods:** Participants completed a 15-item participation scale and rated severity of heat sensitivity, numbness, bowel or bladder problems, imbalance, problems thinking, sexual dysfunction, slurred speech, spasticity, swallowing problems, tremor, vision loss, arm weakness, leg weakness, fatigue, and pain. The sample was partitioned randomly into a training set (n = 847) used for model building and a validation set (n = 424) for cross-validation. A multiple regression model was fit that included 15 symptom severity scores as predictors of participation (adjusted $R^2 = 0.39$). Using backward selection, nonsignificant ($\alpha > .05$) predictor variables were deleted one at a time until only significant predictors remained. **Results:** The resulting model had an adjusted $R^2$ of 0.37 and included problems thinking, spasticity, vision loss, weakness in the legs, and fatigue. In this regression model, the strongest predictors were weakness in the legs ($P < .001$; standardized $\beta$ coefficient $= -0.29$) and fatigue ($P < .001$; standardized $\beta$ coefficient $= -0.26$). When this model was applied in the validation set, vision loss did not add significantly to variance accounted for by the other four predictors. An adjusted $R^2$ of 0.34 was obtained, suggesting that the model is robust and likely to generalize to other samples.

**Conclusions:** Because causal conclusions cannot be made from correlational data, research is needed to test whether interventions for the symptoms identified (eg, stimulants to decrease fatigue, exercise programs to increase strength) improve participation. In the meantime, when a goal of treatment is maximizing patient participation in valued activities, clinicians might consider targeting reduction in MS-related symptoms, particularly reducing leg weakness and fatigue.

**Supported by:** Department of Education, NIDRR grants H133B080024 and H133B080025

**Disclosure:** Nothing to disclose

**Keywords:** Quality of life in MS, Management of activities of daily living in MS
(P15) TELECONFERENCE-DELIVERED FATIGUE MANAGEMENT: EFFICACY AND EFFECTIVENESS
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Background: Fatigue is a commonly experienced symptom of multiple sclerosis (MS) that challenges participation across a full range of daily activities. Previous research has demonstrated the efficacy and effectiveness of a face-to-face, group-based fatigue self-management program for people with MS. A pilot study of a group-based, teleconference version of the program supported the potential of this alternative delivery approach. Objectives: To test the effectiveness and efficacy of a teleconference-delivered fatigue self-management program for people with MS. Methods: A randomly allocated, two-group time-series design with a wait-list control group was used to determine whether the program could reduce the impact and severity of fatigue, improve quality of life, and improve self-efficacy for managing fatigue. A total of 190 people were allocated to groups and started the program, which involved six 70-minute weekly sessions delivered by a licensed occupational therapist. A research assistant administered the outcome measures before and after the program, and then 6 weeks, 3 months, and 6 months post-intervention. Descriptive statistics, t tests, paired t tests, and mixed-effects regression models were used to test the study hypotheses. Results: Effectiveness (intent-to-treat) analysis supported the program’s ability to reduce the impact of fatigue, as measured by the Fatigue Impact Scale (total and three subscales), and to improve the score on the Physical Health Composite of the 36-item Short Form Health Status Survey (SF-36) immediately post-intervention. Efficacy analysis produced the same results. Effectiveness and efficacy were maintained 6 weeks post-intervention, at which time the SF-36 Mental Health Composite also demonstrated significant gains. On average, the positive impacts of the intervention were maintained at the 3- and 6-month follow-ups. Although changes were observed in fatigue severity and self-efficacy, these changes cannot be attributed to the intervention, as analysis demonstrated a time effect but not a time by allocation effect. Conclusions: A group-based, teleconference-delivered fatigue-management program can reduce the impact of fatigue and improve some aspects of quality of life immediately post-intervention. On average, these effects can be maintained over a 6-month follow-up.

Supported by: National Institute of Disability and Rehabilitation Research, grant H133G070006

Disclosure: Nothing to disclose

Keywords: Symptomatic treatment of MS, Rehabilitation strategies and therapy and MS, Quality of life in MS

(P16) IN SICKNESS AND IN HEALTH: WHEN ILLNESS WEDS THE FAMILY
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Background: This workshop will examine two marriages dealing with the biopsychosocial/spiritual and family life cycle dynamics of living with and navigating the challenges and demands of chronic illness. Two marriage and family therapists, who have experienced illness collectively for over 40 years, will use their personal family examples through filmed interviews, in which all members discuss living with illness and how it has affected their lives within the family context. Objectives: Key points of the presentation are foundationally based on clinicians’ significant findings within quantitative methodology using a population of 200 couples in which one partner has a diagnosis of multiple sclerosis (MS). Issues that couples and families commonly deal with will be addressed during the workshop, including inevitable cognitive, physical, emotional, and relational role changes; management and prevention of caregiver burnout for both spouse and children; and conflict experienced by the caregiving family members in the individuation and differentiation process. Methods: The professionally edited videotapes will highlight how the marital structure changes and evolves, the ways in which the family system adapts to the change created, and how therapists can work most effectively with partners and families to lower stress and strengthen resiliency and unity as the illness becomes a significant force within the family unit. Results: Participants will discover unique experiences that families commonly deal with regarding illness and role change within marriage. Participants will gain therapeutic knowledge and evidence-based information regarding biopsychosocial/spiritual issues when living with illness. Participants will obtain concrete tools to work effectively with couples and families dealing with illness. Conclusions: This presentation will give a bird’s-eye view of two therapists’ unique family illness stories that intertwine media and therapist self-reflection and draw from participants’ knowledge, questions, and experience in a group discussion format.

Disclosure: Nothing to disclose

Keywords: MS and the caregiver/family, Psychological issues and MS

(P17) BENEFITS OF GROUP DISCUSSION ABOUT INTIMACY AND SEXUALITY FOR WOMEN WITH MULTIPLE SCLEROSIS
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Background: Problems with intimacy and sexual expression often occur among people with multiple sclerosis (MS). Existing literature suggests that few people who experience these problems report that they have been adequately addressed by their health-care providers, often because such sensitive topics can be difficult to discuss. Objectives: The purpose of this study was to evaluate the effects of a wellness intervention with a component that focused on intimacy and sexuality on study participants’ perceived quality of intimate interpersonal relationships. Methods: A group of 108 women participated in the randomized clinical trial of the Wellness Program for Women with MS. Participants (mean age, 46.15 years) had been diagnosed a mean of 10.76 years previously. The majority were married (58.3%), and most (93.5%) had completed high school. The wellness intervention included an 8-week education/skill-building lifestyle-change program in a small group setting. One weekly session focused on intimacy and sexuality using multiple vignettes to allow participants to explore their experiences and feelings regarding intimacy, body image, self-esteem, and physical relationships. All participants completed a questionnaire at baseline and post-intervention that included measures of demographic, attitudinal, and behavioral variables.
Fatigue is a symptom commonly seen in people with multiple sclerosis (MS) and its impact on their quality of life (QOL). Existing QOL measures specific to MS disease contain little or no assessment of bowel dysfunction. Bowel dysfunction is a health problem that affects the quality of life (QOL) of people with multiple sclerosis (MS). Existing QOL measures specific to MS disease contain little or no assessment of bowel dysfunction. The Quality of Life Scale Related to Bowel Management, originally designed for spinal cord–injured patients, with a sample of 502 MS patients, as many bowel symptoms are similar in both conditions.

**Methods:** A random sample of 700 MS patients with a history of elimination problems was anonymously recruited through the North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry. Data analysis employed Cronbach reliability testing, factor analysis, analysis of variance, and independent t tests to determine scale reliability and validity.**Results:** Factor analysis of the 11-item scale resulted in two factors: Management and Relationships. Construct validity was demonstrated as the total QOL Bowel Management Tool, and factored subscale scores differed significantly according to a) type of bowel dysfunction (constipation, fecal incontinence, both constipation and fecal incontinence); b) disability level (minimal, moderate, severe); and c) disease classification (relapsing-remitting, progressive) (all *P < .001*). Internal consistency reliability coefficients for total scale and subscales were 0.91, 0.86, and 0.83, respectively.**Conclusions:** The Quality of Life Scale Related to Bowel Management demonstrates satisfactory reliability and validity and can be used with MS patients to provide information on their current bowel status and its impact on their QOL.

**Disclosure:** Nothing to disclose

**Keywords:** Psychosocial issues in MS, Quality of life in MS

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**SYMPTOMS AND REHABILITATION**

(accepted) **(P19) EFFECT OF A SINGLE BOUT OF INTERMITTENT VERSUS CONTINUOUS WALKING ON PERCEPTIONS OF FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS**

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**Background:** Fatigue is a symptom commonly seen in individuals with multiple sclerosis (MS) and may limit their ability to benefit from physical therapy. An exercise program that decreases the amount of fatigue a person with MS experiences as a result of the exercise may lead to a greater amount of exercise performed and a greater likelihood of realizing the benefits of exercise.**Objectives:** The purpose of this study was to determine whether subjective feelings of fatigue differ in people with MS depending on whether they engage in intermittent or continuous exercise. It was hypothesized that people with MS who use an intermittent exercise program would have decreased subjective feelings of fatigue compared with those who engage in continuous exercise.**Methods:** Using a repeated-measures, crossover, within-subjects design, a sample of 30 ambulatory individuals with Expanded Disability Status Scale (EDSS) scores between 2 and 6.5 performed 6 minutes of either continuous or intermittent walking. Fatigue was measured on the Visual Analog Scale of Fatigue (VASF). It was expected that people with MS who performed the 6-minute walk in an intermittent manner would have lower scores on the VASF compared with those who performed the 6-minute walk continuously.**Results:** Mean self-rating of fatigue went from 43.53 to 68.73 when the participants walked for 6 minutes continuously, representing an increase of 25.2 on the VASF scale. In contrast, the mean fatigue score went from 48.03 to 57.20 when the participants walked the 6 minutes intermittently, representing an increase of only 9.17 points on the VASF. This indicated that the participants found the intermittent walking to be significantly less fatiguing than the continuous walking. No effect was noted for disease severity, duration, or participant mood.**Conclusions:** Clinicians are often reluctant to treat individuals with MS because of the lack of an established protocol compared with other neurologic disorders. This study provides evidence to support the use of intermittent exercise in people with MS, which may be tolerated better than continuous exercise based on subjective reporting.

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS

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**SYMPTOMS AND REHABILITATION**

(accepted) **(P20) VALIDATION OF THE PERFORMANCE SCALES SPASTICITY SUBSCALE**

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**Background:** The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a self-report registry for patients with multiple sclerosis (MS). NARCOMS participants report spasticity using one question (subscale) from Performance Scales (PS), which has not been validated independently of the other PS subscales.**Objectives:** We aimed to assess the criterion and construct validity of the Performance Scales Spasticity (PSS) subscale and the respon-
siveness of the subscale. Methods: We recruited patients attending routine visits for spasticity management with stable neurologic status at least 3 months prior to enrollment. We assessed the criterion validity of the spasticity subscale by comparing it with a physician-scored Modified Ashworth Scale (MAS) using Spearman rank correlations with casewise deletion. To assess construct validity, we correlated the PSS with age, pain (NARCOMS pain question), and PS subscales for mobility and vision. A subset of participants agreed to a second visit, where they underwent the same evaluation as at the initial visit. Among these participants, we examined the correlations between changes in the mean MAS score and changes in the spasticity score between the first and second visits. Results: Forty patients completed a single study visit, including 31 (77.3%) women, with a mean (SD) age of 50.2 (11.6) years and median (interquartile range [IQR]) EDSS score of 6.5 (5.8–6.8). The median (IQR) PSS score was 3 (2–4). The PSS subscale correlated with the mean MAS score (r = 0.46, P = .003). Correlations between the PSS subscale and age (r = 0.17, P = .29) and vision (r = 0.03, P = .86) were low, indicating convergent validity. Correlations with pain (r = 0.39, P = .04) and mobility (r = 0.24, P = .16) were more moderate, suggesting convergent validity. Eleven patients completed a second visit. The correlation between the changes in the PSS scores and mean MAS scores was 0.57 (P = .07). Conclusions: The PSS subscale has adequate criterion and construct validity in MS. A larger sample will be needed to assess the responsiveness of the subscale; data collection is ongoing.

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Disclosure: R. Marrie; BioMS Technology Corporation, Sanofi Aventis, EMD Serono, Berlex (other financial benefits). F. Beuthou; Medtronic (honorary); IMPAX Laboratories, Biogen Idec (consulting fees); Acorda Therapeutics, Medtronic (other financial benefits). D. Stough; Nothing to disclose.

Keywords: Management of activities of daily living in MS, Rehabilitation strategies and therapy and MS, Symptomatic treatment of MS

(P21) “SPASTICITY: TAKE CONTROL,” A NEW DVD, PRESENTS AN EDUCATIONAL PROGRAM FOR MANAGING MULTIPLE SCLEROSIS SPASTICITY

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Background: Over 70% of people with multiple sclerosis (MS) have spasticity. Spasticity varies from mild stiffness to severe, painful muscle spasms. In 2003 the Spasticity Management in MS guideline was published. Although the written document was disseminated to health-care professionals, currently there is no user-friendly mechanism for disseminating recommendations to people with MS and health-care providers. Objectives: The objective is to provide an educational program for people with MS and health-care professionals on treating and managing MS spasticity. “Spasticity: Take Control” features MS health-care professionals and people with MS discussing spasticity management in an entertaining and informative format. The program alternates between brief professional summaries of the topics and personalized descriptions by people with MS sharing their successful management experiences. Methods: A new DVD that could be shown through websites, physician offices, or face-to-face presentations was created to highlight many of the recommendations of the spasticity guideline. Professionals include Dennis Bourdette, MD, chairman of neurology at Oregon Health & Sciences University and codirector of the VA MS Center of Excellence-West; Jodie Haselkorn, MD, chairman of the spasticity guideline panel and professor, University of Washington, and director of the VA MS Center of Excellence-West; Cinda Hugos, MS, PT, and Lois Copperman, PhD, OTR. The DVD includes 11 people with MS sharing their personal experiences with medications; modifications for homes, cars, and work; exercise; and procedures such as intrathecal baclofen pumps and Botex injections. Excerpts of the DVD will be shown to illustrate the key points of spasticity treatment and management. Results: “Spasticity: Take Control” will be available to educate patients and health-care professionals. Dissemination may occur through websites of the Consortium of Multiple Sclerosis Centers, Paralyzed Veterans of America (PVA), VA MS Center of Excellence MS centers, the National Multiple Sclerosis Society, and Medtronic, as well as through patient and professional presentations. Conclusions: “Spasticity: Take Control” has been created to disseminate the highlights of the spasticity guideline through an easy-to-use DVD program. The engaging presentation is appropriate for both people with MS spasticity and health-care providers.

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Disclosure: C. Hugos; Paralyzed Veterans of America (honorary). L. Copperman; Paralyzed Veterans of America (honorary). D. Bourdette; Paralyzed Veterans of America (honorary).

Keywords: Symptomatic treatment of MS, Comprehensive care and MS, Rehabilitation strategies and therapy and MS

(P22) PHYSICAL ACTIVITY PREDICTS PROGRESSION OF MOBILITY IMPAIRMENTS IN MULTIPLE SCLEROSIS

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Background: Previous researchers have identified demographic (eg, sex) and clinical (eg, age of onset, disease type, occurrence of a relapse) variables as predictors of the progression of mobility impairments in people with multiple sclerosis (MS). To date, researchers have not examined physical activity as a behavioral predictor of mobility impairments using valid outcome measures and a longitudinal research design. Objectives: This study examined physical activity as a behavioral predictor of mobility impairments in people with MS using valid measures of both physical activity and mobility and a prospective research design. Methods: The sample included 272 individuals with a definite diagnosis of relapsing-remitting MS. On two occasions separated by 6 months, the participants completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ), International Physical Activity Questionnaire (IPAQ), Patient Determined Disease Steps (PDDS) scale, and Multiple Sclerosis Walking Scale–12 (MSWS-12). The data were modeled using panel analysis in Mplus. Results: The panel analysis indicated imperfect stability (ie, change in the rank ordering of participants) of physical activity (stability coefficient = 0.67) and mobility impairment (stability coefficient = 0.94) across time.
The panel analysis further identified direct effects between baseline physical activity and mobility impairment (path coefficient = −0.35) and 6-month change in physical activity and mobility impairment (path coefficient = −0.17). The second path coefficient indicated that a 1-SD reduction in physical activity was associated with a 0.17-SD worsening in mobility impairment. **Conclusions:** The findings provide preliminary support for a reduction in physical activity as a behavioral predictor of the progression of mobility impairment in people with MS. One future research direction involves targeting an increase in physical activity as a behavioral approach for combating mobility impairment in MS.

**Supported by:** National Multiple Sclerosis Society, RG 3926A21

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS

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**(P23) VALIDITY, RELIABILITY, AND SENSITIVITY OF THREE GAIT MEASURES IN MULTIPLE SCLEROSIS**

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**Background:** Multiple sclerosis (MS) presents in individual patients with a variety of clinical manifestations that can affect functional mobility, especially ambulation. The importance of walking and functional mobility is increasingly recognized from the patient perspective and as a contributory factor in productivity at home and in the workplace. Establishing gait measures that are sensitive to change in the patient’s ability to ambulate are important for clinical decision-making related to rehabilitation as well as medical management.

**Objectives:** Assess the validity, reliability, and sensitivity of three gait measures—Timed Up and Go (TUG), Dynamic Gait Index (DGI), and 2-Minute Walk—in relation to the gold standard Expanded Disability Status Scale (EDSS) score, course and duration of disease, mobility status, symptoms (urgency, retention, hesitation, incontinence, frequency), postvoid residual (PVR) with bladder ultrasound, Wagner Test, visual analogue scale (VAS), urodynamic investigation, pelvic floor muscle evaluation (Pubo-Coccygeal Grading Test and muscle coordination evaluation), and current pharmacologic therapies. Patients also completed a 5-day bladder diary. Based on the information collected, an individualized urinary rehabilitation program was developed.

At the end of the rehabilitation program (T1) (mean duration, 12 sessions), all patients repeated the same evaluation as was conducted at T0 without the urodynamic investigation. Primary outcomes included urinary incontinence (Wagner Test), mean number of episodes of leakage (bladder diary), mean number of episodes of urinary frequency in 5 days (bladder diary), nocturia and urgency, and urinary retention (PVR). Secondary outcomes included change in VAS and Pubo-Coccygeal Grading Test. **Results:** Of 62 participants enrolled in the study, 54 were female and 8 were male. The mean ± SD age was 52.67 ± 13.14 years. The mean time since disease onset was 13.78 ± 9.38 years. The mean EDSS score at T0 was 5.39 ± 1.39. The data show a mean Wagner Test score at T0 of 67.77 and at T1 of 75.95, with a statistically significant difference (P < .001); and a mean PVR at T0 of 113.39 mL and at T1 of 97.93 mL, with a statistically significant difference (P = .010). **Conclusions:** Statistical analysis showed that primary and secondary outcomes are statistically significant. Urinary rehabilitation seems to be effective in MS patients if performed in a specialized rehabilitation center.

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS

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**(P24) EFFECTIVENESS OF URINARY REHABILITATION IN MULTIPLE SCLEROSIS PATIENTS**

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**Background:** Over 80% of multiple sclerosis (MS) patients have symptoms of urinary dysfunction during the disease course. Urinary dysfunction can have a significant impact on patient quality of life. Comprehensive evaluation is essential for MS specialists to effectively manage these potentially life-disrupting symptoms. **Objectives:** This study evaluated the effectiveness of a rehabilitation program for MS patients with urinary dysfunction being followed in a specialized rehabilitation center. **Methods:** Sixty-two MS patients with urinary symptoms consecutively referred for the first time to the rehabilitation center were enrolled in the study. Data collected at pre-treatment (T0) included age, Expanded Disability Status Scale (EDSS) score, course and duration of disease, mobility status, symptoms (urgency, retention, hesitation, incontinence, frequency), postvoid residual (PVR) with bladder ultrasound, Wagner Test, visual analogue scale (VAS), urodynamic investigation, pelvic floor muscle evaluation (Pubo-Coccygeal Grading Test and muscle coordination evaluation), and current pharmacologic therapies. Patients also completed a 5-day bladder diary. Based on the information collected, an individualized urinary rehabilitation program was developed.

At the end of the rehabilitation program (T1) (mean duration, 12 sessions), all patients repeated the same evaluation as was conducted at T0 without the urodynamic investigation. **Results:** Of 62 participants enrolled in the study, 54 were female and 8 were male. The mean ± SD age was 52.67 ± 13.14 years. The mean time since disease onset was 13.78 ± 9.38 years. The mean EDSS score at T0 was 5.39 ± 1.39. The data show a mean Wagner Test score at T0 of 67.77 and at T1 of 75.95, with a statistically significant difference (P < .001); and a mean PVR at T0 of 113.39 mL and at T1 of 97.93 mL, with a statistically significant difference (P = .010). **Conclusions:** Statistical analysis showed that primary and secondary outcomes are statistically significant. Urinary rehabilitation seems to be effective in MS patients if performed in a specialized rehabilitation center.

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS
(S01) FATIGUE AND COGNITION IMPROVE AFTER ONE YEAR OF NATALIZUMAB TREATMENT

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Background: Fatigue and cognitive dysfunction are common symptoms of multiple sclerosis (MS) and leading causes of disability in MS patients. Objectives: To evaluate changes in patient-reported fatigue and cognitive function after 1 year of natalizumab treatment in MS patients. Methods: The study population consists of MS patients initiating natalizumab treatment who agreed to participate in a 12-month longitudinal study. The study assessed patient experiences with natalizumab using validated patient-reported outcome (PRO) measures prior to treatment initiation and after the 3rd, 6th, and 12th infusions. The current analysis reports change in fatigue and cognition from baseline through the 12th natalizumab infusion. Fatigue is measured by the 5-question Modified Fatigue Impact Scale–5 (MFIS-5, score range 0–20), with lower scores indicating lower impact of fatigue on physical, cognitive, and psychosocial functioning. Cognitive function is measured by the 6-question Medical Outcomes Study Cognitive Functioning Scale (MOS-Cog Scale, score range 6–36), with higher scores indicating better reasoning skills, memory, concentration, ability to start several actions at one time, and ability to react to what is said or done. Regression analysis was used to control for baseline (BL) covariates such as age, years since MS diagnosis, number of natalizumab infusions received, disability and functional status, number of MS drugs used prior to natalizumab, and comorbidity burden. Results: Results from this ongoing study are presented for 192 patients completing the BL through 12th infusion follow-up surveys. The mean (SD) number of years since MS diagnosis was 10.16 (8.23). Most patients were female (78%), and the mean (SD) age was 46.09 (10.78) years. On average, MFIS scores decreased significantly (BL, 12.23 ± 2.2; 12th infusion score, 10.97 ± 2.2; P < .001), and MOS-Cog scores increased significantly over time (BL, 25.8 ± 1.4; 12th infusion score, 26.91 ± 1.4; P < .001) after controlling for covariates. Conclusions: MS patients reported improvements in fatigue impact and overall cognitive function after 1 year of natalizumab treatment.

Supported by: Biogen Idec, Inc and Elan Pharmaceuticals, Inc


Keywords: Quality of life in MS

(S02) COST PER RELAPSE AVOIDED AND BUDGET IMPACT OF INTERFERON BETA-1B (EXTAVIA) IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is one of the most common causes of neurologic disability in young and middle-aged adults. The majority of patients initially have a form of MS described as “relapsing-remitting,” which manifests as a series of relapses followed by periods of partial or complete remission. Interferon beta-1b (IFNβ-1b) is indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Objectives: The purpose of the study is to determine the cost per relapse avoided of IFNβ-1b (Extavia) compared with other disease-modifying treatments (DMTs) and the budgetary impact of its use for the treatment of relapsing-remitting MS (RRMS) from a US payer perspective. Methods: A Microsoft Excel-based model with inputs for acquisition costs, plan rebates, relapse rates and cost, and market share was used. All first-line DMTs for RRMS treatment were included in the analyses. Outcomes included 1-year and 2-year cost per relapse avoided and overall costs to the health plan as well as the per member per month (PMPM) costs. Drug acquisition costs were in 2009 US dollars. Results: The 1-year cost per relapse avoided was lowest for IFNβ-1b (Extavia) at $58,725, followed by $63,190 for IFNβ-1b (Betaseron), $69,438 for subcutaneous (SC) interferon beta-1a (IFNβ-1a), $118,108 for glatiramer acetate (GA), and $195,719 for intramuscular (IM) IFNβ-1a. The 2-year cost per relapse avoided was lowest for SC IFNβ-1a, followed by IFNβ-1b (Extavia), IFNβ-1b (Betaseron), IM IFNβ-1a, and GA. For a typical plan, a 16% uptake of IFNβ-1b (Extavia) utilization in year 1 resulted in an increased savings of $0.03 PMPM in total IFNβ-1b costs. Conclusions: IFNβ-1b (Extavia) is a cost-effective therapy compared with other DMTs as measured by the cost per relapse avoided. From a US payer perspective, entry of IFNβ-1b (Extavia) in the US health market will lead to health plan cost savings.

Supported by: Novartis Pharmaceuticals Corporation


Keywords: Economic issues and MS

(S03) SELF-REPORTED OUTCOMES OF PEDIATRIC MULTIPLE SCLEROSIS PATIENTS TRANSITIONING TO ADULT CARE

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Background: Pediatric multiple sclerosis (MS) patients require expensive disease-modifying treatments in order to maintain their quality of life as well as to limit long-term disability. Little is known about how pediatric MS patients maintain their insurance coverage once they age out of private or publicly funded health plans. Objectives: To assess health insurance coverage and self-reported health status of pediatric MS patients who have aged out of the UAB Center for Pediatric Onset Demyelinating Disease (CPODD) clinic and were aged 19 years or older at the time of the survey. Methods: We interviewed demyelinating patients who had aged out of the UAB Center for Pediatric Onset Demyelinating Disease (CPODD) clinic and were aged 19 years or older at the time of the survey. Three telephone interview attempts were made, and then questionnaires were mailed to the last known address. From the CPODD practice, 24 patients met the requirements of our survey, and 11 patients responded (8 with MS, 1 with pediatric MS).
ON, 1 with NMO, and 1 with TM; 7 female and 4 male patients). Results: Upon leaving the pediatric clinic, 73% of the patients transitioned to an adult MS specialist. At the time they stopped coming to CPODD, 90% of the patients had some form of insurance. At the time of the survey, 90% of the patients still had health insurance coverage. Of the 10 insured patients, 10% were insured through employer-based health insurance, 30% were insured through Medicaid, and 60% were insured through a parent’s employer-based health insurance. We found that 73% of the patients had applied for disability benefits (SSI); 55% indicated that they had been approved and were currently on disability. Of the 6 patients who reported being on disability, 3 had MS, 1 ON, 1 NMO, and 1 TM. However, nearly half of the patients indicated that they were receiving government assistance in the form of food stamps and housing subsidies. Conclusions: We found that our pediatric MS and demyelinating patients successfully transitioned to adult care with proper clinical guidance. A large proportion of them maintain health insurance, either through publicly funded programs or a parent. Only a small percentage reported trouble paying for medications.

Supported by: University of Alabama at Birmingham Center for Pediatric Onset Demyelinating Disease (CPODD)
Disclosure: Nothing to disclose
Keywords: Quality of life in MS

(S04) ACUTE LEUKEMIA IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH MITOXANTRONE
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Background: Leukemia secondary to mitoxantrone treatment has been reported in patients with multiple sclerosis (MS). The package insert for Novantrone (2009) includes data from one cohort study (N = 802) and one safety and tolerability monitoring study (N = 509) that report the postmarketing incidence of leukemia to be 0.25% and 0.60%, respectively. Other published studies have suggested even higher incidences. Objectives: To assess and describe the US postmarketing reports of acute leukemia following treatment with Novantrone (mitoxantrone for injection concentrate) in patients with MS. Methods: Case reports of acute leukemia following mitoxantrone therapy in MS patients, including three cases from the Registry to Evaluate Novantrone in Worsening MS (RENEW), were compiled and submitted to EMD Serono, Inc, between March 2003 and April 2009. Results: A total of 44 cases of acute leukemia secondary to mitoxantrone therapy were identified. Complete patient characteristics were not available for all cases. Women accounted for 70% (31/44) of patients, and the median age was 49 years (range, 29–68; n = 41). Patients received a mean cumulative dose of mitoxantrone of 84.9 mg/m² (SD = 23.1; range, 48–135; n = 20), and the median time to leukemia onset after stopping mitoxantrone therapy was 17 months (range, 0–60; n = 32). Acute myelogenous leukemia and its subtype, acute promyelocytic leukemia, were the most common types of leukemia observed in this analysis, reported in 17 (38.6%) and 16 (36.4%) patients, respectively. Other reports included leukemia and secondary leukemia not otherwise specified (n = 7; 15.9%), chronic myeloid leukemia (n = 2; 4.5%), pre-B cell acute lymphoblastic leukemia (n = 1; 2.3%), and myelodysplasia (n = 1; 2.3%). The incidence of any type of leukemia did not appear to be related to the dose of mitoxantrone. Data were previously presented at the 2010 American Academy of Neurology Annual Meeting. Conclusions: The risk of leukemia secondary to mitoxantrone therapy may be significant in patients with MS. Although the exact incidence has yet to be established, the possibility of this adverse event warrants ongoing investigation and monitoring of patients receiving mitoxantrone for MS.

Supported by: EMD Serono, Inc

(S05) MAGNETIZATION TRANSFER RATIO IMAGING IS FEASIBLE IN MULTICENTER MULTIPLE SCLEROSIS TRIALS
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Background: BG-12 is a novel oral therapy being developed for the treatment of multiple sclerosis (MS). In addition to anti-inflammatory properties, BG-12 may exhibit potential neuroprotective properties through activation of Nrf2 and associated antioxidant and metabolic defense mechanisms. Magnetization transfer ratio (MTR) imaging is a variation on conventional magnetic resonance imaging (MRI). MTR has been proposed for use as a biomarker of changes in myelin content of brain white matter. Objectives: To determine the feasibility of using MTR imaging in large multicenter trials with MS patients. Methods: DEFINE and CONFIRM are two ongoing phase 3, randomized, multicenter, double-blind, placebo-controlled studies assessing efficacy and safety of BG-12 in subjects with relapsing-remitting MS, and will use MTR to further analyze the efficacy of BG-12. MTR scans are being obtained in a subset of patients at baseline and 6, 12, and 24 months, using manufacturer-supplied MT pulse sequences. MTR pulse parameters were provided by central imaging centers (NeuroRx Research for DEFINE and the NMR Research Unit for CONFIRM). Outcome measures include MTR in whole brain at baseline, the percent change in brain MTR over time, MTR in gadolinium (Gd)–enhancing lesions, and the subsequent change of MTR in these lesions. Results: MTR of whole brain was measured in a subgroup of baseline scans and normalized across this group. In DEFINE: 65 of 76 (86%) MRI facilities around the world were capable of performing adequate MTR imaging. Mean (SD) MTR was 40.2 (1.9) on GE scanners (n = 61), 44.6 (3.5) on Philips scanners (n = 31), and 31.7 (1.4) on Siemens scanners (n = 43). In CONFIRM: 107 of 110 (97%) MRI facilities around the world were capable of performing MTR. Mean (SD) MTR was 32.8 (5.8) on GE scanners (n = 78), 42.9 (5.6) on Philips scanners (n = 24), and 30.4 (1.4) on Siemens scanners (n = 58). Conclusions: The collection and analysis of MTR data in the context of large, multicenter clinical trials is feasible and promises to provide valuable data regarding demyelin-
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(S06) THE ROLE OF POSTPARTUM INTRAVENOUS CORTICOSTEROIDS IN THE PREVENTION OF RELAPSES IN MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is prevalent in women of childbearing age. The estimated mean ± SD relapse rate during the first trimester of pregnancy is 0.5 ± 1.3, increasing to 1.2 ± 2.0 during the first trimester postpartum. Intravenous (IV) methylprednisolone (MP) reduces magnetic resonance imaging (MRI) activity over a 2-month period. A dose of 1 g of IVMP after delivery could reduce the risk of postpartum relapses. Objectives: To compare the postpartum relapse rate in MS patients treated with IVMP after delivery with that of patients who did not receive this treatment. Methods: This was a retrospective study. We included 50 relapsing-remitting MS (RRMS) and 2 secondary progressive MS (SPMS) patients with one or more documented pregnancies; each pregnancy was considered a single case. Data recorded from medical records included MS type; number of relapses before, during, and after pregnancy (first, second, and third trimester postpartum); treatment history; breastfeeding duration; and postpartum IV steroid use. All epidemiological data will be provided. Results: This is an ongoing study; so far 52 cases have been analyzed. Of these, 7 patients had at least one relapse during pregnancy. Thirty-nine patients received postpartum IV steroids (1 g); 13 did not receive them. During the first postpartum trimester, we found relapses in 18% of the group of patients who received IV steroids versus 46.2% of the patients who did not receive steroids (P = .0448). During the second and third postpartum trimesters, the relapse percentage was 25.6% in the group that received steroids and 23% in the group that did not receive steroids. Conclusions: The rate of relapse in MS increases during the first trimester postpartum. In our study, we found a significant reduction in the relapse rate during this period in patients who received postpartum IV steroids compared with those who did not receive them. This reduction was not significant over the second and third postpartum trimesters. Our results support prior reports and cause us to consider use of a second steroid infusion just after the third postpartum month.

Disclosure: Nothing to disclose

Keywords: Imaging and MS, Disease-modifying treatment in MS

(S07) SLEEP DISORDERS IN MULTIPLE SCLEROSIS

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Background: Disrupted sleep and poor sleep quality can be associated with fatigue, daytime sleepiness, and possibly dangerous cardiorespiratory events. The prevalence of sleep disorders in multiple sclerosis (MS) has not been well established. Symptomatic narcolepsy has been reported in 8.6% of MS patients. In our preliminary report involving 65 MS patients, we found a prevalence of sleep disorders of 37%. Objectives: To determine the prevalence and to identify the type of sleep disorders in MS patients. Methods: This was a prospective study for all types of MS. A sleep disorder questionnaire including the Epworth sleepiness scale was given to MS patients aged 18 to 64 years during their follow-up visit to the Maxine Mesinger MS Comprehensive Care Center at Baylor College of Medicine. Collected data include demographic information, type of MS, date of diagnosis, use of tobacco and alcohol, sleeping habits, caffeine consumption, and medical history. We also asked about current and previous treatments and other medical conditions. Patients who suffer from congestive heart failure, primary respiratory disorders, and obstructive respiratory disorders or any other neurodegenerative condition were excluded. Informed consent was obtained from all participants. Results: A total of 100 patients were included; 81 were women, and the mean age was 40 years. Most patients were on interferon treatment (50%), 17% on glatiramer acetate, 22% on natalizumab, and 11% on other types of treatment. Family history of sleep disorders was present in 9%. Forty percent of the patients were found to have sleep disturbances, based on an Epworth scale score of >9. Of these patients, 87.5% had significant fatigue. The most common sleep disturbance reported was difficulty falling asleep, followed by frequent awakenings. Demographics will be presented. Conclusions: Insomnia is diagnosed in 6% to 15% of the general population. The prevalence of sleep disorders in our MS population was 40%, and fatigue was present in 87.5% of these patients. Several factors influence the quality of sleep in MS. These can cause daytime somnolence and increased fatigue. Awareness and treatment of these conditions is vital for improving the health and quality of life of MS patients.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS, Sleep and MS

(S08) DISTAL LOWER-LIMB DISCOLORATION IN PATIENTS WITH MULTIPLE SCLEROSIS


Background: Discoloration of the distal lower limb is a common condition in multiple sclerosis (MS) patients. Many MS patients are young adults who are usually active and fit. Our study was to evaluate if MS is associated with distal lower limb discoloration. Methods: We used the database of the Multiple Sclerosis Center at Baylor College of Medicine. Collected data included age, sex, race, personal history of smoking, family history, diabetes, hypertension, and evidence of MS. Results: A total of 100 patients were included; 81 were women, and the mean age was 40 years. Most patients were on interferon treatment (50%), 17% on glatiramer acetate, 22% on natalizumab, and 11% on other types of treatment. Family history of sleep disorders was present in 9%. Forty percent of the patients were found to have sleep disturbances, based on an Epworth scale score of >9. Of these patients, 87.5% had significant fatigue. The most common sleep disturbance reported was difficulty falling asleep, followed by frequent awakenings. Demographics will be presented. Conclusions: Insomnia is diagnosed in 6% to 15% of the general population. The prevalence of sleep disorders in our MS population was 40%, and fatigue was present in 87.5% of these patients. Several factors influence the quality of sleep in MS. These can cause daytime somnolence and increased fatigue. Awareness and treatment of these conditions is vital for improving the health and quality of life of MS patients.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS, Sleep and MS
Autonomic dysfunction in multiple sclerosis (MS) has been recently reported, mostly affecting the bladder, bowel, and sexual functions. Orthostatic dizziness has been found in 50% of MS patients. Until now, studies have focused more on cardiovascular reflex testing and blood pressure responses. We report on 26 MS patients with discoloration in the lower extremities not associated with vascular or other concomitant disease. Objectives: To describe a group of MS patients who developed distinctive discoloration in the distal lower extremities. Methods: Lower-limb discoloration was noticed in MS patients during follow-up visits at the Maxine Mesinger Comprehensive Care Center. Epidemiological data, treatment history, type of MS, and disease duration were documented. Patients with concomitant disease (diabetes mellitus, vascular insufficiency) were excluded. Complete physical and neurologic examinations were performed. Some patients were evaluated by means of arterial Doppler. Results: A total of 26 MS patients were enrolled in the study, including 23 women, with a mean age of 52 years. Eleven patients were diagnosed after 2000; of these, 5 were diagnosed in the past 3 years. Disease type was 69% relapsing-remitting MS, 23% secondary progressive MS, and 7.6% primary progressive MS. Eighty percent of patients were currently on treatment with a disease-modifying agent. All patients demonstrated distal discoloration of the lower extremities; peripheral pulses were normal in all patients. Coloration did not change with leg raising. Of the patients, 11.5% had dysautonomic symptoms. Three patients were evaluated with arterial Doppler evaluation; all were normal. Demographic information and images will be provided. Conclusions: Autonomic dysfunction is seldom recognized by MS patients; it can cause paroxysmal arrhythmias, recurrent syncope, neurogenic pulmonary edema, and decreased venricular ejection fraction, leading to increased morbidity and mortality. MS can involve any part of the central nervous system, including critical areas subserving autonomic function, causing interference of descending autonomic pathways during their course in the brainstem or spinal cord. Demyelinating lesions located among central thermoregulatory pathways may result in regional or global anhydrosis in patients with MS. Skin changes could be a manifestation of autonomic dysfunction, which may affect the quality of life in MS patients.

Supported by: Maxine Mesinger MS Comprehensive Care Center
Disclosure: Nothing to disclose
Keywords: Quality of life in MS

(S09) RECURRENT AND MULTIPHASIC DISSEMINATED ENCEPHALOMYELITIS CASE SERIES
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Background: Disseminated encephalomyelitis (DEM) is an inflammatory demyelinating disease with no well-accepted diagnostic criteria or biological markers for the diagnosis. The course is usually monophasic. Recurrence and multiphasic presentations are rare. Objectives: To report clinical and radiologic features of patients with recurrent and multiphasic DEM. Methods: We describe three patients, two with recurrent and one with multiphasic DEM. Clinical and radiologic features will be provided. Results: Case 1 was a 42-year-old woman with distractibility, headaches, dysnomia, and dysgraphia. Brain magnetic resonance imaging (MRI) showed a large left temporal lesion. Cerebrospinal fluid analysis showed two oligoclonal bands. Brain magnetic resonance spectroscopy (MRS) was consistent with demyelination. She improved after intravenous (IV) steroids. Three months later, she developed incoordination and dysarthria. Brain MRI showed new enhancing lesions, and brain biopsy was consistent with demyelination. Case 2 was a 27-year-old woman with headaches, vomiting, and blurred vision. Brain MRI showed an enhancing right basal ganglia lesion, extending to the caudate and cerebral peduncle. Treatment with IV steroids resulted in clinical and radiographic improvement. Four months later, she developed seizures and respiratory distress and required intubation. Brain MRI showed involvement of the right basal ganglia, thalamus, and medulla, which had increased from the previous study. She received IV steroids and recuperated. Case 3 was a 38-year-old man with aphasia and tonic-clonic seizures. Brain MRI showed a large left temporoparietal cortical-subcortical lesion that was partially enhancing. Brain biopsy revealed demyelination and inflammation. The symptoms partially improved after IV steroid treatment. Seven-month follow-up brain MRI showed improvement and mild enhancement remaining in the temporal lesion. One-year follow-up MRI showed a new enhancing subcortical occipital lesion. The results of cerebrospinal fluid analysis, evoked potentials, and spinal MRI were all normal. The patient received steroid treatment and will continue to be followed. Conclusions: DEM must be considered in the differential diagnosis of MS. Radiologic characteristics can help distinguish the two, including extent of the lesions, involvement of gray matter, preference for basal ganglia, and thalamic and midbrain involvement. Early diagnosis and initial management may improve the clinical outcome.

Supported by: Maxine Mesinger MS Comprehensive Care Center
Disclosure: Nothing to disclose
Keywords: Imaging and MS

(S10) IMPROVEMENT IN LOW-CONTRAST VISUAL ACUITY IN MULTIPLE SCLEROSIS TRIALS OF NATALIZUMAB
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Background: In the AFFIRM trial, natalizumab reduced sustained visual loss as measured by low-contrast letter acuity (LCA), but not high-contrast visual acuity (HCA). Natalizumab was associated with improvements in disability and quality of life. We sought to determine whether visual function improvement could also be demonstrated. Objectives: To analyze the probability of visual improvement and its association with treatment status in the pivotal, phase 3 trial of natalizumab. Methods: Binocular vision testing was performed for HCA and LCA. Cumulative probabilities of visual improvement, sustained over 12 weeks, were determined for increases in score by 1 line (5 letters) and 2 lines (10 letters). Improve-
Elevated serum angiotensin-converting enzyme (ACE) levels have been reported in multiple sclerosis (MS) patients. In a previously reported data set of 75 clinical definite MS patients, serum ACE levels were measured (Supporting Information). In a previously reported data set of 75 clinical definite MS patients, serum ACE levels were measured (Supporting Information). ACE-specific substrate furanacryloyl-modified phenylalanil-glycylglycine, with results expressed in units per milliliter. The upper limit of normal was defined as 50 U/mL. Twenty-three percent of 75 patients were above this level, compared with 6% of 31 age- and sex-matched controls. The highest level reported was 164 U/mL on the graphic display. There was a greater degree of improvement across all visits for natalizumab than for placebo (2.5%: 23% vs. 15% for placebo, P = .013; 1.25%: 28% vs. 23% for placebo, P = .043). There was a greater degree of improvement across all visits for natalizumab than for placebo (Supporting Information). A much lower probability of improvement (≤6%) in HCA was demonstrated, with no differences between treatment groups. Natalizumab treatment was associated with greater proportions of patients showing improvement from baseline for at least 8 of 10 study visits by LCA (2.5%: 23% vs. 15% for placebo, P = .013; 1.25%: 28% vs. 23% for placebo, P = .043). There was a greater degree of improvement across all visits for natalizumab than for placebo (P = .003), with a trend for 1.25% (P = .055). Probabilities of improvement at threshold levels below (5 letters) and above (10 letters) test-retest variability did not show treatment differences. Natalizumab treatment was associated with sustained visual improvement by some measures of visual function; this improvement is particularly well captured by the 2.5% contrast chart. HCA was less sensitive and failed to capture treatment effects on improvements in visual function.

**Supported by:** Biogen Idec, Inc, and Elan Pharmaceuticals, Inc


Keywords: Disease-modifying treatment in MS, Quality of life in MS

**S12) EFFECTS OF LSVT ON VOICE AND RESPIRATION IN INDIVIDUALS WITH MULTIPLE SCLEROSIS**

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**Background:** The Lee Silverman Voice Treatment, commonly referred to as LSVT, is the first and only documented efficacious speech treatment that restores oral communication. With more than $5 million in NIH funding, LSVT was initially developed for the treatment of voice disorders in individuals with idiopathic Parkinson’s disease. Over the last decade, further support for the efficacy of LSVT for various neurologically based speech disorders, including those caused by multiple sclerosis (MS), has emerged. Centered on a very specific therapeutic target, LSVT acts as a “trigger” to increase effort and coordination across the speech production subsystems (respiratory, phonatory, and articulatory). This “trigger” provides a comprehensive motor organizing theme that affects multiple levels of the motor output processes. The purpose of this study was to assess the impact of an intensive respiratory-phonatory treatment program (LSVT) on vocal and respiratory function in five individuals with relapsing-remitting MS (RMS). Five individuals with RMS, three women (mean age, 52 years) and two men (mean age, 45 years) with a history of MS ranging from 13 to 18 years participated in the study. During their initial speech evaluations, all five participants complained of vocal improvements in visual function.

**Results:** Elevations of serum ACE levels ranging from 293 U/L to 434 U/L have been monitored throughout this time, using a comparable spectrophotometric assay commercially available through Quest Labs (normal range: 9–67 U/L). Extensive pulmonary evaluation has yielded no evidence of sarcoidosis. Magnetic resonance imaging has been compatible with MS, including periventricular and subcortical lesions and multiple spinal cord lesions in the cervical and thoracic regions. Prolonged bilateral visual evoked responses were noted. Positron emission tomographic imaging from the vertex to the mid-thighs yielded moderate focal hypermetabolism in the anterior aspect of the proximal thighs. The left proximal thigh skin and subcutaneous tissue was biopsied, with a diagnosis of “chronic septic panniculitis, suggestive of erythema nodosum.” No granulomas were reported. A lumbar puncture yielded clear cerebrospinal fluid (CSF) with 0 white blood cells, 0 red blood cells, protein 44 (normal range: 15–45), 13 oligoclonal bands (none detected in serum), CSF ACE <4 (normal: <4), and CSF VDRL negative.

**Conclusions:** During more than 4 years of follow-up, no clinical evidence of sarcoidosis has emerged, suggesting that the upper range of serum ACE levels in MS patients is much higher than most clinicians have thought.

**Disclosure:** D.A. Barone: Biogen Idec, Teva, EMD Serono, Acorda (consulting fees); Biogen Idec, Teva, Bayer, EMD Serono (honorary). K.A. Barone: Biogen Idec, Teva, EMD Serono (consulting fees); Biogen Idec, Teva, Bayer, EMD Serono (honorary).

Keywords: Natural history of MS, Comprehensive care and MS

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background, shortness of breath, and fatigue when communicating associated with their MS. These voice and respiratory symptoms were chronically present despite not experiencing an MS flare within 3 months prior to their participation. All five participants received 16 1-hour LSVT sessions over a 4-week period. Results: Improvement after treatment was observed in sound pressure level (SPL) both for speech tasks (conversation) and in duration of sustained vowel phonation (/a/). Individuals with MS treated with LSST increased their voice SPL by an average of 7 dB. These observed changes were not only statistically significant but also audible to new communication partners. Significant improvement was also observed in all participants in forced vital lung capacity. Conclusions: These findings provide further support for the efficacy of LSST in populations beyond idiopathic Parkinson’s disease and for the treatment of various neurologically based speech disorders such as those in MS.

Disclosure: Nothing to disclose.

Keywords: Rehabilitation strategies and therapy and MS, Speech/language therapy in MS, Quality of life in MS

(S13) THE IMPACT OF SPASTICITY ON DAILY ACTIVITIES IN PEOPLE WITH MULTIPLE SCLEROSIS

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Background: Few authors have systematically investigated the impact of spasticity on activities of daily life (ADLs) in people with multiple sclerosis (MS). The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a self-report registry for people with MS. Objectives: We aimed to characterize the severity of spasticity-related symptoms and the impact of spasticity on ADLs in a large sample of people with MS enrolled in the NARCOMS Registry. Methods: As part of a semiannual NARCOMS survey in October 2008, questions regarding spasticity severity and interference of spasticity with daily activities were asked. The primary measure of spasticity was the Performance Scales Spasticity (PSS) subscale. We captured how much spasticity interfered with daily activities using a Likert scale from 1 (not at all) to 4 (greatly). Activities included sitting, standing, walking, stair climbing, transfers, self-care, toileting, dressing, eating, household activities, family activities, work or study, sleep, driving, and sexual activity. We examined correlations between PSS score and ADL interference using the Spearman rank correlation. Results: Of 15,679 eligible participants, 10,200 US residents responded (65%). Spasticity affected more than 80% of participants, with 29.6% (n = 3023) reporting moderate to totally disabling spasticity. Most participants reported more difficulty with lower-extremity symptoms. The impact of spasticity on ADLs was substantial. Over 25% of individuals reported that spasticity interfered moderately or greatly with standing, walking, stairs, household activities, sleep, or sexual activity. As the severity of the reported spasticity increased, spasticity was reported to interfere more with ADLs (r = 0.67, P < .0001 for walking). After accounting for mobility, partial correlations between spasticity and interference with ADLs were weaker but still showed an important impact of spasticity. Conclusions: Spasticity is perceived by many people with MS as significantly interfering with a wide range of activities. Further studies are needed to compare patient reports with objective assessments of spasticity and ADL performance, and to better understand the relative impact of spasticity compared with other impairments (particularly weakness).


Keywords: Symptomatic treatment of MS, Rehabilitation strategies and therapy and MS, Quality of life in MS

(S14) EFFECTIVENESS OF BALANCE DISORDERS REHABILITATION TREATMENTS IN MULTIPLE SCLEROSIS PATIENTS: A PILOT RANDOMIZED CONTROLLED TRIAL ASSESSING THE WII BALANCE BOARD GAMING SYSTEM

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Background: Balance disorders are frequently observed in patients with multiple sclerosis (MS), leading to impaired balance and increased risk of falls. New rehabilitation approaches are crucial in order to improve the efficacy of interventions and to stimulate patients’ attention during the rehabilitation treatment. Objectives: The aim of the study was to compare the efficacy of balance disorder rehabilitation in MS patients with a portable and widely available force platform (Wii Balance Board) versus a traditional rehabilitation program. Methods: MS patients with balance disorders were selected among those followed as outpatients at AISM Rehabilitation Centre (Italian Multiple Sclerosis Society). Thirty-six patients were selected and randomized into two groups: Wii Balance Board group (Wgroup, 18 participants) and control group (Cgroup, 18 participants). All participants were evaluated with the Expanded Disability Status Scale (EDSS), Ambulation Index (AI), Berg Balance Scale (BBS), Modified Fatigue Impact Scale (MFIS), and stabilometric recording under two conditions, open eyes (STABOE) and closed eyes (STABCE), at T0 (beginning of rehabilitation program) and T1 (end of rehabilitation program). All participants underwent rehabilitation treatment (12 sessions, 60 min each) with a standardized protocol for the Cgroup and a Wii Balance Board protocol for the Wgroup. The primary outcome was the BBS score, and secondary outcomes were AI, MFIS score, STABOE, and STABCE. Statistical analysis was performed to assess differences between T0 and T1 and between the Wgroup and the Cgroup. Results: Data for the Wgroup showed statistically significant differences between T0 and T1 for all outcomes considered (P < .001 for AI, MFIS, and BBS; P < .05 for STABOE and STABCE). Data for the Cgroup showed statistically significant differences between T0 and T1 for AI and MFIS (P < .05), while non-statistically significant differences were found for BBS, STABOE, and STABCE. Conclusions: Balance rehabilitation treatment with a portable, widely used force platform appeared to be a useful tool in improving balance skills in people with MS. The results of this study will serve as the basis for a larger trial in

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order to better differentiate efficacy among traditional rehabilitation techniques and new approaches.

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S15) EFFECTIVENESS OF THE WII ON STANDING BALANCE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS
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Background: Multiple sclerosis (MS) often affects ambulation and dynamic standing, which are needed to perform activities of daily living. Common signs and symptoms of MS that affect standing balance include fatigue, weakness, spasticity, and balance. Impairments in balance and equilibrium are especially problematic, as central nervous system degeneration has been shown to have adverse effects on the visual, somatosensory, and vestibular systems. Physical therapy typically focuses on therapeutic exercise and neuromuscular retraining to manage these symptoms. A new adjunctive treatment that has been used in rehabilitation is the Wii Fit, a game played on the Nintendo Wii console. The Wii Fit uses a balance board that provides feedback on weight shifting.

Objectives: Examine the effectiveness of the Wii Fit on static and dynamic balance, as measured by the Functional Reach test, Timed Up and Go (TUG), Timed 25-Foot Walk, and Dynamic Gait Index (DGI) for individuals with MS who are ambulatory.

Methods: This one-group pretest-posttest design included five people who were identified from our general exercise program as appropriate candidates to participate in the Wii Pilot Study. All group members completed the standardized measures before participating in the Wii exercise program (Functional Reach, TUG, Timed 25-Foot Walk, DGI). Participants performed the following activities on the Wii once per week for 8 weeks: Soccer Heading, Ski Jump, Ski Slalom, Tight Rope Walking, Penguin Slide, Bubble River. After completion of the 8-week program, all participants were retested on all standardized measures.

Results: All participants successfully completed the 8-week Wii exercise program and reported an interest in continuing in this type of exercise program. Functional Reach showed a trend toward a positive result, with two of five participants showing improvement. The DGI showed improvement, with four of five participants increasing their scores.

Conclusions: The Wii gaming system should be considered as an adjunct exercise program for individuals with MS. The variety of activities that can be performed in a physical therapy clinic or in a safe environment at home creates opportunities for weightbearing exercise. Randomized controlled trials are needed to determine effects on specific functional abilities.

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S16) LIFE COACHING PEOPLE WITH MULTIPLE SCLEROSIS
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Background: During the last decade, life coaching has emerged as an effective tool for motivating individuals to achieve personal and professional goals. While previously used in business, psychology, and human services, life coaching has more recently been applied to assist those with chronic illness. As an example, the Center for Integrative Medicine at Duke University has pioneered a life coaching program for people with heart disease and diabetes that has proven to be effective in changing behaviors and improving health outcomes. Objectives: Based on the success of the Duke program, the Multiple Sclerosis Association of America (MSAA) developed a Life Coaching Program to help multiple sclerosis (MS) patients cope with their challenges. The program was developed with input from 1000 people with MS who requested a focus on resiliency, stress management, family issues, accepting help, managing emotion, cultivating happiness, and employment issues. Methods: MSAA’s program is led by a psychologist, a certified life coach who provides individual and group coaching via toll-free teleconference, enabling participation regardless of location or degree of disability. In the first year 170 clients throughout the nation received 884 hours of life coaching. Results: Eighty-two people used individual life coaching, some for only a single session to explore a defined topic (39%) and others for multiple sessions to resolve complicated challenges (61%). Newly diagnosed people and those recently unemployed because of MS tended to engage in a longer duration of service. A sample of 16 individually coached clients who had set a combined total of 70 personal goals was surveyed; 33% of their goals were “met,” 42% were “significantly improved,” 24% were “somewhat improved,” and 1% were “unchanged.” Ninety clients participated in group coaching teleconferences. Topics included asking for help, coping with fatigue, and stress management. Participant feedback indicated that 98% of the attendees found the programs “helpful,” with 58% indicating they were “very helpful.”

Conclusions: While the MSAA Life Coaching Program has been fully operational for more than a year, these preliminary data indicate its potential effectiveness for those affected by MS. MSAA continues to acquire additional data to determine the long-term effectiveness of goal-focused coaching approaches.

Disclosure: Nothing to disclose

Keywords: Psychosocial issues in MS, Quality of life in MS, Service delivery in MS

(S17) THE MULTIPLE SCLEROSIS COGNITIVE SCREENING BATTERY VERSUS FULL NEUROPSYCHOLOGICAL EVALUATION: A DIRECT COMPARISON
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Background: In 2007, our clinical research team presented a new method to assist health-care providers in detecting cognitive dysfunction related to multiple sclerosis (MS) accurately and objectively. In our initial study, the Cognitive Screening Battery was shown to assess patients with more precise results than the Mini-Mental State Examination (MMSE). The Cognitive Screening Battery was assessed based on normative cut-offs; patients performed either “above the cut-off” (within normal range) or “below the cut-off”
[below expectation]. Objectives: The need for a quick, reliable, cost-effective screening instrument to detect the presence of MS-related cognitive dysfunction in the real-world medical setting is clear. The purpose of this pilot study is to directly compare the Cognitive Screening Battery results of 12 MS patients with their full neuropsychological test results.

Methods: Twelve individuals with MS will be administered the Cognitive Screening Battery during an initial screening evaluation at the Neurology Center of Fairfax. This 30-minute test, which includes the MMSE, will be administered by a technician. Two slightly different screening batteries will be used, one for patients younger than age 50 and another for those older than age 50. All 12 patients will then be referred for full neuropsychological evaluation with a licensed clinical neuropsychologist regardless of their cognitive screening test results. For the purposes of our study, we are focusing on the auditory processing speed and graphomotor processing speed components of the assessment, specifically the Paced Auditory Serial Addition Test (PASAT), Digit-Symbol Coding, and Symbol Search.

Results: Five individuals have completed both portions of testing. Preliminary interim results suggest that the Cognitive Screening Battery provides adequate detection of cognitive impairment in individuals with MS (as validated by the test results of a full, 4-hour neuropsychological evaluation). The results of this study are expected to provide clearer direction to MS health professionals in making recommendations to assist in clinical decisions, as well as identify MS patients who may not have access to formal neuropsychological services.

Disclosure: Nothing to disclose

Keywords: Service delivery in MS, Psychological issues and MS, Comprehensive care and MS

(S18) DIFFERENCES IN GRAY/WHITE MATTER DENSITY AND BRAIN PERFUSION IN PATIENTS WITH RELAPSING NEUROMYELITIS OPTICA: A VOXEL-BASED STUDY

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Background: Relapsing neuromyelitis optica (R-NMO) is the first central nervous system inflammatory autoimmune disease with a defined target molecule: the astrocytic water channel aquaporin-4 (AQP4). We have reported structural brain abnormalities in R-NMO patients by visual analysis on magnetic resonance (MR) images. Objectives: We sought to confirm these structural abnormalities using statistical parametric mapping and also to determine whether brain perfusion shows similar abnormalities. Methods: Brain structure and perfusion were compared between 15 R-NMO patients (13 female, 2 male; mean ± SD age, 40.6 ± 10.7 years) and 15 healthy volunteers (13 female, 2 male; mean age, 55.3 ± 3.4 years) by voxel brain morphometry on MR images and voxel-based perfusion single-photon emission computed tomography (SPECT). Considering the difference in mean age between groups, an analysis of covariance design was used to model age and gender as nuisance covariates.

Results: R-NMO patients showed significantly reduced gray matter (GM) density (one cluster of voxels: P < .05, corrected by multiple comparison) in the bilateral thalamus regions bordering the third ventricle. White matter (WM) density was also significantly reduced, represented by a cluster wider than the GM cluster, located bilaterally in the corpus callosum in WM regions contiguous to the third ventricle and both lateral ventricles, mainly around the posterior lateral horns. GM and WM clusters seemed to be very close to each other in a posterior region of the left thalamus. There was no difference between groups in terms of GM and WM volumes. Brain perfusion showed a very similar pattern to GM density. However, hypoperfusion also extended to the left middle cingulate cortex.

Conclusions: We confirmed structural abnormalities in R-NMO patients represented by differences in gray/white matter density in regions contiguous to ventricular spaces, mainly around the third ventricle, which are known to have high AQP4 expression. Brain hypoperfusion is probably due to GM density reduction or vice versa. Longitudinal studies are needed to clarify this, and further quantitative analysis is required to elucidate the significance of the partial mismatch between GM density and brain perfusion.

Disclosure: Nothing to disclose

Keywords: Imaging and MS

(S19) NEUROMYELITIS OPTICA–IGG PRESENCE IN A SMALL COHORT OF PATIENTS WITH ATYPICAL PRESENTATION FOR MULTIPLE SCLEROSIS

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Background: Neuromyelitis optica (NMO, Devic’s disease) is a severe, inflammatory central nervous system (CNS) demyelinating syndrome characterized by optic neuritis and acute myelitis. Recently, criteria for diagnosis were revised and simplified, and the presence of NMO antibodies was introduced as a supportive feature. Despite the traditional concept that the lesions of NMO are restricted to the spinal cord and optic nerve, new literature reported extra-optic–spinal CNS symptoms in 14% and brain lesions on magnetic resonance imaging (MRI) present in 60%. Objectives: To determine whether the serum autoantibody neuromyelitis optica–IgG (NMO-IgG), a specific marker for neuromyelitis optica, is present in patients with optic nerve and/or spinal cord inflammation in a cohort of patients with atypical presentation for multiple sclerosis (MS). Methods: NMO-IgG presence was assessed in 29 patients who presented to the neurology clinic with a diagnosis of demyelinating disease of the CNS with involvement of the optic nerve(s), spinal cord, and brain but with atypical features for relapsing-remitting MS. Results: NMO-IgG was detected in 4 of 29 patients (13.8%). Seven patients were considered to have NMO (24%), and all were African American females. All patients positive for NMO-IgG had extensive spinal abnormality, compared with only 42% of patients negative for NMO-IgG. In contrast, only 25% of patients positive for NMO-IgG had abnormalities on brain MRI, compared with 72% of patients negative for NMO-IgG. Conclusions: NMO as an atypical presentation of MS was more frequent in African American females. Patients with spinal cord involvement are more likely to be positive for NMO-IgG.
(S20) DECREASE IN NUMBER OF T2/FLAIR LESIONS AFTER STARTING TREATMENT WITH NATALIZUMAB MAY NOT REPRESENT BRAIN TISSUE RECOVERY: A CASE REPORT

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Background: Magnetic resonance imaging (MRI) is used extensively to help in diagnosis, monitoring, and characterization of multiple sclerosis (MS). However, conventional MRI has limitations and cannot differentiate between an inflammatory, demyelinating process and ischemia and is insensitive to changes in normal-appearing white or gray matter. Several advanced (nonconventional) MRI techniques have been applied to detect and understand disease progression and possible neuroprotective effects of treatment. Few studies have been performed using nonconventional MRI to assess the effect of natalizumab treatment. Objectives: To prospectively characterize the evolution of white matter lesions after treatment with natalizumab by using dynamic susceptibility contrast perfusion MRI and diffusion tensor imaging (DTI). Methods: A 47-year-old woman with MS was started on natalizumab after other disease-modifying agents failed, while continuing to have multiple exacerbations. Brain MRI measurements of fractional anisotropy (FA), standard deviation DTI (SD), cerebral blood volume (CBV), and cerebral blood flow (CBF) were obtained before natalizumab treatment and a year after. Conventional MR images showed a slight decrease in the number of visible lesions on T2 views and no enhancement. White matter lesions in eight consecutive brain slices were isolated, marked as regions of interest (ROIs), followed, and analyzed using dynamic susceptibility contrast perfusion MRI and DTI. Results: A number of T2/Flair hyperintense lesions seen on initial MRI disappeared on T2/Flair images a year later, but others remained visible. Compared with initial measurements, FA and SD decreased in all ROIs. CBV and CBF decreased further in T2/Flair lesions seen on follow-up MRI but increased in ROIs corresponding to T2/Flair lesions that disappeared. These changes did not reach statistical significance. Conclusions: These results indicate that reduction in lesion size or disappearance on conventional MRI does not indicate decrease in disease progression or burden in a short follow-up study.

Supported by: Henry Ford Health System
Disclosure: Nothing to disclose
Keywords: Natural history of MS, Etiology of MS

(S21) AGREEMENT BETWEEN MULTIPLE SCLEROSIS–RELATED VARIABLES IN MEDICAL CHARTS AND CLAIMS DATA

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Background: Health-care claims and medical charts provide complementary information with a degree of overlap. Objectives: To evaluate the agreement between data derived from medical charts of patients with multiple sclerosis (MS) and a health-care claims database. Methods: This data source comparison was a secondary objective in a study utilizing both claims and linked medical chart data. Patients with MS were identified in a health-care claims database, and the claims and medical charts for a subset of this population were reviewed to extract information pertaining to disease-modifying therapy, corticosteroid therapy, MS-related procedures, and diagnosis and relapse dates. The agreement between the data sources for each type of information was identified. Results: From a total population of 11,326 MS patients in the claims database, 300 had their medical records reviewed. Among patients with claims for glatiramer acetate (n = 68), 95.6% also had it indicated in their charts. Claims agreed with charts for 91.8% of patients with a claim for intramuscular interferon beta-1a (IFNβ-1a) (n = 85), 81.8% of patients with a claim for subcutaneous IFNβ-1a (n = 55), and 87.5% of patients with a claim for IFNβ-1b (n = 48). Methylprednisolone was the most commonly indicated corticosteroid in both data sources, and among patients with evidence of a methylprednisolone prescription in the claims (n = 114), 66.7% also had a prescription indicated in their chart. Among patients with claims-based evidence of prednisone (n = 63), 49.2% had it noted in their charts. Most patients with claims-based evidence of MS-related procedures also had them indicated in their charts: 71.0% with magnetic resonance imaging (MRI), 81.0% with lumbar puncture, and 66.7% with evoked potential testing. For both diagnosis and relapse dates, at least half of the patients had perfect agreement. The mean difference between claims-based and chart-based diagnosis dates was 42.6 days, and between the date of chart-based relapse and relapse determined by a claims-based algorithm was 28.3 days. Conclusions: Claims appear to approximate chart data with regard to certain MS-related variables, such as dates and disease-modifying therapy, but the data sources also provide unique information that might be differentially suited to addressing diverse research questions.

Supported by: Teva Neuroscience, Kansas City, MO
Keywords: Disease-modifying treatment in MS, Relapse management in MS

(S22) ORAL FINGOLIMOD (FTY720) IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: SAFETY FINDINGS FROM TRANSFORMS AND FREEDOMS TRIALS

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Background: Oral fingolimod (FTY720) is a sphingosine 1-phosphate receptor modulator being evaluated in a phase...
3 multiple sclerosis (MS) study program. **Objectives:** To report safety findings from two relapsing-remitting MS (RRMS) phase 3 studies. **Methods:** In two double-blind studies, RRMS patients were randomized to receive once-daily FTY720 (0.5 mg or 1.25 mg), weekly intramuscular (IM) interferon beta-1a (IFNβ-1a) 30 µg (TRANSFORMS [12 months]), or placebo (FREEDOMS [24 months]). **Results:** Of 1292 patients, 1153 (89%) completed TRANSFORMS, 1123 (87%) on the study drug. Discontinuations were lower with FTY720 0.5 mg (10%) versus 1.25 mg (15%) or IM IFNβ-1a (12%). Of 1272 patients, 1033 (81%) completed FREEDOMS, 945 (74%) on the study drug. Discontinuations were lower with FTY720 0.5 mg (19%) versus 1.25 mg (31%) or placebo (28%). In TRANSFORMS and FREEDOMS, headache, nasopharyngitis, and fatigue were reported in >10% of all participants (also upper respiratory tract infection in FREEDOMS). A transient, generally asymptomatic bradycardia [8–10 bpm] occurred after the first dose (FREEDOMS: 3.3% with FTY720 1.25 mg; 2.1% with 0.5 mg; 0.7% with placebo) (TRANSFORMS: 2.4% with FTY720 1.25 mg; 0.5% with 0.5 mg; 0% with IM IFNβ-1a), as did infrequent atrioventricular (AV) conduction blocks (<0.5% for 0.5 mg group). In some patients, minor increases in blood pressure [1–3 mmHg increase in mean blood pressure] were observed within 6 months and persisted on therapy. Asymptomatic liver enzyme elevations were observed. In the two trials, macular edema occurred in 13 FTY720 patients (11 on 1.25 mg; 2 on 0.5 mg). Serious infections occurred in 1.7%, 0.2%, and 1.4% in the FTY720 1.25 mg, 0.5 mg, and IM IFNβ-1a groups, respectively, in TRANSFORMS; and in 2.6% (1.25 mg), 1.6% (0.5 mg), and 1.9% (placebo), respectively, in FREEDOMS. Five deaths were reported in the two trials: two on placebo, and three (two fatal herpes infections) on FTY720 1.25 mg. Malignancy was more common with FTY720 in the 1-year TRANSFORMS study but more common in the placebo group in the 2-year FREEDOMS study. **Conclusions:** FTY720 is generally well tolerated but is associated with transient bradycardia, infrequent AV conduction block, macular edema, and elevations of liver transaminases. Collective data do not suggest an increased risk of overall infections or malignancies.

**Support by:** Novartis Pharmaceuticals Corporation


**Keywords:** Disease-modifying treatment in MS

**[S23] REDUCTIONS IN MAGNETIC RESONANCE IMAGING ACTIVITY IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS TREATED WITH CLADRIBINE TABLETS**

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**Objectives:** Cladribine is activated preferentially in lymphocytes, resulting in targeted and sustained immunomodulation, providing the rationale for its use as a short-course annual multiple sclerosis (MS) treatment. Magnetic resonance imaging (MRI) parameters were evaluated for two dosing regimens of cladribine tablets versus placebo in patients with relapsing-remitting MS (RRMS) in the CLARITY (CLAdRibine tablets Treating multiple sclerosis orally) study. **Methods:** Patients with RRMS (McDonald criteria) were randomized 1:1:1 to receive cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given in short courses (once daily for 4–5 days) in 2 or 4 consecutive months (28-day periods) in the first 48 weeks, then at weeks 48 and 52 (both groups). Prespecified, hierarchically arranged, secondary MRI end points over 96 weeks included mean number of lesions/patient/scan: T1 gadolinium-enhancing (Gd+) lesions, active T2 lesions, and combined unique (CU) lesions. MRI data were evaluated using a nonparametric analysis of covariance model adjusting for treatment, region, and baseline T1 Gd+ lesion counts. Results were previously presented at the Congress of the European Committee for Treatment and Research in Multiple Sclerosis in 2009. **Results:** The intention to treat (ITT) population comprised 456, 433, and 437 patients in the 5.25 and 3.5 mg/kg cladribine groups and placebo group, respectively; groups were comparable for baseline MRI characteristics. Patients in the cladribine 5.25 or 3.5 mg/kg groups had significantly less MRI activity than those in the placebo group over 96 weeks, as follows: T1 Gd+ lesions: relative reductions of 87.9% and 85.7% [mean [SE] lesion number, 0.11 [0.05] and 0.12 [0.05] vs. 0.91 [0.05]]; active T2 lesions:
relative reductions of 76.9% and 74.4% [mean [SE] lesion number, 0.33 [0.06] and 0.38 [0.07] vs. 1.43 [0.06]]; CU lesions: relative reductions of 77.9% and 74.4% [mean [SE] lesion number, 0.38 [0.08] and 0.43 [0.08] vs. 1.72 [0.08]]; T2 lesion volume: median change from baseline: −1010.75, −583.00, and −227.00 µL, respectively; all P values <.001 versus placebo. Conclusions: MRI evidence of disease activity is reduced by both cladribine tablet regimens. The MRI findings were accompanied by significant improvements in clinical outcomes and a favorable safety profile (reported elsewhere), supporting the potential role of cladribine tablets in RRMS treatment.

Supported by: EMD Serono, Inc, Rockland, MA

Disclosure: G. Comi: Novartis, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, Merck Serono, Bayer Schering (consulting fees); Novartis, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, Merck Serono, Biogen-Dompé, Bayer Schering (other financial benefits). S. Cook: Merck Serono, Bayer Health Care, Gannab (consulting fees); EMD Serono, Bayer Health Care (other financial benefits). G. Giovannoni: Merck Serono, Bayer-Schering Pharma (consulting fees); Biogen Idec, Merck Serono, Bayer-Schering Pharma (other financial benefits). K. Ram-mohan: Bayer Pharmaceuticalids, EMD Serono/Pfizer, Teva, Genentech, Biogen, Genzyme, Acorda, UCB Pharma, Novartis (consulting fees); Bayer, EMD Serono/Pfizer, Teva, Biogen, Genzyme, Acorda, UCB Pharma (other financial benefits). P. Rieckmann: Merck Serono, Biogen Idec, Teva, Bayer, Novartis (consulting fees); Merck Serono, Biogen Idec, Teva (other financial benefits). P. Soelberg-Sorensen: Merck Serono, Biogen Idec, Teva, Gennab, Novartis (consulting fees); Bayer Schering, Merck Serono, Biogen Idec, Teva (other financial benefits). P. Verner- sch: Merck Serono, Bayer Schering, Teva-Aventis, Biogen Idec, Novartis (consulting fees); Merck Serono, Biogen Idec, Bayer Schering, Novartis (other financial benefits). P. Chang: EMD Serono (salary). A. Hamlett: EMD Serono (salary). B. Musch: EMD Serono (salary). V. Viglietta: EMD Serono (salary). S. Greenberg: EMD Serono (salary).

Keywords: Disease-modifying treatment in MS, Imaging and MS

(S24) SAFETY AND TOLERABILITY OF CLADRIBINE TABLETS DURING THE CLARITY STUDY

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Objectives: Cladribine is activated preferentially in lymphocytes, resulting in targeted and sustained immunomodulation, providing the rationale for its use as a short-course annual multiple sclerosis (MS) treatment. We assessed the safety and tolerability of cladribine tablets versus placebo over 96 weeks in the CLARITY (CLAdRibe tablet treating Multiple sclerosis orally) study. CLARITY is the largest placebo-controlled trial to be completed in relapsing-remitting MS (RRMS).

Methods: Patients with RRMS (McDonald criteria) were randomized 1:1:1 to receive cladribine tablets (cumulative dose 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given in short courses (once daily for 4–5 days) in 2 or 4 consecutive months (28-day periods) in the first 48 weeks, then at weeks 48 and 52 (both groups). Safety and tolerability assessments were conducted throughout the study. Results were previously presented at the Congress of the European Committee for Treatment and Research in Multiple Sclerosis in 2009. Results: Of 456, 433, and 437 patients randomized to cladribine 5.25 or 3.5 mg/kg or placebo, 454, 430, and 435 received the study drug and were evaluable for safety analysis, with 86.2%, 91.2%, and 86.3% successfully completing full-course treatment, respectively. Lymphopenia occurred more commonly with cladribine treatment (26.7%) than with placebo (1.8%), as anticipated based on its mechanism of action. Similar proportions of patients developed infections during the study (48.3% vs. 42.5%), with 20 patients treated with cladribine developing dermatomal herpes zoster (2.3%). Three isolated malignancies were reported during the study in the cladribine 3.5 mg/kg group (ovarian and pancreatic carcinomas and a malignant melanoma), and a precocious cervical in situ case (stage 0) was reported in the 5.25 mg/kg group. A choriciarcinoma was reported in post-study surveillance. There were two deaths in each treatment group, including one in the 5.25 mg/kg group secondary to reactivation of latent tuberculosis infection.

Conclusions: Together with the efficacy data (reported elsewhere), the results suggest that cladribine tablets may provide an important new option in MS therapy. Longer-term safety of cladribine tablets is being further investigated in a 96-week CLARITY EXTENSION study.

Supported by: EMD Serono, Inc, Rockland, MA


Keywords: Disease-modifying treatment in MS, Imaging and MS

(S25) TIME COURSE OF INJECTION-SITE REACTIONS TO SUBCUTANEOUS INTERFERON BETA-1A OR GLATIRAMER ACETATE IN THE REGARD STUDY

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Background: The REGARD study compared the efficacy and safety of subcutaneous interferon beta-1a (IFNβ-1a; 44 µg 3 times weekly) with that of glatiramer acetate (GA; 20 mg once daily) in patients with relapsing-remitting multiple sclerosis (RRMS). Overall safety was consistent with known profiles for both treatments. Injection-site pruritus, swelling, and induration were significantly more common with GA

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than with IFNβ-1a; injection-site erythema, pain, and bruising were similar in both groups; and "flu-like" symptoms were more common with IFNβ-1a than with GA. No unexpected, and few serious, adverse events occurred. Objectives: This post hoc safety analysis explored the prevalence and incidence of injection-site reactions (ISRs) in the REGARD study. Methods: REGARD was a 96-week, open-label, active-controlled, assessor-blinded study, in which treatment-naive patients were randomized to receive IFNβ-1a (n = 386) or GA (n = 378). Adverse-event data were spontaneously provided by the patient and/or resulted from nonleading questions by the investigator. In this post hoc analysis, data were re-examined to assess the prevalence and incidence of ISRs as a composite outcome during weeks 0–4, 4–12, 12–24, 24–48, 48–72, and 72–96. Results: Overall ISRs occurred in a lower proportion of patients in the IFNβ-1a group (44%) compared with the GA group (54%), and time to first ISR was longer with IFNβ-1a than with GA (40th percentile: 23.86 vs. 2.71 weeks). The difference in ISR prevalence between the GA and IFNβ-1a groups was noted to be greatest during weeks 0–4 (43% vs. 30%) and weeks 4–12 (48% vs. 35%). In general, the incidence of new ISRs was low from week 12 onward. More patients on GA withdrew from the study due to ISRs [six patients on GA vs. two patients on IFNβ-1a]. Conclusions: In the REGARD study, ISRs occurred earlier in patients with RMS receiving GA than in patients receiving subcutaneous IFNβ-1a. During the first 12 weeks of the study, ISRs were also more common in patients receiving GA; after 12 weeks, new ISRs occurred infrequently in both groups.

Supported by: Merck Serono SA–Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany


Keywords: Disease-modifying treatment in MS

(S26) THE BETASERON (INTERFERON BETA-1B) PREGNANCY REGISTRY
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Background: The United States–based Betaseron (interferon beta-1b) Pregnancy Registry was initiated in April 2006 by Bayer HealthCare Pharmaceuticals following FDA requirements issued to all disease-modifying therapy (DMT) manufacturers. Objectives: The Registry aims to monitor women with multiple sclerosis (MS) whose pregnancies were exposed to Betaseron to examine rates of birth defects, spontaneous abortions (SAs), and other pregnancy outcomes. Methods: This prospective, observational registry enrolls pregnant women exposed to Betaseron around the time of conception and/or during pregnancy but prior to prenatal screening that identifies potential abnormalities. Women are followed throughout pregnancy; their infants are followed until the 4-month pediatrician visit. The plan is to enroll 420 women exposed to Betaseron to reach 340 evaluable cases or to enroll patients until January 2011, whichever comes first. Results: As of December 31, 2009, 81 cases were enrolled. All women were exposed to Betaseron during their first trimester except for one woman with a third-trimester exposure. The Registry has collected pregnancy outcomes data on 69 of the 81 pregnancies; 7 are pending outcome information; 5 were either lost to follow-up or not valid. Of the 69 pregnancies with known outcomes, 59 (85.5%) resulted in live births, 8 (11.6%) resulted in SA (the National Center for Health Statistics reports an SA rate of 16% in the general population), and 2 (2.9%) resulted in stillbirths. Among the live-born infants, birth defects were reported in three: a case of trisomy 21 considered unlikely to be related to drug exposure; a case of multiple hemangiomas, which was not defined specifically enough to assess causality from drug exposure; and a case with cardiovascular defects, in which exposure was not temporally related to the development of the heart defects, and hip dysplasia, a defect with sufficiently ambiguous pathogenesis that temporality could not be ruled out. Conclusions: Preliminary data do not suggest an increased risk for negative pregnancy outcomes; however, caution is urged until the study is completed. This study highlights the difficulties encountered by registries of this nature in enrolling patients to reach valid conclusions. To report a pregnancy exposure, contact the Registry at 800-478-7049 (www.BetaseronPregnancyRegistry.com).

Supported by: Bayer HealthCare Pharmaceuticals


Keywords: Disease-modifying treatment in MS

(S27) THERAPY-RELATED ACUTE LEUKEMIA IN MITOXANTRONE-TREATED VETERANS WITH MULTIPLE SCLEROSIS
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Background: Mitoxantrone is one of two drugs approved for patients with worsening relapsing-remitting and progressive-relapsing multiple sclerosis (MS). However, serious and potentially life-threatening side effects are associated with its use. In addition to the widely publicized cardiotoxic effects, there are several reports from the cancer and MS literature suggesting that mitoxantrone use is associated with an increased risk of acute leukemia that appears to be dose-dependent. Objectives: To assess whether treatment with mitoxantrone increases the risk of developing therapy-related acute leukemia within the VHA MS population. Methods: During the period from October 1998 through September 2008, we identified 20,344 veterans with MS. Of these, 445 had received mitoxantrone; 43 died within 10 months of their first dose, leaving 402 patients for analysis. From the VHA inpatient and outpatient utilization databases we deter-
mined the date of death and date of first occurrence of an acute leukemia diagnosis (ICD9: 204–208, 238). We also calculated the total dosage, duration of use, and dates of administration from the VHA pharmacy databases. Results: A total of 278 (1.4%) of MS patients had been diagnosed with an acute leukemia. However, only six patients had also been treated with mitoxantrone at least 1 year prior to the leukemia diagnosis. The odds ratio for acute leukemia given treatment with mitoxantrone was 0.99 (95% confidence interval, 0.44-2.40). All of these cases occurred in male patients. Additional analyses are under way to assess the impact of the cumulative dose and duration of treatment on the risk of developing treatment-related acute leukemia. Conclusions: These preliminary findings suggest that there was not an increased risk of treatment-related acute leukemia among the VHA MS population treated with mitoxantrone. Results from the additional analyses currently under way should help clarify whether MS patients treated with mitoxantrone have an increased risk of developing an acute leukemia.

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Disclosure: Nothing to disclose
Keywords: Disease-modifying treatment in MS, Symptomatic treatment of MS

(S28) CARdiovascular Adverse Events with MitoxAntrone: RENEW Study RESULTS
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Background: Mitoxantrone has been associated with cardiotoxicity, which may occur at any time during treatment or months to years after discontinuation. Objectives: To characterize cardiovascular adverse events with Novantrone (mitoxantrone for injection concentrate) treatment over 5 years from the Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis (RENEW) study. Methods: Patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (MS) enrolled in this prospective, open-label, multicenter, phase 4 observational trial. Intravenous infusion of mitoxantrone 12 mg/m² was administered on a quarterly basis until patients reached a cumulative dose of 140 mg/m² or treatment was discontinued. Cardiovascular assessments included left ventricular ejection fraction (LVEF; monitored after every dose), symptoms of congestive heart failure (CHF), and cardiac-related events considered serious (SAEs). Patients were assessed at baseline, every 3 months during treatment, and annually after treatment discontinuation for up to 5 years (observational period [OBS]). Results: The 5-year trial was completed by 172 (33.8%) of the 509 patients who enrolled and received at least one dose of mitoxantrone. The mean treatment duration was 1.5 years, and patients achieved a mean cumulative dose of 69.8 mg/m². An LVEF ≤50% of baseline was reported in 27 of 509 (5.3%) patients during treatment and 14 of 250 (5.6%) patients during OBS. Symptoms of CHF were reported by 10 of 509 (2.0%) patients [treatment phase, 6; OBS, 4]. Cardiac-related AEs were reported by 25 of 509 (4.9%) patients [treatment phase, 22; OBS, 4], with reduced LVEF being the most common SAE. Two cardiac-related deaths occurred in this study, including cardiomyopathy/CHF/reduced LVEF (n = 1) and cardiopulmonary arrest (n = 1). Additional data from a post hoc analysis, assessing potential contributing factors to cardiotoxicity, will be shown. Conclusions: As stated in the Novantrone package insert, mitoxantrone may result in cardiac dysfunction in some patients, including reduced LVEF or irreversible CHF. Clinical monitoring for cardiac adverse events is important both during mitoxantrone treatment and after discontinuation.

Supported by: EMD Serono, Inc

(S29) RESULTS FROM TWO PHASE 1 CLINICAL STUDIES OF PEGYLATED INTERFERON BETA-1A
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Background: PEGylated interferon beta-1a (PEG IFNβ-1a) is being developed to reduce dosing frequency and improve patient convenience, while maintaining the established efficacy and safety of IFNβ-1a. Objectives: To determine the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability profile of single or multiple doses of PEG IFNβ-1a. Methods: Two randomized, blinded phase 1 studies were conducted in healthy volunteers: a phase 1a single-dose (SD) study compared intramuscular (IM) or subcutaneous (SC) PEG IFNβ-1a [63, 125, or 188 µg] with IFNβ-1a IM 30 µg; a phase 1b multiple-dose (MD) study compared SC PEG IFNβ-1a [63, 125, or 188 µg] every 2 or every 4 weeks with placebo. Serum IFNβ-1a levels were evaluated by enzyme-linked immunosorbent assay (ELISA) and cell-based activity assays. Neopterin and 2',5'-oligoadenylate synthetase (2',5'-OAS), were measured using an enzyme immunoassay and quantitative reverse transcriptase polymerase chain reaction, respectively. PK/PD parameters were calculated using noncompartmental analysis. Safety and tolerability were evaluated in both studies. Results: In the SD study, higher exposures and longer half-life for IFNβ-1a were observed following SC or IM administration of PEG IFNβ-1a of at least 63 µg (6 MIU) compared with IFNβ-1a IM 30 µg (6 MIU). Neopterin and 2',5'-OAS showed prolonged elevations with PEG IFNβ-1a at these doses. Serum IFNβ-1a concentration peaked around 24 to 36 hours post-dose, followed by a monophasic decline with a median half-life of 33 to 67 hours. PK and PD parameters in the IM and SC routes were similar. In the MD study, the PK of PEG IFNβ-1a was similar to that in the SD study, and no drug accumulation was observed. Serum neopterin levels peaked at approximately 72 hours, returning to baseline approximately 10 days postdose. There was no evidence of decrease in pharmacologic responses following multiple doses. The safety and tolerability of PEG IFNβ-1a was similar to what has been observed historically for IFNβ-1a IM 30 µg. Conclusions: PEG IFNβ-1a was safe and well tolerated. Dose-related increases in exposure to IFNβ-1a and PD activity.
were observed with PEG IFNβ-1a at or above 63 µg compared with IFNβ-1a IM 30 µg. Results of these phase 1 studies support further clinical development of PEG IFNβ-1a as a potentially safe, efficacious, and convenient treatment option for patients with MS.

**Disclosure:**

- G. Davar: Biogen Idec, Inc (salary, ownership interests).
- S. Richman: Biogen Idec, Inc (salary, ownership interests).
- S. Hitchman: Biogen Idec, Inc (salary, ownership interests).
- G. Glick: Biogen Idec, Inc (salary, ownership interests).
- M. Subramanyam: Biogen Idec, Inc (salary, ownership interests).
- X. Hu: Biogen Idec, Inc (salary, ownership interests).
- M. Lerner: Biogen Idec, Inc (salary, ownership interests).
- L. Miller: Biogen Idec, Inc (salary, ownership interests).
- I. Nestorov: Biogen Idec, Inc (salary, ownership interests).
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**Keywords:** Disease-modifying treatment in MS

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**S30) DEVELOPMENT OF A COMPREHENSIVE FATIGUE ASSESSMENT BATTERY FOR MULTIPLE SCLEROSIS**

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**Background:** Fatigue is a prevalent and debilitating symptom for people living with multiple sclerosis (MS). Assessment and treatment of fatigue in MS is complicated by the breadth of factors that contribute to fatigue. To date, only screening measures are used to evaluate the presence of fatigue in MS. There is no tool to comprehensively assess fatigue that addresses the factors that contribute to the fatigue experience, advances clinical reasoning, and guides treatment strategies.

**Objectives:** The purpose of this mixed-methods study is to develop a comprehensive fatigue assessment battery (CFAB) specific to MS (CFAB-MS).

**Methods:** The development of the CFAB-MS comprised three microstudies.

1. A literature review was conducted to identify factors contributing to fatigue in MS. Scales and outcome measures were then compiled for each of the identified correlates contributing to the fatigue experience. Where there was no measure for the identified factors, these were developed. A decisional process schema was developed to evaluate the applicability to MS, psychometric properties, and clinical utility of each assessment for inclusion.
2. An item analysis of the CFAB-MS was completed using the Person-Environment-Occupation model and Canadian Model of Occupational Performance. Redundancies and gaps in the assessment battery were identified and the CFAB-MS modified.
3. Face validity and clinical utility for clinical practice were then established through semi-structured interviews with clinicians. Individuals with MS completed the CFAB and provided feedback to establish content validity of the battery.

**Results:** A self-report tool, the CFAB-MS, was systematically developed, content validity established, and good clinical utility demonstrated to capture the unique experience of fatigue among individuals with MS.

**Conclusions:** The CFAB-MS supports practitioners’ clinical reasoning and planning for appropriate treatment strategies to intervene in factors that contribute to the debilitating fatigue experience in MS.


**Keywords:** Management of activities of daily living in MS, Rehabilitation strategies and therapy and MS, Symptomatic treatment of MS

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**S31) ORAL FINGOLIMOD (FTY720) VERSUS PLACEBO IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: TWO-YEAR EFFICACY RESULTS OF THE PHASE 3 FREEDOMS TRIAL**


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2. St. Michael’s Hospital, Toronto, Ontario, Canada; 3. VU Medical Center, Amsterdam, Netherlands; 4. Institute for Clinical Neuroimmunology, Munich, Germany; 5. University Hospital Basel, Basel, Switzerland; 6. The Johns Hopkins Hospital, Baltimore, MD; 7. University Hospital Clinic, Lodz, Poland; 8. Novartis Pharma AG, Basel, Switzerland

**Background:** Oral fingolimod (FTY720), a sphingosine 1-phosphate receptor modulator, has shown efficacy on magnetic resonance imaging (MRI) data and relapse-related outcomes in a 6-month, placebo-controlled, phase 2 study and a 12-month, comparative, phase 3 study with intramuscular interferon beta-1a. **Objectives:** To report 24-month efficacy results from the FREEDOMS phase 3 trial of fingolimod once daily versus placebo in patients with relapsing-remitting MS (RRMS).

**Methods:** In this randomized, double-blind study, RRMS patients (18–55 years) with Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and ≥1 relapse in the previous year (or ≥2 in the previous 2 years) were randomized to receive fingolimod (0.5 mg or 1.25 mg) or placebo. The 24-month primary efficacy end point was annualized relapse rate (ARR). The principal secondary end point was time-to-3-month-confirmed disability progression (1-point EDSS increase from baseline or 0.5-point increase if baseline EDSS was ≥5.5). Other clinical and MRI measures were included as secondary outcome measures.

**Results:** Of 1272 patients, 1033 (81%) completed the study; baseline demographics of the groups were similar. The ARR was reduced by 54% with fingolimod 0.5 mg (0.18 relapses/year) and 60% with fingolimod 1.25 mg (0.16) versus placebo (0.40; P < .001 for both comparisons). Fingolimod reduced the risk of 3-month confirmed disability progression, compared with placebo, over 24 months by 30% to 32% (0.5 mg and 1.25 mg, respectively; P = .02 for both comparisons). The reduction in risk of 6-month confirmed disability progression was 37% to 40% (1.25 mg; P ≤ .01 for both comparisons). At month 24, 70% to 75% of fingolimod-treated patients were free from relapses versus 46% of placebo-treated patients (P < .001 for both comparisons). Time-to-first relapse was delayed in the two fingolimod groups, as was the risk of relapse (the latter by 52% to 62% vs. placebo; P < .001 for both comparisons). Mean T2 lesion count was reduced by 74% with fingolimod compared with placebo.

**Conclusions:** Both oral fingolimod doses had beneficial effects on ARR, disability progression, and MRI outcomes compared with placebo in patients with RRMS.

**Disclosure:**

- V. Devonshire: Merck Serono, EMD Serono, Biogen Idec, Teva Neurosciences, Bayer Pharmaceuticals, Novartis, Allergan (honorary).
- P.W. O’Connor: Biogen, Teva, Bayer, EMD Serono, Novartis, Sanofi-Aventis (consulting fees); Biogen, Bayer, Teva, EMD Serono, Novartis, Sanofi-Aventis (honoraria).
- C.H. Polman: Actelion, Bayer, Teva, EMD Serono, Novartis, Sanofi-Aventis (consulting fees); Biogen, Bayer, Teva, EMD Serono, Novartis, Sanofi-Aventis (honoraria).
- R. Hohlfeld: Bayer, Novartis, Biogen Idec, Merck-Serono, Teva.

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**Disclosure:**

- V. Devonshire: Merck Serono, EMD Serono, Biogen Idec, Teva Neurosciences, Bayer Pharmaceuticals, Novartis, Allergan (honorary).
- P.W. O’Connor: Biogen, Teva, Bayer, EMD Serono, Novartis, Sanofi-Aventis (consulting fees); Biogen, Bayer, Teva, EMD Serono, Novartis, Sanofi-Aventis (honoraria).
- C.H. Polman: Actelion, Bayer Schering, Biogen Idec, Glaxo Smith Kline, Merck Serono, Roche, UCB, Teva, Novartis (consulting fees); Actelion, Bayer Schering, Biogen Idec, Glaxo Smith Kline, Merck Serono, Roche, UCB, Teva, Novartis (honoraria).
- R. Hohlfeld: Bayer, Novartis, Biogen Idec, Merck-Serono, Teva.

Keywords: Disease-modifying treatment in MS

(S32) COGNITION IN A MAN WITH KENNEDY’S DISEASE AND A DEMYELINATING DISORDER

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Background: This patient is a 49-year-old, right-handed, white man with 16 years of education. He was diagnosed with a progressive demyelinating disorder in June 2008. Multiple brain magnetic resonance imaging (MRI) studies over the last few years demonstrate a progressive, widespread bilateral demyelinating process that extends from the subcortical white matter to the brainstem. At present, no cause has been identified, although several etiologies have been proposed, including multiple sclerosis (MS), central nervous system lymphoma, and delayed effects of chemotherapy. He was diagnosed with Kennedy’s disease in January 2009, which was confirmed by genetic testing (47 CAG repeats). More remote medical history for this patient includes aplastic anemia (March 1991) and myelodysplasia with monosomy 7 (November 1996); both remitted after treatment. Objectives: To examine the neurocognitive profile of a man with genetically confirmed Kennedy’s disease and a co-occurring severe demyelinating disorder of unknown etiology. Methods: This patient underwent neurocognitive testing in August 2008 and August 2009 at two different medical centers. Results: The patient reported multiple physical, cognitive, and emotional symptoms often observed in patients with MS. Symptoms included cognitive problems, fatigue, depression, muscle weakness, dysphagia, bilateral tremor, neurogenic bladder, decreased vision, facial fasciculations, and decreased appetite. Symptoms have progressed over time, and he currently uses a wheelchair and is dependent for all instrumental and select activities of daily living. Neurocognitive testing in August 2008 revealed that function was largely intact, with a circumscribed deficit in processing speed. Follow-up testing (August 2009) was significant for global deficits, including impaired orientation, verbal learning and memory, and aspects of language. Conclusions: This patient shows progressive cognitive deficits, most notably in the areas of orientation, memory, processing speed, and language. This pattern of deficits and the progression documented over time is largely consistent with a subcortical neurodegenerative process. Further understanding of the etiology of this rapid demyelination may inform prognosis and treatment options.

Disclosure: Nothing to disclose

Keywords: Psychological issues and MS

(S33) COMPUTERIZED TESTING TO SCREEN FOR COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

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Background: Cognitive changes affect the lives of multiple sclerosis (MS) patients, and cognition is an important outcome variable when assessing treatment and disease progression. Objectives: To further validate the use of a brief computerized battery (the ANAM: automated neuropsychological assessment metrics) to measure impairment in MS patients. Methods: Participants in this study were 60 patients diagnosed with MS and 30 healthy controls. All participants were administered a conventional test battery and the ANAM. One MS group consisted of 30 cognitively unimpaired relapsing-remitting MS (RRMS) patients, and the other MS group consisted of 30 cognitively impaired RRMS patients. Results: MS patients had a mean (SD) age of 45.38 (9.2) years and a mean (SD) education level of 14.2 (2.7) years. Controls had a mean age of 45.17 (9.9) years and a mean education level of 14.96 (2.1) years (not significant). Data analysis assessed the degree to which ANAM test performance classified participants as cognitively impaired (CI) or not cognitively impaired (NCI) based on their performance of a longer conventional battery. Performance on the ANAM was calibrated using z scores computed from the means and SDs of the healthy controls. ANAM throughput scores were used in this analysis. The z scores were used in a logistic regression to assess the degree to which impairment classification was concordant between the ANAM and the conventional test battery. Eight tests from the ANAM battery produced an overall rate of agreement of 87.4% (82.8% for CI; 89.7% for NCI) compared with conventional test battery-based classification for all participants. Restricting the analysis to just patients produced an overall classification rate of 82.8% (86.2% for CI; 79.3% for NCI). Similar classification rates were achieved using one and two tests from the ANAM battery. Conclusions: The ANAM is suitable for assessing CI in multicenter trials.

Supported by: EMD Serono and Pfizer


Keywords: Psychological issues and MS, Employment in MS, Quality of life in MS

(S34) DIFFERENTIAL IMPACT OF DEPRESSION AND FATIGUE ON MEMORY FUNCTION IN MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) patients often experience varying degrees of cognitive, physical, and psychological symptoms. Memory dysfunction, a cognitive symptom of MS, is highly associated with depression and fatigue. Because MS patients are likely to report depression and...
fatigue to their physician, it is imperative that members of the medical community assess for these factors and their impact on memory function. Objectives: This study evaluates the impact of depression and fatigue, as assessed by the Beck Depression Inventory (BDI-II), Geriatric Depression Scale (GDS), and 36-item Short Form Health Status Survey (SF-36) Vitality scale, on cognitive performance in MS patients.

Methods: Twenty-nine individuals diagnosed with MS who were followed in an MS clinic (21 female, 8 male; mean age, 43.03 years) were administered a standardized Cognitive Screening Battery evaluating simple attention, verbal learning, recall, recognition, information processing speed, executive function, mental status, and mood. To evaluate quality of life in MS, we added the SF-36 (mean completion time, 7.21 min). Results: Forty-eight percent of MS patients reported significant fatigue; 79% of patients reported clinical depression. Forty-one percent of patients reported both fatigue and depression; 83% of these patients performed below expectations on one or more measures of the cognitive screen. These patients were impaired on measures of information processing speed (78%), verbal learning (67%), recall (67%), recognition (67%), executive function (33%), and language (78%). Thirty-eight percent of patients reported depression without fatigue. Of this group, 73% of patients were below expectations on one or more measures of the cognitive screen. These patients were impaired on measures of information processing speed (75%), verbal learning (50%), recall (50%), recognition (13%), executive function (63%), language (50%), and simple attention (38%). Conclusions: The results of this pilot study reveal 50% impairment of recall and 13% impairment of recognition for depressed patients, with 67% impairment of recall and 67% impairment of recognition for patients reporting both depression and fatigue. Memory function did not improve with cues for depressed and fatigued patients, suggesting significant differences between the groups. Further analysis of these differences is critical for appropriate pharmacologic management of memory dysfunction in patients with MS.

Supported by: Neurology Center of Fairfax
Disclosure: Nothing to disclose
Keywords: Quality of life in MS

(S35) BRAIN MAGNETIC RESONANCE IMAGING ACTIVITY AND EXPANDED DISABILITY STATUS SCALE SCORE PROGRESSION IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH NATALIZUMAB FOLLOWING OTHER DISEASE-MODIFYING TREATMENTS

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Background: The efficacy of natalizumab (Tysabri) in reducing new or newly enlarging T2 magnetic resonance imaging (MRI) lesions and improving Expanded Disability Status Scale (EDSS) score has been demonstrated in relapsing-remitting multiple sclerosis (RRMS) patients who are naive to disease-modifying therapies (DMTs). However, most patients currently receiving natalizumab have not responded to first-line DMTs. Objectives: To describe the MRI and EDSS progression of the patient cohort with RRMS that had initiated natalizumab after not responding to other therapies.

Methods: In a retrospective chart review, 39 RRMS patients were followed for a minimum of 6 and a maximum of 24 months. Patients had a neurologic examination (EDSS) and MRI repeated every 6 months. Descriptive statistics and difference scores compared with baseline are reported for EDSS, T2-hyperintense (T2) lesions, gadolinium-enhancing (Gd+) lesions, and T1-hypointense lesions (black holes).

Results: Of the 39 patients, 11 were previously treated with glatiramer acetate (Copaxone), 16 with interferon beta-1b (IFNβ-1b; Betaseron), 11 patients with IFNβ-1a (Avonex: 3 patients; Rebif: 8 patients), and 1 with azathioprine (Imuran). Patients may have received concomitant steroidal treatment or other agents not mentioned above, such as mitoxantrone. The median EDSS score was 3.0, and median counts for T2 lesions and black holes were 18 and 4, respectively. Gd+ lesions could not be significantly studied because only one new Gd+ lesion presented throughout the treatment course.

No statistically significant changes in EDSS or MRI measures were observed at any of the examinations at 6, 12, 18, and 24 months. Through month 18, EDSS score appeared slightly worse (41% of patients worse, 32% the same, and 27% improved compared with month 0). This change was reversed at month 24, but only 13 patients completed treatment up to this point. Conversely, T2 lesion counts stayed the same or improved through month 24 (54% of patients stayed the same, 38% improved, and 8% were worst compared with month 0). The majority of patients had no change in black holes.

Conclusions: At 18 months and up to 24 months of natalizumab treatment, 87% of RRMS patients previously treated with DMTs showed stable to improved MRI scans. Disability scores as measured by the EDSS were stable or improved in 59% of patients.

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Keywords: Disease-modifying treatment in MS, Imaging and MS

(S36) A COMBINATION OF ROBOT-ASSISTED AND BODY WEIGHT–SUPPORTED TREADMILL TRAINING IMPROVES GAIT IN PEOPLE WITH MULTIPLE SCLEROSIS

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Background: The majority of multiple sclerosis (MS) patients experience problems with gait and characterize them as highly disabling symptoms that adversely affect quality of life. Currently, none of the disease-modifying medications halt or reverse gait disability; thus other forms of intervention must be explored. Objectives: To determine whether combination gait training, using robot-assisted treadmill training followed by body weight–supported treadmill training within the same session, is effective for improving gait. Methods: This randomized pilot trial tested combination gait training in seven MS patients (Expanded Disability Status Scale score, 3.5–6.0). Outcome measures included velocity, cadence, double-support time, Timed 25-Foot Walk (T25FW) test,
6-Minute Walk (6MW) test, and functional reach test (FRT).

Results: Combination gait training resulted in significant improvements in 6MW (P = .077) and FRT (P = .034) and trends toward improvements in T25FW time and velocity when compared with the control group. Significant longitudinal improvements following combination gait training were found in 6MW (P = .018), FRT (P = .063), and double-support time (P = .018), and trends toward improvement were found in T25FW time, velocity, and cadence. Conclusions: Combination gait training is well tolerated by MS patients and improves walking ability.

Supported by: Saint Frances Foundation, Mount Sinai Foundation, and CT Chapter of the National Multiple Sclerosis Society

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S37) EVALUATION OF A LOW-COST VIDEOCONFERRING APPLICATION FOR REMOTE NEUROLOGIC EVALUATION OF PATIENTS WITH MULTIPLE SCLEROSIS


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Background: Physician care is routinely carried out in physicians’ offices and hospitals, requiring patients to travel to these facilities. Patients with multiple sclerosis (MS) are often separated from specialty care due to disability or distance. Low-cost webcams are being widely used in video chat programs; however, the value of regular webcams as a tool for remote neurologic examination has not been systematically evaluated. Objectives: A videoconferencing application utilizing low-cost webcams was developed to assist patients in virtual doctor visits. This study evaluated the feasibility of using regular webcams as a tool to aid in the management of multiple sclerosis (MS). Methods: A total of 20 consecutive patients with MS were recruited at the University of Maryland MS Center. Two clinicians experienced in MS examined each patient at the clinic located in Baltimore using the Kurtzke Expanded Disability Status Scale (EDSS). At a single visit, each patient underwent two identical sets of neurologic assessments: one clinician performed a traditional in-person evaluation and the other performed a remote evaluation using the videoconferencing system. The remote system used Logitech portable webcams and two personal computers running Windows XP. For the remote assessment, a research assistant without medical training functioned as a care provider for positioning and assistance. Results: The scores from Kurtzke’s Functional Systems (FSS) and the EDSS were compared between the in-person and remote evaluations. EDSS scores and subcategories of the FSS (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral functions) were analyzed by the Fisher exact test. For all scores, P values were greater than .05, indicating no statistically significant difference between in-person and remote assessments. Overall, the remote assessment system received positive ratings from both patients and providers: 100% of patients responded that they felt comfortable with the equipment used, and 90% of providers were able to obtain adequate information from interviewing the patients using the videoconferencing application. Conclusions: The videoconferencing application provided an efficient and reliable way of assessing patients with MS. It has potential for the remote evaluation of patients with MS.

Disclosure: Nothing to disclose

Keywords: Service delivery in MS

(S38) PARTICIPANTS’ PROGRESS THROUGH A TELECONFERENCE FATIGUE-MANAGEMENT PROGRAM

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Background: Fatigue is one of the most common and disabling symptoms of multiple sclerosis (MS). A recently completed randomized controlled trial of a group-based, teleconference-delivered fatigue self-management program produced expected outcomes for fatigue impact and quality of life. Several theoretical perspectives suggest reasons why changes may have occurred, but these have not been explored in previous fatigue-management interventions. Objectives: To explore and document participants’ experiences and progress through the program in order to better understand the intervention’s mechanisms of action. Methods: The fatigue-management program included a total of six 70-minute weekly sessions. Over the duration of the study, 31 groups (4–7 participants per group) were conducted by a licensed occupational therapist who prepared a narrative note to summarize the discussions and process of each session (186 notes). Four members of the research team analyzed these notes using constant-comparison methods to identify major themes reflecting participants’ progress through the program. Results: Seven themes emerged through the analysis. The first two themes, “struggles of living with MS fatigue” and “external challenges,” were found primarily in the early sessions of the program. Participants described their fatigue experience, how fatigue interfered with everyday living, and dissatisfaction with the negative daily consequences of fatigue. Four of the themes, “being ready to change,” “struggling to change,” “amazed by results of small changes,” and “self-tailoring” started to occur in the second and third sessions and increased as the program continued. Session notes described participants’ challenges in applying the course content to their lives. Small successes prompted ongoing attempts to self-tailor knowledge for their own situations. The last theme, “supportive interpersonal interactions,” supported the value of social learning for behavior change. Conclusions: The results are consistent with major concepts from the Trans-theoretical Model of Behavioral Change and social learning theory. The themes lend support to increasing interest in self-management approaches in MS care and illustrate the value of peer-to-peer interaction to support behavioral change.

Disclosure: Nothing to disclose

Keywords: Symptomatic treatment of MS, Rehabilitation strategies and therapy and MS, Quality of life in MS
Posters

(S39) THERMOSENSITIVITY AND FATIGUE AFFECT PARTICIPATION IN PHYSICAL ACTIVITY IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

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Background: Thermosensitivity (TS), characterized by worsening of neurologic symptoms due to increased body temperature (minimum increase of 0.5°C), is common in individuals with multiple sclerosis (MS) because of further slowing of axonal conductivity in previously demyelinated nerve fibers. Common symptoms induced by TS include blurred vision and paresthesias. Fatigue, described as lassitude, is one of the most common complaints expressed by people with MS. Both TS and fatigue can lead to decreased participation in physical activity (PA) in this population. Objectives: The primary objective of this study was to determine through self-report whether TS or fatigue affects PA levels in individuals diagnosed with MS. Methods: Seventy-seven men and women between the ages of 18 and 69 years (mean ± SD age, 45.2 ± 1.4 years) with a diagnosis of MS according to McDonald criteria participated in this study. Physical activity level was measured by the Godin Leisure-Time Exercise Questionnaire. Fatigue was measured by the Fatigue Severity Scale (FSS). TS was recorded by self-report. Results: Of the group, 83.3% reported TS (91.8% of females and 65.2% of males). Individuals who reported TS participated significantly less in PA than individuals who did not report TS (P < .05). There was a moderate negative correlation (P < .01) between PA and FSS. Significant gender differences were seen for FSS (P < .05) and PA (P < .05), with men reporting less fatigue and more participation in PA than women. Type of MS did not influence participation in PA or FSS (P > .05). Conclusions: Individuals with MS who scored higher on the FSS and those who reported TS had lower participation in PA. Conversely, individuals with higher rates of PA had lower scores on the FSS and no reports of TS. According to our results, both TS and fatigue have a negative effect on participation in PA in individuals diagnosed with MS. 

Disclosure: Nothing to disclose 

Keywords: Rehabilitation strategies and therapy and MS

(S40) OUTCOMES FROM THE AVONEX (INTERFERON BETA-1A) PREGNANCY EXPOSURE REGISTRY

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Background: The onset of multiple sclerosis (MS) typically occurs between the ages of 20 and 40 years. Because this commonly coincides with a woman’s reproductive years, disease-modifying therapies (DMTs) are likely to be widely used by women of childbearing potential. However, there is limited published information on the effects of DMTs on pregnancy outcomes. Objectives: To analyze pregnancy outcomes in women with MS who were exposed to intramuscular (IM) interferon beta-1a (IFNβ-1a) during the first trimester of pregnancy (including 1 week preconception). Methods: Pregnant women with MS in the United States who were exposed to IM IFNβ-1a within approximately 1 week of conception or during the first trimester of pregnancy were enrolled in an observational, exposure-registration and follow-up study, the AVONEX Pregnancy Exposure Registry. Information on IM IFNβ-1a exposure, potential confounding factors (e.g., medical history, other medications, smoking), and pregnancy outcomes was collected at 4 to 5 months of pregnancy and 8 to 12 weeks after delivery. Reported rates from the registry were compared with available background rates from data sources such as the Metropolitan Atlanta Congenital Defects Program, March of Dimes, and National Vital Statistics Reports. Results: As of October 2, 2009, a total of 262 pregnancies have been enrolled, and of these, 30 are pending outcome. Of the 232 pregnancy outcomes, there have been 193 live births, 28 spontaneous abortions, 4 induced abortions, 1 stillbirth, and 6 lost to follow-up. Fifteen of the 193 live births have been associated with defects. The rate of major or serious birth defects was not increased with IM IFNβ-1a exposure. No malformations or groups of malformations were overrepresented compared with rates in the general population. Conclusions: IM IFNβ-1a was associated with no increase in the rate of major or serious birth defects, and no malformations or groups of malformations were overrepresented in this prospective registry compared with the general population. These data should be reassuring for cases in which IM IFNβ-1a exposure has occurred during pregnancy. 

Supported by: Biogen Idec, Inc 


Keywords: Disease-modifying treatment in MS

(S41) POSTMARKETING UTILIZATION AND SAFETY OF INTRAMUSCULAR INTERFERON BETA-1A

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Background: Intramuscular interferon beta-1a (IM IFNβ-1a) was first approved by the US Food and Drug Administration for multiple sclerosis (MS) in May 1996 and is now authorized in 77 countries. Since first approval, an estimated 375,450 patients have been treated with IM IFNβ-1a, with 1,239,934 cumulative years of exposure. Objectives: To report utilization and safety data for IM IFNβ-1a in the postmarketing setting. Methods: Suspected adverse events (AEs) with IM IFNβ-1a that have been reported worldwide to Biogen Idec, Inc, since first approval have been maintained in a safety database. Terms have been classified in accordance with regulatory authorities. All suspected adverse drug reactions (ADRs) in the database from the most recent 3-year reporting period (May 2006–May 2009), including spontaneous reports, literature case reports, and serious suspected ADRs from clinical trials, were analyzed. ADRs of special interest and the safety profile in special populations (e.g., pediatric, elderly, pregnant women) were also evaluated. Results: During the reporting period, an estimated 51,950 new patients with 373,971 person-years of exposure were treated with IM IFNβ-1a. The most frequent ADR was flu-like symptoms, as indicated on the package insert. Reporting rates of malignancies were consistent with background incidence rates, and there was no indication of a causal relation-
ship with IM IFNβ-1a. ADRs in children and adolescents (age <18 years) suggest that the safety profile of IM IFNβ-1a in this population is consistent with that in adults. ADRs reported in elderly patients (age ≥65 years) were in agreement with those in patients aged <65 years. The nature and character of pregnancy-related events did not indicate that IM IFNβ-1a produced any teratogenicity or maturation defect. Conclusions: The overall safety profile of IM IFNβ-1a in MS is consistent with current prescribing information, and no new safety issues were identified during this reporting period. The nature of ADRs over time has remained constant, and there has been no increased risk in the occurrence of any unexpected AEs not seen with shorter-term use.

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Keywords: Disease-modifying treatment in MS

(S42) ALEMUTUZUMAB AND IMMUNE THROMBOCYTOPENIA SAFETY MONITORING PROGRAM IN CAMMS223
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Background: Alemtuzumab demonstrated efficacy superior to that of subcutaneous interferon beta-1a (SC IFNβ-1a) in a 3-year efficacy and safety trial with early, active relapsing-remitting multiple sclerosis (MS) patients, significantly reducing the relapse rate and risk for sustained accumulation of disability and reducing mean disability compared with baseline (all comparisons P < .001). One notable adverse event was immune thrombocytopenia (ITP), affecting six alemtuzumab-treated patients and one IFNβ-1a patient. Objectives: To present long-term follow-up of ITP cases occurring after alemtuzumab treatment and to review the safety monitoring program for early detection of ITP. Methods: A total of 334 patients were randomized 1:1:1 to receive IFNβ-1a (44 µg SC 3 times per week), 12 mg/day alemtuzumab, or 24 mg/day alemtuzumab. Alemtuzumab was administered intravenously (IV) during two or three brief annual cycles. After the identification of ITP among alemtuzumab-treated patients, the protocol was amended to provide patient and investigator education and surveillance via monthly complete blood counts and ITP symptom surveys. ITP patients are monitored for 4 years from ITP diagnosis. Results: The index case was fatal. A risk monitoring program was put into place, and five additional cases were identified. ITP onset occurred between 1.5 and 16 months after the last alemtuzumab dose. After the fatal index case, all ITP patients achieved durable remission. At 35 to 48 months after ITP diagnosis, all five surviving patients have normal platelet counts with no sequelae. No additional cases of ITP have been identified so far from CAMMS223. Details of the treatment of ITP case histories will be presented along with specifics of the ITP patient and physician education and safety monitoring program. Conclusions: Long-term follow-up indicates that ITP occurring after alemtuzumab appears self-limited in some cases and responsive to medical treatment in other cases. Alemtuzumab-associated ITP appears to be monophasic: once achieved, remission is durable. To date, with increased surveillance, identification of ITP has been timely, and so far no cases have been diagnosed more than 16 months following the last alemtuzumab cycle.

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Disclosure: E.J. Fox: Genzyme (other financial benefits); CAMMS223 Study Group: Genzyme (other financial benefits).
Keywords: Disease-modifying treatment in MS

(S43) BASELINE CHARACTERISTICS OF PATIENTS IN PHASE 3 STUDIES OF BG-12 IN RELAPSING-REMITTING MULTIPLE SCLEROSIS
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Background: BG-12, an oral therapy that exhibits anti-inflammatory and potentially neuroprotective mechanisms of action, is in phase 3 clinical trials for relapsing-remitting multiple sclerosis (RRMS). DEFINE and CONFIRM are ongoing trials with the primary objective of determining whether BG-12 is effective in reducing clinical relapses at 2 years. Objectives: To describe the baseline patient characteristics in two randomized, multicenter, double-blind, placebo-controlled phase 3 studies. Methods: The main inclusion criteria for DEFINE and CONFIRM were age 18 to 55 years; confirmed diagnosis of RRMS (McDonald criteria); baseline Expanded Disability Status Scale (EDSS) score of ≤5.0; and at least one relapse within the 12 months prior to randomization or having gadolinium-enhancing lesion(s) on brain magnetic resonance imaging (MRI) performed within the 6 weeks prior to randomization. Participants had to have a prior brain MRI study demonstrating lesion(s) consistent with MS. BG-12 was administered at a dose of 240 mg either two or three times daily in both studies. In CONFIRM, glatiramer acetate was used as the reference comparator and was administered at 20 mg daily subcutaneously. Assessments included relapses, MRI lesions, brain atrophy, and magnetization transfer ratio, as well as progression of disability as determined by EDSS scores. Results: A total of 1237 and 1431 patients were randomized in DEFINE and CONFIRM, respectively. Baseline demographics for DEFINE and CONFIRM were mean ± SD age at baseline, 38.4 ± 9.1 and 37.6 ± 9.2 years; female, 74% and 71%; white, 83% and 89%. In DEFINE, a mean of 5.5 years had elapsed since diagnosis. Over the previous 3 years, patients had a mean of 2.5 relapses, and in the last 12 months they had a mean of 1.3 relapses. A mean of 6.5 months had elapsed since the last relapse. In CONFIRM, a mean of 4.9 years had elapsed since diagnosis. Over the previous 3 years, patients had a mean of 2.5 relapses, and in the last 12 months they had a mean of 1.4 relapses. A mean of 6.2 months had elapsed since the last relapse. Patients’ mean baseline EDSS score was 2.41, with 17% having EDSS scores ≥4 (DEFINE), and 2.53, with 16% having EDSS scores ≥4 (CONFIRM). Conclusions: Baseline demographics for patients in these studies suggest that these groups have characteristics broadly comparable with contemporary trials and each other. This comparability will be further evaluated with the presentation of baseline MRI results.

Supported by: Biogen Idec, Inc

Keywords: Disease-modifying treatment in MS

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SCLEROSIS?
(S44) IS MULTIPARITY PROTECTIVE IN MULTIPLE
SCLEROSIS?
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Background: Multiple sclerosis (MS) is an immune-mediated
disease of the central nervous system (CNS) with underlying
mechanisms of CNS demyelination and inflammation. Pregnancy seems to be associated with a dampened immune
response; thus MS patients often enjoy a stabilization of the MS
disease process during pregnancy. The first 3 postpartum
months, however, may bring an increased MS exacerbation
rate for uncertain reasons. Objectives: We examined
effects of multiparity (defined as two or more full-term births)
on MS progression to determine whether it confers a neu-
roprotective effect and lower Estimated Disability Status
Scale (EDSS) score compared with fewer full-term births.

Methods: Electronic medical records were gathered with
the ICD-9 Code 340, “multiple sclerosis,” for the purpose of
retrospective review. Thirty of 153 charts were found to
contain necessary documentation to be included in the review
study. Age at diagnosis, number of children born before and
after diagnosis, and EDSS score at last examination were
recorded. Each parity group then had average age at MS
onset as well as average EDSS score calculated and com-
pared with those of other parity groups. Results: The average
age at MS diagnosis of those patients with no children
born prior to diagnosis was 32.4 years; with one child born
prior to diagnosis was 39.8 years; with two children born
prior to diagnosis was 47.6 years; and with more than two
children born prior to diagnosis was 50.3 years. Analysis of
variance (ANOVA) comparing ages at diagnosis revealed
statistically significant differences between the parity groups,
with an F score of 4.727 and a P value of .010. The average
EDSS scores for the parity groups were then compared,
but ANOVA testing revealed no statistically significant dif-
ferences between scores. Conclusions: Patients with more
children were diagnosed later in life than those with fewer
children. This could indicate a less aggressive form of MS
or a delay in diagnosis due to less clinically evident disease,
potentially due to a cumulative protective effect of multiple
pregnancies. A lower EDSS score was noted in those women
with more children, but the differences among groups were
not statistically significant and may reflect small sample size.
Prospective, long-term studies would help further delineate
the impact of multiple pregnancies on the disease course of MS.

Disclosure: Nothing to disclose

(S45) VALIDITY OF SELF-REPORTED EXPANDED
DISABILITY STATUS SCALE SCORES
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Background: Clinicians and researchers often administer
the Expanded Disability Status Scale (EDSS) as a measure of
impairments in people with multiple sclerosis (MS). EDSS
assessments can be costly, may not be feasible for wide-
spread screening in clinical trials, and require expertise
and training. Self-reported versions of the EDSS have been
developed that overcome those limitations, but they have
not undergone thorough psychometric testing. Objectives:
This study examined the agreement between self-reported
and clinician-administered EDSS scores and then examined
the comparative validity of scores based on correlations with
performance and self-report measures of ambulatory func-
tion in people with MS. Methods: The sample included 34
individuals with a definite diagnosis of MS who underwent
testing as part of their participation in the University of Utah
rehabilitation and wellness program. The battery of tests
included a traditional neurologic examination–based EDSS
(NE-EDSS) conducted by a trained physical therapist, self-
reported EDSS, Timed 25-Foot Walk (T25FW), 6-Minute
Walk (6MW), Timed Up and Go (TUG), Berg Balance Test
(BBT), Multiple Sclerosis Walking Scale–12 (MSWS-12),
and objective assessment of walking via the Step Activity Monitor
(SAM). Results: The sample had a range of NE-EDSS scores
between 3.5 and 7.5 and a median of 6.0. There was 38%
perfect agreement and 72% agreement of ±0.5 EDSS steps
between NE-EDSS and self-reported EDSS scores. The intra-
class correlation coefficient (ICC) for absolute agreement
between NE-EDSS and self-reported EDSS scores was strong
(ICC = 0.80). The bivariate correlation between NE-EDSS
and self-reported EDSS scores was large in magnitude (ρ =
0.95). The bivariate correlations were similar and large in
magnitude between NE-EDSS and self-reported EDSS with
T25FW (ρ = 0.79 and ρ = 0.79, respectively), 6MW (ρ =
−0.84 and ρ = −0.77, respectively), TUG (ρ = 0.85 and ρ =
0.84, respectively), BBT (ρ = −0.93 and ρ = −0.87, respec-
them at additional time points. Conclusions: These findings provide additional support for the psy-
chometric properties of a self-reported EDSS scale in people with MS. This scale can be included in clinical research and
practice when a clinician-administered EDSS scale is impractical.

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S46) PROFILE OF THE PATIENT WITH MULTIPLE
SCLEROSIS: BEHAVIORAL TENDENCY STUDY
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Background: Multiple sclerosis (MS) is an inflammatory
illness resulting in chronic and progressive degeneration. Its
unpredictability can result in feelings of helplessness. Behav-
ioral tendency can be a useful tool with which to approach

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Disclosure:

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the patient who seeks recovery of his life expectations. **Objectives:** Through a qualitative survey, evaluate the behavior of people with MS and analyze the Quantum Method of establishing behavioral markers of the patient. **Methods:** The survey was conducted in 341 patients during orientation lectures and a psychological treatment process. Four emotional states or “primary emotions” were observed—domination, induction, submission, and conformity—corresponding to Action (A), Communication (C), Stability (E), and References (R), respectively. **Results:** Low A (55%): The person is useful, cooperative, and manipulative. He avoids taking risks, and in group interaction always searches for a more comfortable position, waiting for somebody else to take the initiative. High C (57%): This person is nice, seductive, extroverted, persuasive, and with a great capacity for adaptation. He is able to persuade and instigate the group to reach an objective. High R (56%): This person needs clear rules. He only follows what has been determined. He prefers well-structured environments. He has the capability to be obedient and to follow rules, and he fears taking risks. High E (62%): This person is persistent and methodical. He is highly perfectionistic, meticulous, and able to do only one thing at a time. He performs well in medium- and long-term processes that demand routine and patience. **Conclusions:** Awareness of the patient’s psychological profile can help in understanding attitudes to call to the attention of the patient. This method is presented as a useful tool in the search for behavioral understanding of the MS patient.

**Supported by:** Brazilian Multiple Sclerosis Society and Quantum Lab

**Disclosure:** Nothing to disclose

**Keywords:** Psychological issues and MS, Quality of life in MS, Rehabilitation strategies and therapy and MS

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**S47** THE REHABILITATION NEUROFUNCTIONAL AND VIRTUAL REALITY IN REHABILITATION


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**Background:** Multiple sclerosis (MS) is a chronic degenerative neurologic and demyelinating disease affecting the central nervous system. Fatigue and loss of balance during gait are the most frequent symptoms. The use of virtual reality in rehabilitation complements therapies with fun, improving sight, touch, and hearing. It can be executed in a functional context with body movements through virtual space as with performing daily activities. **Objectives:** Compare conventional physiotherapy with a virtual reality program. **Methods:** Twelve patients with Expanded Disability Status Scale (EDSS) scores up to 6 were randomly divided into three groups. They were evaluated before and after the program with the following scales: EDSS, Chalder Fatigue Scale, Berg Balance Scale, Dynamic Gait Index. The first group had 18 sessions of conventional physiotherapy, the second had 18 sessions of playing virtual reality games, and the third had 9 sessions of conventional physiotherapy and 9 sessions of playing virtual reality games. **Results:** On the Berg Balance Scale, there was an improvement of 16% in the group receiving only physiotherapy, 6.2% in the group receiving physiotherapy and virtual reality, and 6.35% in the group receiving only the virtual rehabilitation. On the Dynamic Gait Index, there was an improvement of 38%, 7.6%, and 41% for the physiotherapy, physiotherapy and virtual reality, and virtual reality groups, respectively. On the Chalder Fatigue Scale, there was a reduction in fatigue of 8.8% in the physiotherapy group, 14.8% in the physiotherapy and virtual reality group, and 24.6% in the virtual reality group. **Conclusions:** Virtual reality was found to be an efficient tool in the balance rehabilitation of MS patients. The similar improvement among the three groups shows that virtual reality should be a complement to conventional rehabilitation, improving motor performance and making treatment more fun.

**Supported by:** Brazilian Multiple Sclerosis Society

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS, Quality of life in MS, Complementary/alternative therapies in MS
mg/kg group (both \( P < .001 \)). Conclusions: Treatment with cladribine tablets resulted in a substantial proportion of patients achieving a disease activity-free status over 96 weeks. These robust results support the potential for cladribine tablets as an MS therapy.

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Keywords: Disease-modifying treatment in MS

(S50) PATIENT PERCEPTIONS OF MULTIPLE SCLEROSIS SUPPORT AND CALL CENTER SERVICES: 2007–2009

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Background: MS Lifelines is an educational patient support service that provides multiple sclerosis (MS) patients with important information about their disease. Objectives: To evaluate patient usage of and satisfaction with MS Lifelines, and to track and compare these findings over time. Methods: Patients using MS Lifelines who had at least one interaction within the past month were invited to complete a self-administered questionnaire on the Harris Interactive website. Honorarium was not provided. Qualified patients were receiving interferon beta-1a (IFNβ-1a) subcutaneous (SC) therapy or had received IFNβ-1a SC within the past 3 months, and remembered the approximate date of interaction with MS Lifelines. Survey participation was limited to once every 6 months. Data were collected in five waves (5–6 months each) between 2007 and 2009. Key end points included overall satisfaction with MS Lifelines, likelihood of recommending the program, and likelihood of continuing IFNβ-1a SC therapy, each rated on a 7-point scale (1 = most negative, 7 = most positive). Satisfaction with specific MS Lifelines services and overall satisfaction with competitor programs was also evaluated. Results: For each wave (W), 759 (W1), 764 (W2), 749 (W3), 693 (W4), and 681 (W5) patients participated; there was 1% overlap among waves. The proportion of patients rating their overall satisfaction ≥6 was high throughout all waves (W1 = 82%; W2 = 83%; W3 = 83%; W4 = 79%; W5 = 92%), with a significant increase between W4 and W5 (P < .05). Most patients also reported scores ≥6 for likelihood of recommending the program (W1 = 85%; W2 = 88%; W3 = 86%; W4 = 83%; W5 = 93%; P < .05 for W5 vs. W4) and likelihood of continuing IFNβ-1a SC (W1 = 82%; W2 = 81%; W3 = 81%; W4 = 81%; W5 = 84%). Patient satisfaction was significantly higher (P < .05) in W5 versus W4 for specific services, including welcome call and reimbursement interactions (new patients), call center nurses (2–6 month group), and calls to MS Lifelines (≥7 month group). Among patients in W5 who used a competitor program (n = 171), 95% were as or more satisfied with MS Lifelines. Conclusions: Participants provided positive satisf-

International Journal of MS Care
(S51) INTRATHecal BACLOfen therapy: An effective treatment for trigeminal neuralgia in multiple sclerosis patients treated for severe spasticity

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Background: Trigeminal neuralgia (TN) occurring in multiple sclerosis (MS) patients can often be effectively treated using one of several oral medications, including baclofen. However, TN in MS can also be refractory to multiple oral medications and eventually require gamma knife radiosurgery treatment. MS patients with TN can experience severe pain, but can also concurrently be significantly physically disabled, thus limiting their access to advanced treatments. Oral baclofen is also an effective treatment for spasticity. Intrathecal baclofen (ITB) is a more effective treatment for severe spasticity than are oral antispastic medications. It achieves higher cerebrospinal fluid (CSF) baclofen concentration by direct intrathecal delivery than can be attained by oral baclofen or clinically tolerated. There are no reported cases of refractory TN subsequently treated as a consequence of ITB therapy used for spasticity. Objectives: To report the effectiveness of ITB in TN. Methods: Retrospective chart review of >100 MS patients with ITB implant, identifying who had concurrent refractory TN refractory to two different oral medications, and TN persisting >1 year prior to ITB implant. Results: Three patients were identified who fulfilled these select criteria. These patients had persistent or recurrent TN for >1 year despite increasing doses of oral medication but also experienced concurrent refractory TN with >2 attempted eliminations of oral medication. All patients had complete TN resolution after ITB implant and were also able to successfully eliminate oral medications used to treat TN without TN recurrence up to >3 years. Conclusions: MS patients with both TN and severe spasticity requiring treatment with ITB may achieve resolution of painful TN directly from ITB delivery. A lumbar-cervical-cerebral gradient of medication likely delivers sufficient ITB to the basilar CSF to provide effective TN treatment. This report does not suggest that ITB be considered as the treatment of TN in MS but describes an additional unrecognized potential benefit of ITB therapy.

Keywords: Rehabilitation strategies and therapy and MS, Quality of life in MS, Comprehensive care and MS

(S52) Post-baseline changes in health-related quality of life among multiple sclerosis patients in a real-world observational outcomes study (ROBUST)

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Background: ROBUST was a 12-month, United States-based, prospective, observational, open-label, single-arm, multicenter outcomes study of interferon beta-1b (IFNβ-1b) given every other day for relapsing forms of multiple sclerosis (MS). Objectives: The objective of this analysis was to assess health-related quality of life (HRQOL) over the course of 12 months among MS patients in a real-world observational study. Methods: HRQOL was rated at baseline and monthly via the 12-item Short Form Health Status Survey (SF-12) and summarized in the Physical Component Score (PCS-12) and Mental Component Score (MCS-12). A one-sample t test was used to test significance of difference from zero in change from baseline in the SF-12 component scores.

Results: Analyses of covariance methods were used to test differences between various clinical substrates of change from baseline in SF-12 score, while controlling for baseline SF-12 score. A total of 184 patients were included in the final analysis. Results: At baseline, the mean (SD) PCS-12 was 40.6 (11.15), and the mean (SD) MCS-12 was 42.5 (11.45). Patients experienced improvement in both PCS-12 and MCS-12 from baseline through month 12. While none of the monthly changes from baseline in PCS-12 were statistically significant, the change in MCS-12 was statistically significant at all months except month 2. Patients in both PCS-12 and MCS-12 were greater for patients with higher Expanded Disability Status Scale (EDSS) score at baseline, while changes in MCS-12 were greater with lower baseline EDSS score, although neither of these trends was statistically significant (P = .8107 and P = .0803, respectively). Changes from baseline in MCS-12 were statistically associated with baseline Timed 25-Foot Walk (T25FW): T25FW ≤7 seconds versus >7 seconds (3.78 vs. 0.62, P = .0013).

Conclusions: The significant improvement in comparison with baseline in MCS-12 that was seen in participants in the ROBUST study suggests a positive role of IFNβ-1b in this improved mental HRQOL. Mental QOL improved more for patients with better ambulation at baseline.

Supported by: Bayer HealthCare Pharmaceuticals, Inc
Keywords: Quality of life in MS, Disease-modifying treatment in MS, Natural history of MS

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(S53) COMPARISON OF MEDICAL SERVICES IN MULTIPLE SCLEROSIS PATIENTS USING FIRST-LINE THERAPIES

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Background: Disease-modifying therapies (DMTs) decrease the frequency of relapses in multiple sclerosis (MS) patients. This study examined relationships between DMTs and medical services associated with relapse. Objectives: Compare utilization of relapse-related medical services (hospitalizations, emergency room [ER] visits, or corticosteroid use + office visits associated with MS) among MS patients on first-line intramuscular (IM) or subcutaneous (SC) interferon beta-1a (IFNβ-1a), interferon beta-1b (IFNβ-1b), or glatiramer acetate (GA). Methods: This analysis used data from medical and pharmacy claims associated with a large US health plan, and MS patients on first-line DMTs IM IFNβ-1a, SC IFNβ-1a, GA, or IFNβ-1b from 1/1/2000 to 9/30/2008. DMT initiation was the index date. Patients were continuously enrolled for 6 months pre-index and 12 to 36 months post-index. Relapse-related utilization included hospitalizations and ER visits with primary MS diagnoses (ICD-9 340) or claims for steroids (corticosteroid, dexamethasone, methylprednisolone, prednisolone, prednisone) within 7 days after outpatient visits with primary MS diagnoses. Relapse-related utilization was modeled with Cox proportional hazards regression. Covariates included DMT (reference: IM IFNβ-1a), age, gender, pre-index Charlson comorbidity score, and pre-index MS-related inpatient stay and ER visit. Results: A total of 6680 first-line patients were identified: 34.5% on IM IFNβ-1a, 13.4% on IFNβ-1b, 34.0% on GA, and 18.1% on SC IFNβ-1a. The mean (±SD) age was 42.2 (±10.1) years, and 77.4% were female. Thirty percent of patients had relapse-related utilization while on first-line DMT. Most patients with relapse-related utilization (83.0%) had steroid use; 83.6% had MS-related hospitalizations, 6.6% had MS-related ER visits; 2.1% had multiple types of utilization. IFNβ-1b patients were 16.8% more likely to have relapse-related utilization (95% confidence interval [CI], 1.018-1.340), and SC IFNβ-1a patients were 14.0% more likely (95% CI, 1.004-1.295) compared with IM IFNβ-1a patients. Conclusions: Patients on first-line IM IFNβ-1a therapy were significantly less likely to have relapse-related utilization compared with those on IFNβ-1b or SC IFNβ-1a.

Supported by: Biogen Idec
Keywords: Disease-modifying treatment in MS, Service delivery in MS

(S54) SECOND-LINE THERAPY SWITCHING AMONG MULTIPLE SCLEROSIS PATIENTS

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Background: Switching between disease-modifying therapies (DMTs) for multiple sclerosis (MS) often indicates problems with tolerance or effectiveness. Objectives: Compare switching between MS patients on second-line DMTs intramuscular (IM) interferon beta-1a (IFNβ-1a), subcutaneous (SC) IFNβ-1a, interferon beta-1b (IFNβ-1b), glatiramer acetate (GA), and natalizumab. Methods: Study data were medical and pharmacy claims data for adult commercial health plan enrollees with MS initiating second-line DMTs from 1/1/2000 to 9/30/2008; second-line DMTs were the second therapies patients used as indicated by medical and pharmacy claims. DMTs were IM IFNβ-1a, SC IFNβ-1a, GA, IFNβ-1b, or natalizumab. The start date of the second-line DMT was the index date. Patients were observed for 3 months pre-index and 3 to 36 months post-index. Switching occurred at initiation of the third-line DMT with no subsequent use of the second-line DMT for ≥90 days. Switching was modeled with Cox proportional hazards regression to account for variable post-index length. Covariates were second-line DMT (reference group: natalizumab), age, gender, and pre-index Charlson comorbidity score, MS-related hospitalization, and MS-related emergency visit. Results: A total of 3071 second-line patients included 429 (14.0%) on IM IFNβ-1a, 415 (13.5%) on IFNβ-1b, 1067 (34.7%) on GA, 872 (28.4%) on SC IFNβ-1a, and 288 (9.4%) on natalizumab. The mean (±SD) age was 40.9 (±9.7) years; 79.7% were female. Descriptive analysis showed that 19.4% of patients switched to a third-line DMT: 10.4% of natalizumab patients, compared with 16.9% to 23.5% in other cohorts (all P < .01). Patients on IM IFNβ-1a, SC IFNβ-1a, and IFNβ-1b were significantly more likely to switch to a third-line DMT than were natalizumab patients. Hazard ratios (95% confidence intervals) were 1.74 (1.15-2.61) for IM IFNβ-1a, 1.77 (1.17-2.67) for SC IFNβ-1a, and 1.62 (1.10-2.38) for SC IFNβ-1a. Conclusions: Patients on second-line natalizumab were significantly less likely than those on IM IFNβ-1a, IFNβ-1b, and SC IFNβ-1a to switch to third-line therapy.

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Keywords: Disease-modifying treatment in MS

(S55) ADHERENCE TO DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS

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Background: Disease-modifying therapies (DMTs) slow the progression of relapsing-remitting multiple sclerosis (MS). DMT adherence is important in the clinical management of MS. Objectives: Compare adherence and persistence in MS patients initiated on intramuscular (IM) interferon beta-1a (IFNβ-1a), subcutaneous (SC) IFNβ-1a, interferon beta-1b (IFNβ-1b), and glatiramer acetate (GA). Methods: This retrospective medical and pharmacy claims analysis used data from a large commercial US health plan. Subjects were adults with MS starting first-line IM IFNβ-1a, SC IFNβ-1a, GA, or IFNβ-1b from 1/1/2000 to 9/30/2008. The first DMT claim was the index date; patients were observed for 6 months pre-index and 12 to 36 months post-index. Adherence was measured with a medication possession ratio (MPR): [days of DMT/days until earlier of DMT switch or end of post-index period]; patients with an MPR ≥ 0.80 were...
“adherent.” Persistence was the number of days until the earlier of a minimum 60-day therapy gap or the last DMT claim. Adherence was analyzed with logistic regression; persistence was analyzed with Cox proportional hazards regression. Regressions controlled for DMT (reference: IM IFNβ-1a), age, gender, pre-index Charlson comorbidity score, and pre-index MS-related inpatient stay and emergency visit.

**Results:** The study population comprised 6680 first-line patients: 2305 (34.5%) on IM IFNβ-1a, 894 (13.4%) on IFNβ-1b, 2270 (34.0%) on GA, and 1211 (18.1%) on SC IFNβ-1a. Patients were 42.2 (±10.1) years old, on average (±SD), and 77.4% female. Unadjusted proportions of adherent patients were 62.3% for IM IFNβ-1a, 52.2% for IFNβ-1b, 55.4% for GA, and 58.5% for SC IFNβ-1a (overall P<0.05). In regression-adjusted results, patients on IFNβ-1b, GA, and SC IFNβ-1a were significantly less likely to be adherent compared with those on IM IFNβ-1a: odds ratios (95% confidence intervals) were as follows: IFNβ-1b, 0.66 (0.56-0.77); GA, 0.75 (0.67-0.84); SC IFNβ-1a, 0.85 (0.74-0.98). SC IFNβ-1a patients were 12% more likely to stop therapy during the post-index period than were IM IFNβ-1a patients (hazard ratio, 1.12 [1.01-1.23]). **Conclusions:** Patients on first-line IM IFNβ-1a therapy were more likely to be adherent than were those on other DMTs and had more persistence than those on SC IFNβ-1a.

**Supported by:** Biogen Idec


**Keywords:** Disease-modifying treatment in MS

**S56) ADHERENCE AND PERSISTENCE AMONG SECOND-LINE DISEASE-MODIFYING THERAPIES**

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**Background:** Adherence to disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (MS) is key for its clinical management. Some patients experience inadequate response or tolerance problems with first-line DMTs. Consistent use of second-line DMTs is therefore important for continuing disease management. **Objectives:** Compare persistence and adherence on second-line MS DMTs intramuscular (IM) interferon beta-1a (IFNβ-1a), subcutaneous (SC) IFNβ-1a, interferon beta-1b (IFNβ-1b), glatiramer acetate (GA), and natalizumab. **Methods:** Data were retrospective medical and pharmacy claims for adult commercial health plan enrollees with MS starting second-line DMTs from 1/1/2000 to 9/30/2008. Second-line DMTs were the second observed therapies and included IM IFNβ-1a, SC IFNβ-1a, GA, IFNβ-1b, or natalizumab. Second-line DMT initiation was the index date. Patients were observed for 3 to 36 months post-index and 3 months pre-index. Medication possession ratio (MPR) was the adherence measure: [days of DMT/days until earlier of switch or end of post-index]; “adherence” was an MPR ≥0.80. Persistence was time until the earlier of ≥60-day therapy gap or last DMT claim. Adherence and persistence were modeled with logistic and Cox proportional hazards regressions, respectively, controlling for DMT (reference: natalizumab), age, gender, and pre-index Charlson comorbidity score, MSRELATED hospitalization, and MS-related emergency visit.

**Results:** The study sample was 3071 patients: 429 (14.0%) IM IFNβ-1a, 415 (13.5%) IFNβ-1b, 1067 (34.7%) GA, 872 (28.4%) SC IFNβ-1a, 288 (9.4%) natalizumab. Patients were 40.9 (±9.7) years old, on average (±SD), and 79.7% female. Regression results showed that natalizumab patients were significantly more likely to be adherent and persistent: odds ratios (95% confidence intervals) were 0.54 (0.39-0.76) for IM IFNβ-1a, 0.43 (0.31-0.59) for IFNβ-1b, 0.41 (0.30-0.55) for GA, and 0.53 (0.39-0.72) for SC IFNβ-1a. Patients on IFNβ-1b, GA, and SC IFNβ-1a were significantly more likely to stop second-line DMT than were natalizumab patients. Hazard ratios were 1.28 (1.00-1.63) for IFNβ-1b, 1.27 (1.02-1.58) for GA, and 1.25 (1.00-1.56) for SC IFNβ-1a. **Conclusions:** Patients on second-line natalizumab were more likely to be adherent and tended to have longer persistence compared with those on other DMTs.

**Supported by:** Biogen Idec


**Keywords:** Disease-modifying treatment in MS

**S57) BRAIN MAGNETIC RESONANCE IMAGING USE AS A SURROGATE MARKER IN ROUTINE CLINICAL PRACTICE: A RETROSPECTIVE ANALYSIS**

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**Background:** Magnetic resonance imaging (MRI) has advanced our ability to diagnose multiple sclerosis (MS) and provide insights into the pathology of the disease. MRI is a standard part of the MS diagnostic process. While there is consensus on the technical aspects of MRI in MS, there is no consensus on its use for disease monitoring. There is a wide range of practices regarding the use of MRI monitoring in MS. Some clinicians use relapses and progression of disability as their gauge of disease stability, while others add periodic MRI monitoring. **Objectives:** To determine the frequency of MRI changes (new T2 and/or new enhancing lesions on routine follow-up MRI scans), and to justify/argue for the use of screening MRI in stable relapsing-remitting MS (RRMS) annually. **Methods:** The study examined 360 clinically stable MS subjects who had had two brain MRI studies. Clinical information including demographics, duration of MS, and type/duration of therapy was gathered. Patients included had confirmed diagnosis of MS and two MRI studies available for review. Patients were excluded if they were enrolled in a clinical trial, their films were unavailable, or they had had just one MRI study. **Results:** A total of 445 charts were reviewed. Of those, 145 were excluded due to the following factors: unstable MS, only one MRI available, not on disease-modifying therapy (DMT), problems other than MS found on MRI. A total of 284 charts were analyzed, of which 67 (23.59%) had at least one new T2 brain lesion. A full assessment of newly acquired T2 lesions, both new enhancing lesions and total volume, is pending. The patient population consisted of 207 patients with RRMS and 66 patients with progressive MS. The BOD was measured as light, moderate, or heavy. There was minimal change in BOD from the first to the second MRI study. The change from light to moderate was 62.3% for IM IFNβ-1a therapy were more likely to be adherent than were those on other DMTs and had more persistence than those on SC IFNβ-1a.

**Supported by:** Biogen Idec


**Keywords:** Disease-modifying treatment in MS

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study. A follow-up assessment will address changes in patient therapy during the evaluation period and a possible link to clinical MRI findings. **Conclusions:** Periodic MRI monitoring in clinically stable MS patients may be of value for several reasons. This records review demonstrates that one-fourth of these “stable” patients have ongoing disease activity on MRI. The presence of clinically silent lesions may yield information about adherence to therapy for some patients or lead to a switch in therapy for others. Several studies have suggested that an individual’s disease may be better controlled by switching between first-line therapies. 

**Supported by:** EMD Serono and Pfizer Inc  
**Disclosure:** Nothing to disclose  
**Keywords:** Imaging and MS

**S58** AN URGENT MULTIPLE SCLEROSIS CLINIC: A NEW MODEL OF CARE  
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**Background:** In the current economic and health insurance overhaul environment, it is imperative to provide timely, high-quality, cost-effective care. Although multiple sclerosis (MS) is a chronic, progressive disease, there are times when patients require immediate care and interventions. For this reason, we have created an MS Urgent Clinic model of care run by advanced-practice nurses. **Objectives:** To explain and discuss a new model of care for MS patients requiring immediate attention. **Methods:** We will outline the new model of care for the MS Urgent Clinic. We will delineate how the clinic runs, what types of patients are seen, how they are scheduled, and how both patients and other clinicians have responded to this novel model of care. **Results:** As a result of this new model of care, MS patients have had better, more timely care. They have been evaluated within the same week they were having new symptoms, which has resulted in better health outcomes and improved patient satisfaction. Clinicians have benefited as well from this MS Urgent Clinic, as they have not had to add patients to their already overbooked schedules. Caring for patients by telephone has been minimized, as clinicians have been able to add patients to the Urgent Clinic to be evaluated in person. This is beneficial to the patients as well as to the clinic, as phone care is not financially compensated. **Conclusions:** This project will lead to a better understanding of a new model of care designed for MS patients who require immediate intervention. We will further discuss the patients’ response and other health-care providers’ perspectives regarding this new model of care. Economic and quality-of-life benefits will be explored.  

**Disclosure:** C. Hara-Cleaver: Serono, Biogen Idec, MSAA (honoraria). R. Rudick: Biogen Idec, Genzyme, Millennium Pharmaceuticals, Novartis, Teva, Wyeth (consulting fees).  
**Keywords:** Nursing management in MS, Relapse management in MS, Quality of life in MS

**S59** DEVELOPING A WELLNESS PROGRAM FOR PEOPLE WITH MULTIPLE SCLEROSIS: DESCRIPTION AND INITIAL RESULTS  
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**Background:** Multiple sclerosis (MS) is multidimensional. A comprehensive wellness program was designed to facilitate positive health choices, initial data analyses, and program strengths/weaknesses. **Methods:** A standardized outcomes data collection process reduced patient/clinician burden while facilitating multiple construct data collection: patient self-reported outcomes and clinician data. Multiple constructs were quantified during a 12-week program: functional status, pain, fear-avoidance beliefs about physical activities, fatigue, depression, and somatization. We assessed change in constructs while controlling confounding variables using one-way analyses of covariance.  

**Results:** We analyzed data from 68 people with MS from the CentraState MS Wellness Program, part of Linda E. Cardinale MS Center [2008–2009]. Age averaged 51 years (minimum 30, maximum 71, SD 9). Eighty percent were female, 93% were white, and 95% were non-Hispanic. Sixty-seven percent had a college degree or some college training, 15% had a high school diploma, and 8% had less than an 8th-grade education. Fifty-eight percent lived in households with incomes of >$75,000/year. Fifty-one percent had four or more comorbid conditions. Ninety-five percent had chronic MS symptoms, and 66% classified their symptoms as relapsing-remitting. Functional status increased while fatigue, pain, depression, somatization, and fear-avoidance of physical activities decreased (P < .05). When people were classified as having elevated compared with minimal risk of depression, those at minimal risk reported better improvement in functional status at program discharge (P < .05).  

**Conclusions:** The data suggested that the wellness program positively influenced participants. Use of multiple constructs allowed classification of people in different ways. Initial analyses focused on the need for complete data and additional methods of classifying MS severity. The data suggested that we need a scale to assess participants’ balance. Multidimensional data facilitated statistical risk adjustment of outcomes. More data from more clinics performing similar wellness approaches are needed for comparative effective-ness research related to conservative care of people with MS.  

**Supported by:** CentraState Healthcare System  
**Disclosure:** D.L. Hart: Focus On Therapeutic Outcomes, Inc (salary). R.I. Memoli, B. Mason: Nothing to disclose.  
**Keywords:** Rehabilitation strategies and therapy and MS, Complementary/alternative therapies in MS, Management of activities of daily living in MS

**S60** SEVERE ANEMIA ASSOCIATED WITH NATALIZUMAB THERAPY: A REPORT OF TWO CASES  
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**Background:** Natalizumab is a humanized monoclonal antibody to the VLA-4 antigen for treatment of relapsing-remitting multiple sclerosis (MS) and Crohn’s disease. Overall, natalizumab is well tolerated, with known side effects including infusion reactions, hepatic transaminase elevations,
antibody formation, and progressive multifocal leukoencephalopathy. Severe anemia has not previously been reported in association with natalizumab therapy. **Objectives:** To describe two cases of severe anemia during treatment with natalizumab in MS patients. **Methods:** Descriptive case reports and discussion based on review of the literature. **Results:** Two female patients with relapsing-remitting MS were referred to our center after development of severe anemia requiring packed red blood cell transfusions while on natalizumab. MS disease duration was 18 years (age 50) and 7 years (age 45). Prior disease-modifying treatments included interferon beta-1a, interferon beta-1b, and glatiramer acetate, without exposure to myelosuppressive agents. Numbers of monthly natalizumab infusions were 30 and 13 prior to onset of symptoms. The patients presented with shortness of breath and severe fatigue within 3 days of the last infusion. The hemoglobin nadir was 7 and 4.1 (g/dL). One patient stabilized after a single transfusion without further treatment. The other underwent bone marrow biopsy, which revealed normal cellularity, focal lymphoid aggregates, and a shift toward immaturity in erythroid lineage consistent with regeneration after a toxic event. She required repeated transfusions and was treated with oral prednisone (60 mg/day) and stabilized after 3 months. Other etiologies for anemia including infection, gastrointestinal bleeding, iron deficiency, and autoimmune hemolysis were ruled out. Natalizumab antibodies were absent. Natalizumab therapy was discontinued in both patients, with subsequent normalization of hemoglobin. **Conclusions:** Severe anemia has not previously been reported in association with natalizumab treatment and does not have a higher incidence in MS patients. The currently known mechanism of action of natalizumab does not explain the development of severe anemia in these two patients, although a rare, transient idiosyncratic reaction is possible. Further cases of anemia while on natalizumab therapy should be reported to improve medical knowledge.

**Supported by:** National Multiple Sclerosis Society


**Keywords:** Disease-modifying treatment in MS, Immunology and MS

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**Posters**

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**NATALIZUMAB TREATMENT SCORE IMPROVEMENTS AFTER ONE YEAR OF (S61) MULTIPLE SCLEROSIS IMPACT SCALE–29**

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**Background:** Multiple sclerosis (MS) has significant social, psychological, and physical effects that can adversely affect patients’ quality of life (QOL). The Multiple Sclerosis Impact Scale–29 (MSIS-29) is a reliable and valid disease-specific QOL scale that assesses the impact of MS on QOL from a patient’s perspective. **Objectives:** To assess changes in the physical and psychological impact of MS over time in MS patients receiving treatment with natalizumab. **Methods:** In the United States, MS patients starting natalizumab were recruited to participate in a longitudinal observational study and completed the MSIS-29 before natalizumab initiation and after the 3rd, 6th, and 12th infusions. The MSIS-29 scale consists of 20 items evaluating the physical impact and 9 items evaluating the psychological impact of MS. Scores range from 0 to 100, with lower scores indicating better QOL. Statistical regression models were used to evaluate changes in MSIS-29 scores over time after controlling for age, years since MS diagnosis, number of natalizumab infusions received, baseline (BL) disability and functional status, number of MS drugs used prior to natalizumab, and comorbidity burden. **Results:** Data from 192 patients who received 12 infusions and completed all assessments in this ongoing study indicated that the mean ± SD age was 46.09 ± 10.78 years, 78% were female, and they had been diagnosed with MS an average of 10.16 ± 8.23 years previously. After controlling for covariates, a statistically significant improvement was observed in physical impact scores (BL, 48.78 ± 17.06; 12th, 41.66 ± 15.22; P < .0001); similarly, psychological impact scores showed statistically significant improvements over time (BL, 42.52 ± 5.68; 12th, 33.10 ± 5.68; P < .0001) over time. **Conclusions:** MS adversely affects patients’ quality of life. Patients receiving natalizumab for 1 year reported physical and psychological improvements in MS-specific QOL and thereby in everyday functioning. This effect was seen as early as after three infusions and has been sustained over time.

**Supported by:** Biogen Idec, Inc, and Elan Pharmaceuticals, Inc


**Keywords:** Quality of life in MS

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**S62) FACTORS CONTRIBUTING TO THE QUALITY OF LIFE AMONG INDIVIDUALS WITH MULTIPLE SCLEROSIS**

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**Background:** Research indicates that the effective use of coping strategies and availability of social support resources improves the quality of life (QOL) of individuals dealing with chronic illness. However, little research has examined the relationship among QOL, coping strategies, and social support resources among individuals with multiple sclerosis (MS). This research identified effective strategies for coping with MS. Approach-oriented coping was defined as dealing directly with the problems related to having MS. Avoidance-oriented coping was defined as inappropriately managing the emotions associated with the problem. **Objectives:** This study examined variation in the QOL among individuals with MS. Three hypotheses were tested: 1) Variation in coping strategies and social support resources were expected to be related to the overall QOL among individuals with MS. 2) Approach-oriented coping strategies were expected to be positively associated with a better QOL. 3) Avoidance-oriented coping strategies were expected to be negatively related to QOL. **Methods:** This quantitative, cross-sectional study compared coping strategies and social support resources relative to physical and mental QOL among individuals with MS. A survey packet was administered to assess demographics, coping strategies, and QOL. Predictors included the course of the disease, severity of symptoms, and satisfaction with social support. Data were collected from three MS chapters in three different states. **Results:** We began to identify coping strategies and social support systems used to
successfully cope with MS. A total of 97 people with MS, aged 28 to 72, completed the survey packets. More of the participants employed avoidance-oriented coping strategies than approach-oriented coping strategies. As hypothesized, approach-oriented coping was positively related to QOL, while avoidance-oriented coping was negatively related to QOL. Conclusions: Findings from this study can facilitate improvement in coping strategies for individuals living with MS by exploring more effective ways to cope with the disease. Once effective strategies are identified, individuals with MS can be taught how to adopt these strategies to improve their QOL.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS, Psychosocial issues in MS

(S63) CENTRAL AUDITORY PROCESSING DEFICITS IN MULTIPLE SCLEROSIS PATIENTS

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Background: Demyelination of axons in patients with multiple sclerosis (MS) can cause a wide spectrum of symptoms, including difficulties processing auditory stimuli. Behavioral test results indicate that these perceptual problems are a result of central auditory processing (CAP) deficits. Objectives: 1) To conduct behavioral assessments of CAP in MS patients and compare the results with those from age-matched control subjects. 2) To record a variety of auditory evoked potentials (AEPs) from patients with MS and compare the responses with those recorded from control subjects. These electrophysiologic results will be correlated with behavioral tests of CAP. Methods: Behavioral tests of central auditory function included 1) the Staggered-Spondaic Word (SSW) test, 2) the Dichotic Digits Test (DDT), 3) the Frequency Pattern Sequences Test, 4) the Gaps-In-Noise (GIN) test, 5) masking-level-difference (MLD) measurements for a 500-Hz pure tone, 6) the Words-In-Noise (WIN) Test, and 7) the SCAN-A battery. AEPs were recorded from scalp surface electrodes and included auditory brainstem responses (ABRs), middle latency responses (MLRs), and long-latency responses (LLRs) to repeated click and tonal stimuli. LLR recordings included the auditory P300 component, an indicator of cognitive processing that includes memory and selective attention. Results: To date, data have been collected from 20 MS patients and 20 control subjects. Significant differences between these subject groups were observed for the following behavioral tests: SSW, DDT, GIN, WIN, SCAN-A. AEP results indicate significant differences in amplitude of the binaural interaction component (BIC) and auditory P300 component between these populations, which suggests impaired central auditory processing in the MS group. Conclusions: MS contributes to a variety of CAP deficits that can be identified via particular behavioral and electrophysiologic tests. Results from this study can be used to facilitate improvements in patient evaluations, development of rehabilitative interventions, and assessments of treatment efficacy.

Supported by: Veterans Affairs RR&D
Disclosure: Nothing to disclose

(S64) PATIENT PERSISTENCE ON INTERFERON BETA-1A IN THE MULTIPLE SUPPORT PROGRAM (MSP)

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Background: Interferon beta-1a (IFNβ-1a) is a disease-modifying drug approved in Canada for use in multiple sclerosis (MS). The Multiple Support Program (MSP), an MS patient support program, provides information on MS and specific treatments, as well as injection training and reimbursement support for patients on IFNβ-1a (Rebif®). Follow-up data are available for all patients registered with MSP, including some who initiated treatment in clinical trials as early as 1993. Objectives: To evaluate treatment persistence and reasons for discontinuation in a Canadian MS patient cohort receiving IFNβ-1a twice weekly. Methods: Treatment persistence data were analyzed for MSP participants initiating IFNβ-1a between 1993 and October 31, 2008. Persistence was assessed for patients initiating treatment between 2001 and 2008, a cohort receiving consistent follow-ups from MSP. Cohorts initiating earlier (eg, before 1998) were analyzed separately. Patients suspending IFNβ-1a for >6 months (eg, during pregnancy) were considered to have discontinued. Results: Overall, 8732 MSP registrants were followed for periods ranging from 1 to 14 years. Of patients initiating IFNβ-1a in clinical trials before 1998, 99 of 136 (72.8%) remained on therapy in October 2009. Of patients initiating IFNβ-1a between 2001 and 2008, 4608 of 6849 (67.3%) persisted on therapy in 2009. Of the 2241 discontinuations recorded in this 8-year period, 66.4% occurred during patients’ first 2 years on treatment. Furthermore, for each of the year-of-start cohorts between 2001 and 2008, annual discontinuation rates ranged from 11.1% to 22.7% in year 1 of treatment, 6.2% to 10.2% in year 2, and 1.4% to 6.3% in subsequent years. The most commonly cited reasons for treatment discontinuation (or suspension for >6 months) were flu-like symptoms, liver enzyme elevation, and pregnancy/desire to conceive. Potential factors influencing persistence will be presented. Conclusions: Results from this analysis suggest that treatment with IFNβ-1a in a clinical practice setting is well tolerated during long-term use. Despite expanded therapeutic options for MS since the MSP began, more than two-thirds of patients remained on IFNβ-1a over a period of up to 14 years. Patients persisting at least 2 years on IFNβ-1a had the lowest discontinuation rate.

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Keywords: Disease-modifying treatment in MS

(S65) ORAL FINGOLIMOD (FTY720) VERSUS PLACEBO IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: BASELINE DATA FROM A TWO-YEAR PHASE 3 TRIAL (FREEDOMS II)

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Results from earlier phase III trials suggested that oral fingolimod (FTY720) significantly reduces the risk of relapse and progression in patients with multiple sclerosis (MS) compared with placebo. This analysis presents baseline data from a 2-year phase 3 study comparing FTY720 1.25 mg and 2.5 mg once daily with placebo across four geographic regions of the United States, Canada, and Europe.

Supported by: Veterans Affairs RR&D
Disclosure: Nothing to disclose

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Background: Oral fingolimod (FTY720), a sphingosine-1-phosphate receptor modulator, is the first in a novel class of drugs under evaluation for the treatment of relapsing-remitting multiple sclerosis (RRMS). In two completed phase 3 studies (TRANSFORMS and FREEDOMS), daily oral FTY720 for 12 months was significantly more effective on clinical and magnetic resonance imaging (MRI) measures than both intramuscular (IM) interferon beta-1a (IFN-β-1a) and placebo in patients with RRMS. FREEDOMS II is a further 24-month, global, randomized, double-blind, placebo-controlled phase 3 trial to assess the safety and efficacy of FTY720 in patients with RRMS. Objectives: To report trial design, demographics, and MS disease characteristics of the FREEDOMS II trial. Methods: In this study, RRMS patients (aged 18–55 years; 2005 McDonald criteria) with Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and ≥1 relapse in the previous year (or ≥2 in the previous 2 years) are randomized to once-daily FTY720 (0.5 mg or 1.25 mg) or placebo. The primary end point is annualized relapse rate. The key secondary end point is treatment effect on 3-months confirmed disability progression (1-point EDSS score increase from baseline or 0.5-point increase if baseline EDSS score was ≥5.5). Other end points include MRI measures of disease activity and brain volume, other relapse and disability measures, quality of life, and performance of daily activities measured by the Patient-Reported Indices in Multiple Sclerosis (PRIMUS) instrument and the Modified Fatigue Impact Scale. Results: A total of 1083 patients (mean/median age, 41 years; 78% female) were randomized. At baseline, the mean (median) duration of MS was 10.0 (8.5) years, with patients experiencing an average of 1.5 relapses in the year prior to randomization and 2.3 relapses in the 2 years prior to randomization. Mean (median) baseline EDSS score was 2.5 (2.5). Approximately 73% of patients had previously received disease-modifying treatment: 38% received IM IFN-β-1a, 26% subcutaneous IFN-β-1a, 22% IFN-β-1b, 41% glatiramer acetate, and 6% natalizumab. Conclusions: The baseline characteristics of patients in FREEDOMS II are consistent with a relapsing MS population, a finding similar to those of previous therapeutic studies in MS.

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(S66) POST-BASELINE CHANGES IN WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT AMONG MULTIPLE SCLEROSIS PATIENTS IN A REAL-WORLD OBSERVATIONAL OUTCOMES STUDY (ROBUST)

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Background: ROBUST was a 12-month, United States-based, prospective, observational, open-label, single-arm, multicenter outcomes study of patients taking interferon beta-1b (IFN-β-1b) given every other day for relapsing forms of multiple sclerosis (MS). Objectives: The objectives of this analysis were to assess work productivity and activity impairment over the course of 12 months among MS patients in a real-world observational study. Methods: ROBUST collected, monthly via a web-based data-capture system, responses from patients to the Work Productivity and Activity Impairment questionnaire (WPAI). Higher WPAI scores represent greater impairment, and reductions in WPAI scores over time represent improvement in outcomes. A one-sample t test was used to explore the statistical significance of the changes in WPAI domain scores from their baseline values. A total of 184 patients were included in the final analysis. Results: At baseline, the mean WPAI scores among all 184 patients...
were as follows: absenteeism: 17.84; presenteeism: 33.64; work productivity loss: 43.31; activity impairment: 46.89. Absenteeism (–11.92, P = .0001), presenteeism (–4.36, P = .0091), work productivity loss (–11.39, P = .0005), and activity impairment (–7.65, P = .0036) scores all decreased from baseline to month 12, indicating an improvement after the initiation of IFNβ-1b. The decreases from baseline in the absenteeism, work productivity loss, and activity impairment scores were statistically significant at each and every month (months 1 through 12) throughout the study. The largest mean decrease in presenteeism occurred at the first month following initiation of IFNβ-1b (–4.95, P = .0111); the largest mean decrease in activity impairment occurred at month 11 (–8.62, P = .0013). Conclusions: Work productivity and activity impairment improved significantly in the ROBUST study participants, suggesting an effect of IFNβ-1b in these outcome measures.

Supported by: Bayer HealthCare Pharmaceuticals, Inc

Keywords: Management of activities of daily living in MS, Economic issues and MS, Disease-modifying treatment in MS

(S67) ADRENOCORTICOTROPIC HORMONE: MODULATION OF ANTIGEN-PRESENTING CELL PHENOTYPE AND FUNCTION

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Background: During relapses of relapsing-remitting multiple sclerosis (RRMS), T-cell reactivity to numerous myelin antigens increases. Severity of attacks is linked to T-cell migration into the central nervous system (CNS). Autoreactive T cells recognize peptides derived from self-proteins [ie, proteins of the myelin sheath] when bound to major histocompatibility complex (MHC) II molecules expressed on the surface of antigen-presenting cells (APCs; ie, monocytes, macrophages, dendritic cells). APCs also express several co-signaling molecules that are either inhibitory or stimulatory toward T-cell activation. Relative expression of these co-signaling molecules by APCs dictates whether an APC will activate or anergize T cells encountered. APCs that express high levels of CD86 but low levels of immunoglobulin-like transcript 3 (ILT3) activate T cells, while APCs with high ILT3 but low CD86 levels anergize T cells [ie, tolerogenic APCs]. Objectives: To measure levels of ILT3 (inhibitory) and CD86 (activatory) on APCs from RRMS patients in relapse and during stable disease, and on APCs of healthy controls, and to determine the effect of adrenocorticotropic hormone (ACTH) on APC-expressed ILT3 and CD86 and on APC-mediated activation of T cells. Methods: Levels of ILT3 and CD86 on freshly isolated APCs of active RRMS patients, stable RRMS patients, and controls were measured by flow cytometry. ILT3 and CD86 were also measured on APCs after culture with and without ACTH. Results: ILT3 levels on APCs of RRMS patients in relapse are significantly decreased compared with levels seen in stable RRMS and in healthy controls. Levels of CD86 are comparable in patients with active RRMS, patients with stable RRMS, and controls. The ILT3 to CD86 ratio on APCs of RRMS during relapse appears to favor T-cell activation. ACTH dampens CD86 up-regulation on APCs of RRMS and controls and favors the formation of tolerogenic APCs. Conclusions: ACTH may exert a beneficial effect in RRMS through modulation of APC phenotype and function.

Supported by: Questcor Pharmaceuticals, Inc

Keywords: Immunology and MS, Disease-modifying treatment in MS

(S68) MEASURING PHYSICAL FUNCTION IN MULTIPLE SCLEROSIS: EXTENDING THE PROMIS BANK FOR ASSISTIVE TECHNOLOGY USERS

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Background: Individuals with multiple sclerosis (MS) and other disabilities often use assistive technology (AT) to help with their mobility or in performing instrumental activities of daily living. However, many patient-reported outcome measures include items that are not appropriate for users of AT or items that do not adequately measure functioning of these individuals. Objectives: The objective of this study was to ensure that the newly developed PROMIS Physical Function (PROMIS-PF) bank was appropriate and relevant to users of wheelchairs, mobility aids, and other AT. Methods: Interviews with panels of experts comprising physical therapists, occupational therapists, and physicians were completed to generate an operational definition of physical function for AT users. Next, PROMIS-PF items were reviewed by experts and categorized regarding relevance and appropriateness for users of AT. For instance, items that reference ability to walk or run were flagged as potentially inappropriate for wheelchair users. Items were revised and new items were generated to ensure that aspects of PF most relevant to users with disabilities were included. All new and revised items were submitted to several rounds of reviews by expert panels and individuals with disabilities. Results: Based on results, the candidate item bank was finalized and administered to over 600 participants, including over 274 with MS. A subset of unchanged PROMIS items was also administered for anchoring the subsequent Item Response Theory (IRT) calibration to the original PROMIS-PF metric. Expert review led to the addition of 53 new or modified items and identified 17 items that were inappropriate for AT users. Factor analytic results indicate that the final bank with 112 items is sufficiently unidimensional. Conclusions: Clinicians and researchers have voiced preference for availability of separate banks for measuring upper and lower body PF. Fifty-three items were identified for inclusion in an upper-body and 22 in a lower-body PF bank. New items will be added to the publicly available PROMIS bank. Items flagged as inappropriate for some users of AT will be maintained in the bank but would not be administered to specific populations.

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Disclosure: Nothing to disclose
(S69) LONGITUDINAL CD4 AND CD8 COUNTS IN MULTIPLE SCLEROSIS PATIENTS ON NATALIZUMAB
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Background: Natalizumab is a humanized monoclonal antibody directed against alpha-4 integrin, which reduces disease activity in patients with multiple sclerosis (MS) by blocking migration of lymphocytes into the central nervous system (CNS). There has been concern over the degree of immunomodulation or immunosuppression of the CNS in patients treated with natalizumab, with 31 reported cases of progressive multifocal leukoencephalopathy (PML) noted in 60,000+ patients treated worldwide. PML is a rare condition previously seen only in severely immunocompromised patients such as those with AIDS or artificially immunosuppressed organ transplant. Recent reports suggest that the risk of developing PML in natalizumab-treated MS patients rises after 2 years of therapy. Objectives: To assess the degree of immunomodulation or immunocompromise seen in patients treated with natalizumab for up to 41 months of therapy.

Methods: The CD4 and CD8 counts and CD4/CD8 ratios of 24 patients treated with natalizumab over the course of 19 months were collected in a tertiary MS center in Seattle, WA. The patients had variable months of exposure at the time of initial data collection, ranging from 2 months to 23 months. The longest duration of natalizumab exposure for which these counts were available was 41 months of therapy. Results: A gradual drop of CD4 counts and CD4/CD8 ratio were noted at approximately 24 months of drug exposure. CD8 counts showed a mild initial drop at 6 months of therapy with return to baseline and remained stable after 10 months of therapy.

Conclusions: There appears to be a drop in CD4/helper T lymphocytes both in absolute numbers and in CD4/CD8 ratios at approximately 2 years of natalizumab drug exposure, which may result in decreased immune response that predisposes to PML.


Keywords: Disease-modifying treatment in MS, Immunology and MS

(S70) MUSCULAR AND GAIT ABNORMALITIES IN PATIENTS WITH A FIRST CLINICALLY DEMYELINATING EPISODE SUGGESTIVE OF MULTIPLE SCLEROSIS
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Background: Muscular and gait abnormalities are common complaints among patients with multiple sclerosis (MS). Objectives: The aim of this study was to characterize the extent of and the associations between spatiotemporal gait parameters, isometric strength, and fatigue of major lower-limb muscles in patients with a first clinically demyelinating event suggestive of MS. Methods: Fifty-two patients with clinically isolated syndrome (CIS; 36 female, 16 male) with a mean (SE) age of 33.8 (0.2) years, mean (SE) disease duration of 54 (6.2) days, and mean (SE) Expanded Disability Status Scale (EDSS) score of 1.7 (0.2) participated in the study. The tested muscle groups were the knee flexors and extensors and ankle plantarflexors and dorsiflexors. For each muscle, the group peak isometric torque and fatigue index were collected. A number of spatiotemporal parameters were also evaluated. Twenty-eight age- and gender-matched healthy subjects served as a control group. Results: Motor fatigue was greater in CIS patients. Pooling over all movements, fatigue increased by approximately 40% compared with healthy subjects (P < .01). The gait parameters of double support and base of support were elevated in the CIS group.

Conclusions: These data provide evidence of a reduction in lower-limb motor performance following a first clinically demyelinating event. Motor deficits related to altered cortical activity and diffuse axonal dysfunction appear to occur very early in the disease process. Identification of lower-limb muscle abnormalities in the early stage of MS is important in order to establish proper intervention programs.

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S71) RELATIONSHIP BETWEEN COGNITIVE PERFORMANCE AND CLINICAL/MAGNETIC RESONANCE IMAGING VARIABLES IN EARLY MULTIPLE SCLEROSIS
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Background: Cognitive dysfunction in early stages of multiple sclerosis (MS) is well documented. While data are also available on correlations between magnetic resonance imaging (MRI) and cognitive function, correlations with other clinical variables or the predictive value of cognition for disease course are scarce and inconsistent. Objectives: Data from the BENEFIT study in patients with a first event suggestive of MS (clinically isolated syndrome [CIS]) were reanalyzed in an exploratory fashion to assess the relationship between cognitive performance (Paced Auditory Serial Addition Test [PASAT]) and other clinical/MRI variables. Methods: A total of 468 patients with CIS were randomized (5:3) to receive interferon beta-1b (IFN β-1b) 250 µg subcutaneously every other day or placebo for 2 years or until diagnosis of clinically definite MS (CDMS), after which open-label IFN β-1b was offered for up to 5 years. We evaluated associations between PASAT and clinical/MRI findings at baseline and year 5 and the impact of baseline PASAT on the development of PML in natalizumab-treated MS patients rises after 2 years of therapy.

Results: At screening and year 5, low Expanded Disability Status Scale (EDSS) scores were associated with better PASAT performance (P < .01; r = −0.2), but no significant or consistent associations with MRI were found. PASAT performance at year 5 did not differ in patients with versus without CDMS (P = .44) and did not correlate with MRI outcomes (absolute changes in T2, gadolinium-enhancing T1 and T1-hypointense lesion volumes,

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and percent change in brain volume, all \( P > .1 \) but was worse in patients with confirmed EDSS progression \( (P = .02) \). Baseline PASAT performance did not predict time to CDMS \( (P = .8) \); hazard ratio \( [HR, 0.998; 95\% \text{ confidence interval} \{CI\}, 0.980-1.015] \) or time to McDonald MS \( (P = .7; HR, 0.997; 95\% CI, 0.984-1.011) \). Higher baseline performance was associated with a lower risk of confirmed EDSS progression \( (P = .01; HR, 0.975; 95\% CI, 0.956-0.994) \).

Conclusions: Our findings suggest a possible causal relation between cognitive impairment and neurologic disability at CIS and during early MS. Low cognitive performance at CIS may even predict later neurologic disability in early MS. However, at this early disease stage, cognitive impairment was not associated with conventional MRI measures of cerebral pathology and did not predict CDMS diagnosis as defined by relapse or new MS activity.

Supported by: Bayer Schering Pharma AG, Berlin


Keywords: Psychological issues and MS, Natural history of MS, Disease-modifying treatment in MS.

(S72) PERSONALITY TRAITS AND ADAPTATION TO NEUROLOGIC DISABILITY IN MULTIPLE SCLEROSIS

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Background: Personality is reliably assessed using the Five Factor Model and has known associations with a broad range of physical/mental health outcomes. Given the relative unpredictability of symptoms and disease progression in multiple sclerosis (MS), personality may be of particular importance in terms of adaptation to illness. Objectives: We aimed to investigate the relationship between personality and quality of life QOL in a diverse sample of MS patients, while controlling for the effects of disease characteristics and cognitive capacity. Methods: Subjects were 65 MS patients roughly equivalent across demographic variables; 88% had relapsing-remitting MS and 12% had a secondary progressive course. T tests were performed to identify differences in individual personality traits [NEO Five-Factor Inventory (NEO-FFI)] in patients with poor QOL (Sickness Impact Profile Total >19) versus MS patients with good adaptation. Logistic regression was then performed to determine which personality traits optimally predicted poor quality of life in MS patients based on both patient self-report and informant report on the NEO-FFI. Cognition was assessed with the Symbol Digit Modalities Test (SDMT). Results: Neuroticism, extroversion, and conscientiousness on both self- and informant report significantly differed between patients with poor QOL versus other MS patients. Controlling for age, education, gender, Expanded Disability Status Scale (EDSS) score, and cognition, the only informant-reported trait retained in the model predicting poor QOL was conscientiousness \( (\chi^2 = 17.768, P < .01) \). Controlling for the same variables, the only informant-reported trait retained in the model predicting poor QOL was neuroticism \( (\chi^2 = 17.008, P < .01) \). In each case low conscientiousness and high neuroticism were associated with poorer QOL. Conclusions: The results confirm the relationship between personality and QOL in MS above and beyond neurologic disability and cognition. Other research has revealed associations between elevated neuroticism and low conscientiousness and cognitive dysfunction and brain atrophy in MS. With a larger patient sample, future research might focus on identifying potential type differences and associated clinical outcomes in MS patients.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS.

(S73) BOWEL OBSESSION SYNDROME IN MULTIPLE SCLEROSIS PATIENTS

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Background: Bowel and bladder dysfunction is common in patients with multiple sclerosis (MS). This symptom is rated as third in importance by patients and affects their function and quality of life. Fecal incontinence in particular can become a significant factor in the patient’s psychosocial disability, leading to bowel obsession syndrome (BOS). Bowel obsession has long been recognized in patients with gastrointestinal problems, usually presenting as an overwhelming and irrational fear of losing bowel control in public. There are no published data on BOS in patients with MS. Objectives: To develop an information poster outlining progression of bowel dysfunction to a more complex disability involving a psychological component, and to describe BOS in MS patients and possible interventions, including psychological treatment techniques that can be accommodated to MS patients. Methods: Case reviews of two patients with potential BOS. Results: A 62-year-old woman with primary progressive MS (PPMS) had an episode of incontinence 20 years ago; as a result, she has developed an uncontrolled potential BOS. The patient is now onset in the morning and bowel urgency after eating. A 25-year-old man has been complaining of bowel urgency after eating. He refrains from eating breakfast and lunch and eats only once a day. He has long been recognized in patients with gastrointestinal problems, usually presenting as an overwhelming and irrational fear of losing bowel control in public. There are no published data on BOS in patients with MS.

Disclosure: Nothing to disclose

Keywords: Psychological issues and MS.
(S74) TRANSFORMS: ORAL FINGOLIMOD (FTY720) VERSUS INTERFERON BETA-1A IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: CLINICAL EFFICACY RESULTS


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Background: Oral fingolimod (FTY720), a sphingosine 1-phosphate receptor modulator, is under evaluation for the treatment of relapsing-remitting multiple sclerosis (RRMS). TRANSFORMS compared daily oral FTY720 with intramuscular (IM) interferon beta-1a (IFNβ-1a) in RRMS patients for 12 months. Objectives: To report TRANSFORMS clinical efficacy results. Methods: In this 12-month, randomized, double-blind, double-dummy study, RRMS patients (aged 18–55 years) with Expanded Disability Status Scale (EDSS) scores of 0 to 5.5 and ≤1 relapse in the previous year (or ≤2 in the previous 2 years) were randomized to receive daily FTY720 0.5 mg or 1.25 mg or weekly IM IFNβ-1a 30 µg. Clinical measures included annualized relapse rate (ARR) and disability progression (defined as a 1-point EDSS increase from baseline or a 0.5-point increase if baseline was ≤5.5, confirmed after 3 months). Results: ARR at 12 months was lower with FTY720 0.5 mg (0.16) and 1.25 mg (0.20) versus IM IFNβ-1a (0.33, P < .001 for both comparisons). The proportion of relapse-free patients at 12 months was higher with FTY720 0.5 mg (0.83) and 1.25 mg (0.80) versus IM IFNβ-1a (0.69, P < .001 for both comparisons). Fewer FTY720-treated patients experienced relapses requiring steroids and/or hospitalization (13.1% and 16.2%, respectively) versus IM IFNβ-1a (25.3%, P < .01 for both comparisons). Time to EDSS progression confirmed at 3 months (main disability outcome) was not statistically improved, although risk of progression favored fingolimod (Kaplan-Meier estimate; hazard ratio [HR], 0.70 for 0.5 mg and 0.87 for 1.25 mg group) compared with IM IFNβ-1a. Mean change in EDSS score compared with control (mean change, +0.01) was improved in the 1.25 mg group (+0.01, P = .02) and approached significance in the 0.5 mg group (+0.08, P = .06). Conclusions: FTY720 significantly reduced ARR for 12 months, including relapses requiring steroids and/or hospitalization. Time to disability progression was not significantly improved, although disability measures suggested a treatment effect. The short study duration limits an ability to detect differences in disability progression between groups.

Supported by: Novartis Pharmaceuticals Corporation


Keywords: Disease-modifying treatment in MS

(S75) ORAL FINGOLIMOD IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: MAGNETIC RESONANCE IMAGING FINDINGS FROM TRANSFORMS AND FREEDOMS PHASE 3 TRIALS


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Background: Oral fingolimod (FTY720), a sphingosine 1-phosphate receptor modulator, targets multiple sclerosis (MS) via actions in the immune system and demonstrated effects on magnetic resonance imaging (MRI)–detected inflammatory activity and brain-volume loss. Objectives: To report MRI findings from a 12-month phase 3 study that evaluated fingolimod versus intramuscular (IM) interferon beta-1a (IFNβ-1a; TRANSFORMS) and from a 24-month phase 3 study that evaluated fingolimod versus placebo (FREEDOMS) in patients with relapsing-remitting MS (RRMS). Methods: In two phase 3, double-blind studies, RRMS patients (aged 18–55 years; 2005 revised McDonald criteria) with Expanded Disability Status Scale (EDSS) scores of 0 to 5.5 and ≤1 relapse in the previous year (or ≤2 in the previous 2 years) were randomized to receive once-daily fingolimod (0.5 mg or 1.25 mg), weekly IFNβ-1a 30 µg (TRANSFORMS), or placebo (FREEDOMS). The principal MRI end point in both studies was the number of new or enlarging T2 lesions (at 12 months in TRANSFORMS and at 24 months in FREEDOMS). Other measures included T1 gadolinium-enhancing and T1-hypointense lesion counts, lesion-volume change, and change in brain volume. Results: Baseline MRI characteristics were well balanced across all groups in both studies. MRI data are presented for patients in whom scans were available. T2 lesion count was significantly reduced compared with controls in both studies. In TRANSFORMS, there was a 31% to 42% reduction in mean lesion count (1.7 lesions for fingolimod 0.5 mg, 1.5 for fingolimod 1.25 mg) compared with IM IFNβ-1a (2.6 lesions), while in FREEDOMS, there was a 74% reduction in mean lesion count (2.5 lesions for fingolimod 0.5 mg, 2.2 for fingolimod 1.25 mg) compared with placebo (2.9 lesions). Conclusions: FTY720 reduced MRI lesion burden consistently across two phase 3 trials of RRMS patients treated with or without placebo. FTY720 has the potential to modify the natural course of multiple sclerosis by reducing MRI lesion burden.
lesions) compared with placebo (9.8 lesions; \( P < .01 \) for all comparisons). Other MRI lesion measures showed similar treatment benefit and will be presented. Brain-volume loss was significantly greater in control groups than in fingolimod groups in both studies at all time points measured. **Conclusions:** Treatment with oral fingolimod significantly reduced MRI inflammatory activity and brain-volume loss compared with IM IFNβ-1a and placebo in two separate studies involving patients with RMS.

**Supported by:** Novartis Pharmaceuticals Corporation


**Keywords:** Disease-modifying treatment in MS, Imaging and MS appearance. In contrast, the functional electrical stimulation (FES) neuroprostheses use electrical stimulation of muscles around the calf to produce dorsiflexion and eversion of the ankle at appropriate times while eliminating the negative effects of AFOs. **Objectives:** To compare the energy cost and efficiency of walking in ambulatory patients with MS between the AFO and the FES neuroprosthesis. **Methods:** Twenty ambulatory community-dwelling adults aged 18 to 75 years diagnosed with MS (Expanded Disability Status Scale [EDSS] score ≤6.5) resulting in footdrop were enrolled in a randomized, crossover, controlled, proof-of-principle pilot study. On each of two testing days, subjects underwent two 10-minute walking trials. The order of device presentation, AFO or FES, for each of the two walks was counterbalanced. The open-circuit method was used for metabolic monitoring. A heart monitor was used to collect heart rate, and a face mask was used to measure oxygen consumption. Walks were at a self-selected pace and separated by 1 hour of rest. Participants rated their perceived exertion after each walk trial. Testing was repeated between 1 week and 1 month later with the testing device order during walking trials reversed.

**Results:** Averages were calculated for the two testing days. Significant results were seen in the following measures of velocity, energy cost, caloric expenditure, and metabolic efficiency between the AFO and FES. The perceived exertion for the AFO was increased compared with the FES. **Conclusions:** We found the FES to be more metabolically efficient and have decreased energy cost, decreased caloric expenditure, and less perceived exertion compared with the AFO. On average, subjects had increased speed when using the AFO versus the FES, which may be due to small sample size, familiarity with the AFO device, and increased time to adjust to FES use. Our preliminary results suggest that the FES may be more efficacious compared with the AFO.

**Supported by:** Consortium of Multiple Sclerosis Centers

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS, Equipment in MS, Symptomatic treatment of MS

**Posters**

**S76** **COMPARISON OF FUNCTIONAL ELECTRICAL STIMULATION NEUROPROSTHESIS AND ANKLE-FOOT ORTHOSIS IN PEOPLE WITH MULTIPLE SCLEROSIS**

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**Background:** Footdrop is one of the most disabling sequelae of multiple sclerosis (MS). Research has shown that people with MS and footdrop have shorter stride lengths, slower free-speed walking rates, and higher cadence than those without MS. The current standard of care to correct footdrop is an ankle-foot orthosis (AFO), which restricts ankle movement, allows muscle wasting, limits choice of footwear, can promote skin breakdown, and offers poor cosmetic appearance. In contrast, the functional electrical stimulation (FES) neuroprosthesis uses electrical stimulation of muscles around the calf to produce dorsiflexion and eversion of the ankle at appropriate times while eliminating the negative effects of AFOs. **Objectives:** To compare the energy cost and efficiency of walking in ambulatory patients with MS between the AFO and the FES neuroprosthesis. **Methods:** Twenty ambulatory community-dwelling adults aged 18 to 75 years diagnosed with MS (Expanded Disability Status Scale [EDSS] score ≤6.5) resulting in footdrop were enrolled in a randomized, crossover, controlled, proof-of-principle pilot study. On each of two testing days, subjects underwent two 10-minute walking trials. The order of device presentation, AFO or FES, for each of the two walks was counterbalanced. The open-circuit method was used for metabolic monitoring. A heart monitor was used to collect heart rate, and a face mask was used to measure oxygen consumption. Walks were at a self-selected pace and separated by 1 hour of rest. Participants rated their perceived exertion after each walk trial. Testing was repeated between 1 week and 1 month later with the testing device order during walking trials reversed.

**Results:** Averages were calculated for the two testing days. Significant results were seen in the following measures of velocity, energy cost, caloric expenditure, and metabolic efficiency between the AFO and FES. The perceived exertion for the AFO was increased compared with the FES.

**Conclusions:** We found the FES to be more metabolically efficient and have decreased energy cost, decreased caloric expenditure, and less perceived exertion compared with the AFO. On average, subjects had increased speed when using the AFO versus the FES, which may be due to small sample size, familiarity with the AFO device, and increased time to adjust to FES use. Our preliminary results suggest that the FES may be more efficacious compared with the AFO.

**Supported by:** Consortium of Multiple Sclerosis Centers

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS, Equipment in MS, Symptomatic treatment of MS

**S77** **EARLY MAGNETIC RESONANCE IMAGING ACTIVITY ON INTRAMUSCULAR INTERFERON BETA-1A PREDICTS DISEASE ACTIVITY AT TEN YEARS**

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**Background:** Analyses from the CHAMPIONS open-label extension study of CHAMPS showed that new T2 or gadolinium-enhancing (Gd+) lesions on magnetic resonance imaging (MRI) scan 6 months after starting treatment with intramuscular (IM) interferon beta-1a (IFNβ-1a) predicts disease activity, Expanded Disability Status Scale (EDSS) status, and conversion to clinically definite multiple sclerosis (CDMS) at 5 years. **Objectives:** To determine whether MRI activity 6 months after initiating IM IFNβ-1a predicts disease activity at 10 years. **Methods:** CHAMPS was a randomized, double-blind, placebo-controlled, phase 3 study in which patients with a first demyelinating event and cranial MRI evidence of subclinical demyelination were treated with either IM IFNβ-1a 30 µg (n = 193) or placebo (n = 190) once weekly for up to 36 months. All patients who did not experience a
relapse consistent with CDMS underwent MRI scans 6, 12, and 18 months after randomization. Forty percent of patients from CHAMPS (155/383) enrolled in the CHAMPIONS 10 follow-up extension study. Results: Of the 73 patients who received immediate treatment with IM IFN-β-1a, underwent an MRI scan 6 months after initiating treatment, and enrolled in CHAMPIONS 10, 30.1% had lesion activity ≤2 new T2 or ≥2 Gd+ lesions suggesting a suboptimal response to treatment. In these patients, the risk of developing CDMS by year 10 was significantly higher compared with patients with <2 new T2 and <2 Gd+ lesions at month 6 [hazard ratio, 3.83; 95% confidence interval, 2.32-6.33; P < .0001]. Trends were observed at 10 years for a difference in EDSS scores in patients with <2 new T2 and <2 Gd+ lesions at 6 months and those with ≥2 new T2 or ≥2 Gd+ lesions (mean EDSS, 1.6 ± 1.36 vs. 2.3 ± 2.02; P = .2740). Patients with <2 new T2 and <2 Gd+ lesions were more likely to have an EDSS score ≤2.0 than those with ≥2 new T2 or ≥2 Gd+ lesions [80.4% vs. 59.1%, P = .1068]. Patients with ≥2 new T2 or ≥2 Gd+ lesions were also less likely to have stable disease compared with patients with <2 new T2 and <2 Gd+ lesions (50.0% vs. 74.5%, P = .4423). Conclusions: MRI lesion activity 6 months after initiating treatment with IM IFN-β-1a is a predictor of disease activity and conversion to CDMS at 5 years, and this trend continued at 10 years.

Supported by: Biogen Idec, Inc

Keywords: Disease-modifying treatment in MS, Imaging and MS

(S78) MEETING THE NEEDS OF PEOPLE WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS
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Background: With most of the attention focused on the relapsing-remitting form of multiple sclerosis (MS), people with primary progressive MS (PPMS) often describe themselves as “orphans” of the MS world. Aware of this sentiment, in 2008 the National MS Society and MS Association of America (MSAA) hosted a meeting, bringing together a diverse group from across the country, with one goal in mind—to develop a better understanding of the needs of this population. Objectives: One of the top recommendations to come out of this gathering was to expand and enhance the available programs, services, and resources. Both organizations took on this challenge and developed a range of resources for people living with PPMS and the health-care community. Results: Primary Progressive Multiple Sclerosis—What You Need to Know is a book that discusses diagnosis, treatment and research, rehabilitation, wellness, family and social issues, and life planning. The companion DVD, “Primary Progressive Multiple Sclerosis—Perspectives on Moving Forward,” profiles four people with PPMS who share their strategies for maintaining a healthy quality of life and planning for life with PPMS. MSAA developed a booklet for the PPMS community, which provides important information on managing symptoms as well as improving function through rehabilitation. Technology and adaptations aimed at making life easier are highlighted, along with strategies for maintaining physical and emotional wellness. Both organizations now have sections on their websites dedicated to progressive forms of MS, including information specific to PPMS. Visitors will find resources on a wide range of progressive MS-related topics to include course descriptions, treatment options, and research. For the health-care team there is “Talking About Primary-Progressive MS,” part of the Society’s “Talking with Your MS Patients about Difficult Topics” series. Opening Doors: The Palliative Care Continuum in Multiple Sclerosis is a new clinical bulletin covering the spectrum of palliative care and its relevance to the care and treatment of people with MS. Conclusions: The National MS Society and MSAA are committed to expanding knowledge of MS and empowering people with MS to live as independently as possible within the limits of their disabilities and to the maximum of their capabilities. We believe these resources help to achieve this goal.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS

(S79) MS NEXT STEP: INFORMATION FOR PEOPLE NEWLY DIAGNOSED
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Background: One of the goals of the National Multiple Sclerosis Society is to address the challenges of each person living with multiple sclerosis (MS) through outreach to neurologists and other health-care professionals to ensure referral of people with MS early in the disease. To assist health-care professionals in their work with people newly diagnosed, the Society is proud to announce the availability of the updated MS Next Step product. Objectives: MS Next Step is an introduction to MS and the Society’s resources for people living with MS. MS Next Step is designed to be the very first information a person receives following a diagnosis, including the information someone should know about topics that are most important during the days and weeks after a diagnosis. Topics discussed include what causes MS, who gets MS, types of MS, treatment options, disclosure, and so on. Methods: The new MS Next Step is packaged much like an audio CD and includes a DVD with video content, electronic versions of the booklet and video transcripts, and Spanish translations of all content. The DVD is narrated by Meredith Vieira. Conclusions: MS Next Step focuses on engaging those who have been newly diagnosed in specific ways to work with their doctor closely to take control of their MS; to participate in Knowledge Is Power; to get accurate information, which they can do by exploring Society resources; and to “Join the Movement” in a way that makes sense for them.

Disclosure: Nothing to disclose
(S80) IMPACT OF ORAL HEALTH IN MULTIPLE SCLEROSIS AND EPILEPSY: A NEUROLOGY CLINIC SURVEY

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Background: Autoimmune disease may affect saliva secretion in animal models and humans. Saliva production is significantly lower in females than in males. It would therefore be expected that multiple sclerosis (MS), which has been characterized as an autoimmune demyelinating disease affecting predominantly females and may also be treated with symptomatic anticholinergic medications, may adversely affect oral health. Objectives: We sought to characterize the impact of oral health on neurologic disorders using the Oral Health Impact Profile (OHIP), a validated survey instrument. Methods: A total of 460 patients completed the OHIP, including 141 controls without neurologic conditions. Results: Of the 319 patients with neurologic diagnoses who were enrolled, 31% had MS, 34% had epilepsy, and 34% had other neurologic conditions. Compared with the control group, mean age, education, and household income levels were significantly lower among epilepsy patients than in the other groups. The majority of the study population was white, and the percentage was highest in those with MS (87%). Patients with any neurologic diagnosis had greater physical pain and disability than controls. Adjusting for demographic variables, impact of physical disability was significantly higher in patients with any neurologic diagnosis (including MS and epilepsy) (odds ratio [OR], 4.49; 95% confidence interval [CI], 1.56-12.96). In multinomial regression, the strongest association of physical disability impact was noted with epilepsy patients (OR, 5.17; 95% CI, 1.39-19.21).

Conclusions: The physical disability domain of the OHIP is more commonly associated with a neurologic diagnosis, including MS, and the association is strongest in patients with a diagnosis of epilepsy.

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Disclosure: Nothing to disclose

Keywords: Epidemiology of MS, Comprehensive care and MS

(S81) MULTIPLE SCLEROSIS RELAPSES IN THE EMERGENCY DEPARTMENT (DATA FROM RESUMES—RESOURCE UTILIZATION IN MS)

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Background: Multiple sclerosis (MS) research has focused on relapse prevention, but the urgent care needs of MS patients experiencing a relapse have not been comprehensively evaluated. Objectives: To evaluate the emergency medical needs of MS patients experiencing an MS relapse and the resources used in their care. Methods: All MS patient visits to the Mount Sinai Emergency Department (ED) between 2005 and 2007 were identified, and the charts systematically reviewed. Results: A total of 569 ED visits were made by 224 MS patients. Of the patients, 73.7% were female; the mean age was 47.7 years; and 54% needed an assistive device for mobility (Expanded Disability Status Scale [EDSS] score ≥6). Patients with relapsing-remitting MS (RRMS) comprised 42.4%, and only 50.5% of the RRMS patients were identified as being on a disease-modifying agent (DMA). The majority of ED visits were for non-neurologic complaints (424 ED visits, 74.5%). Of the 145 neurologic chief complaints (25.5%), the most common were weakness (46.2%), altered mental status (14.5%), numbness and vision loss (each 9.0%), and diplopia and seizure (each 3.4%). MS patients with seizures and altered mental status presented to the ED after a mean duration of symptoms of 1.1 and 1.8 days, respectively. Patients with weakness and vision loss waited a mean duration of 10.5 and 7.6 days, respectively, before coming to the ED. Seventy-five of the 569 ED visits (13.2%) were associated with a diagnosis of an MS relapse, and there were 43 admissions. Of the acutely relapsing patients who underwent magnetic resonance imaging (MRI), 61% had gadolinium-enhancing lesions. Eighty-four percent of patients received intravenous steroids. The mean length of stay for patients admitted for MS relapse was 6.5 days (median, 5 days; range, 1–24 days), with a total of 278 inpatient days for all MS relapses associated with admission by the ED.

Conclusions: MS patients utilizing the Mount Sinai ED have high levels of disability and appear to be undertreated with DMAs. Emergent neurologic presentations are a substantial portion of ED visits, although relapses constitute a small fraction. While MS patients with altered mental status and seizure presented to the ED promptly, patients with symptoms consistent with an MS relapse, including weakness and vision loss, waited more than a week to be evaluated. MS relapses continue to warrant the use of both ED and inpatient neurolgy resources, and improved patient education is needed to ensure that MS relapses are addressed expeditiously.

Disclosure: S. Krieger: Bayer Healthcare, Biogen Idec, EMD Serono (consulting fees); Novartis, Teva Neurosciences (honoraria). F. Lublin: Bayer Healthcare, EMD Serono (consulting fees); Pfizer (honoraria); Acorda Therapeutics, Biogen Idec, Genentech, Novartis, Teva Neurosciences, Genzyme, Sanofi-Aventis (other financial benefits). S. Oynhausen, C. Hannigan, Y. Bencosme, M. Alcauskas, M. Müller: Nothing to disclose.

Keywords: Relapse management in MS, Comprehensive care and MS, Service delivery in MS

(S82) DO CLINICAL FACTORS IMPROVE APPLICATION OF THE MULTIPLE SCLEROSIS SEVERITY SCORE TO INDIVIDUAL PATIENTS?

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Background: Physicians typically advise patients that the multiple sclerosis (MS) course is too variable to allow prediction for individuals. The Multiple Sclerosis Severity Score (MSSS), by combining the Expanded Disability Status Scale (EDSS) and disease duration, divides patient groups into prognostic deciles. Its developers contend that it cannot be used to predict disability in individuals. We assessed the impact of initial MSSS when combined with established prognostic factors on long-term outcome in individual patients.

Objectives: To assess whether the prognostic value of the
MSSS for individual patients is improved when combined with clinical factors. **Methods:** Patients followed by a single physician (AM) were assigned an MSSS at approximately annual visits. All patients seen in 2008 who had been followed for at least 8 years (mean, 12.1 years; range, 8–26 years) were included (n = 122). Charts were systematically reviewed, and MSSS and EDSS at initial and final evaluations were analyzed. We examined the likelihood of a patient remaining within 1 point on the MSSS scale. Stepwise logistic regression was used to evaluate the impact of prognostic factors. **Results:** At final evaluation, 44.3% remained within 1 point of their initial MSSS; 33.6% were in a lower decile (improved); and 22.1% were in a higher decile (worsened). Patients deviated up to 5.6 deciles better or worse than their initial MSSS. Sex, age at onset, functional system affected at onset (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, or cerebral), and degree of recovery from initial attack were evaluated to assess whether these factors predicted which patients varied by more than 1 decile from initial MSSS. None of the variables, individually or in combination, identified who had a better or worse prognosis than predicted by their initial MSSS. **Conclusions:** The MSSS calculated at initial presentation is a modestly accurate predictor of disease course, although a majority of patients did not remain in their expected decile at a mean of 12 years’ follow-up. Furthermore, taking into account established prognostic factors did not identify which patients had a better or worse prognosis than their initial MSSS decile. This counterintuitive result suggests that there is either too much stochastic variability or too many heretofore-unidentified prognostic variables to allow for precise application of the MSSS at the individual patient level.


**Keywords:** Natural history of MS

**MSSS**

**Posters**

**Disclosure:** Nothing to disclose

**(834) THE USEFULNESS OF THE EXPANDED DISABILITY STATUS SCALE IN PREDICTING NEUROPSYCHOLOGICAL FUNCTIONING IN MULTIPLE SCLEROSIS**

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**Background:** Patients with multiple sclerosis (MS) often exhibit cognitive deficits in multiple domains, including complex attention, information processing, executive functioning, processing speed, and memory. The literature is mixed regarding the predictive utility of the Expanded Disability Status Scale (EDSS) in cognition. **Objectives:** To examine the utility of the EDSS in predicting cognitive functioning in MS in an understudied demographic cohort. **Methods:** Patients (n = 69) enrolled in a multicenter longitudinal monitoring program were studied cross-sectionally. They were given the Minimal Assessment of Cognitive Function in MS (MACFIMS), a consensus neuropsychological battery with established reliability and validity. Physicians rated participants using the EDSS, a method of quantifying MS disability. Participants were 72% male and 53% African American with a mean (SD) age of 46.5 (9.2) years. Linear regressions were conducted examining the relationship between age, sex, race, EDSS Total Score (EDSS TS), and EDSS Functional System Score (FSS)—Cerebellar with specific MACFIMS tests.
Results: Linear regressions controlling for age, sex, and race found that greater impairment on the EDSS TS predicted poorer performance on visual (Brief Visuospatial Memory Test–Revised [BVMT-R] delayed recall, P = .05) and verbal (California Verbal Learning Test–Second Edition [CVLT-II] long delayed free recall, P < .01) memory, and efficiency of visual information processing (Symbol Digit Modality Test [SDMT] oral, P = .04). Greater impairment on EDSS-Cerebellar predicted poorer performance on visual (P < .03) and verbal memory (P < .01) and executive functioning (Delis-Kaplan Executive Function System [DKEFS] Sorting, P < .04). Neither EDSS TS nor EDSS-Cerebellar predicted word productivity or visuospatial judgment. Conclusions: The findings indicated that overall disability in MS predicted poorer performance on memory (verbal and visual) and processing speed tests. EDSS-Cerebellar predicted poorer performance on memory and executive functioning tests. The latter is consistent with the previously identified role of the cerebellum in learning/memory. Although this sample differs demographically (Afri- can American, male veterans) from those often studied in the literature, the cognitive pattern did not vary significantly. However, differential symptom manifestation of MS in diverse groups requires further investigation.

Supported by: United States Department of Veterans Affairs

Disclosure: Nothing to disclose

Keywords: Psychological issues and MS

(S85) POSTVOID RESIDUAL EVALUATION IN MULTIPLE SCLEROSIS PATIENTS

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Background: Over 80% of multiple sclerosis (MS) patients have symptoms of lower urinary dysfunction during the disease course, and 96% of patients with MS with more than 10 years of disease complain of a urinary symptom. One of the most common symptoms is retention, which is usually not perceived by the person. Comprehensive evaluation is essential for MS specialists to effectively manage these potentially life-disrupting symptoms. Objectives: This study was designed to identify MS patients with retention who are followed at home by the rehabilitation service and to evaluate the correlation between symptoms and postvoid residual (PVR). Methods: We studied 509 MS patients with Bladder Scan followed at home by the AISM Rehabilitation Centre. The following data were recorded: age, disease duration, Expanded Disability Status Scale (EDSS) score, symptoms (with a standardized questionnaire), current bladder management (therapy, aids), number of urinary tract infections in the last year, and urologic investigations. All data were analyzed with descriptive analysis, multifactorial analysis, and linear regression analysis. Results: Of 509 subjects, 352 were female (69.2%), while 157 were male (30.8%). Based on the urinary symptoms questionnaire, patients were divided into asymptomatic (55 subjects; 10.8%) and symptomatic (454 subjects; 89.2%) groups. The mean ± SD PVR for both groups was 131.38 ± 130.73 mL. The mean PVR for the asymptomatic group was 78.81 ± 97.93 mL, while in the symptomatic group it was 137.67 ± 132.81 mL. PVR analysis showed a high prevalence of PVR >100 mL in the whole MS population (symptomatic and asymptomatic groups). Statistical analysis showed no statistically significant correlation between all parameters considered and PVR with the exception of the retention symptom. Linear correlation showed a significant correlation between EDSS score and PVR. Conclusions: The results showed that about 90% of the MS population included in the study experienced bladder problems during the course of the disease. The high prevalence of PVR >100 mL in MS subjects underlined the importance of detecting bladder disturbances at an early stage of the disease in order to protect and preserve renal function. Lack of correlations between urinary symptoms and PVR and the high prevalence of urinary disorders suggest that the Bladder Scan should be used routinely as a screening device to detect retention in all MS subjects.

Supported by: Astra Tech

Disclosure: Nothing to disclose

Keywords: Nursing management in MS, Rehabilitation strategies and therapy and MS

(S86) DISEASE-MODIFYING DRUG THERAPY INITIATION PATTERNS IN NEWLY DIAGNOSED MULTIPLE SCLEROSIS PATIENTS

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Background: The Disease Management Consensus Statement recommends initiating disease-modifying drug (DMD) therapy following a definite diagnosis of multiple sclerosis (MS) to reduce relapses and slow progression. Objectives: The goal of this research was to compare the demographics, clinical characteristics, and treatment patterns for newly diagnosed MS patients in a commercial managed-care population who received DMD therapy versus those not receiving DMD therapy. Methods: A retrospective cohort study using administrative health-care claims from a database of US-based employers and health plans identified individuals newly diagnosed with MS (ICD-9-CM code 340.xx) and ≥18 years old during 2001 to 2007 to characterize them based on demographics, clinical characteristics, and pharmaco-economic issues. The study included only those with at least one DMD therapy claim during the study period with no MS diagnoses or treatment following a definite diagnosis of multiple sclerosis. The Cox model showed that overall disability in MS predicted poorer performance on memory (< .01) and executive functioning (< .04). Neither EDSS TS nor EDSS-Cerebellar predicted postvoid residual (PVR). The results showed that about 90% of the MS population included in the study experienced bladder problems during the course of the disease. The high prevalence of PVR >100 mL in MS subjects underlined the importance of detecting bladder disturbances at an early stage of the disease in order to protect and preserve renal function. Lack of correlations between urinary symptoms and PVR and the high prevalence of urinary disorders suggest that the Bladder Scan should be used routinely as a screening device to detect retention in all MS subjects.

Supported by: Astra Tech

Disclosure: Nothing to disclose

Keywords: Nursing management in MS, Rehabilitation strategies and therapy and MS
remained untreated, while over a quarter of treated patients stopped therapy and one-sixth experienced treatment gaps despite the risk of disease progression or a return of pretreatment disease activity.

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LEARNED NONUSE IN MULTIPLE SCLEROSIS


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Background: Multiple sclerosis (MS) commonly leads to reduced limb use in the real world despite retained movement ability. Reduced limb use may be conditioned by prolonged difficulty with limb movement and compensation by either another part of the body, an assistive device, or the help of a separate individual to conduct real-world tasks. The reduced limb use appears to involve a conditioned inhibition and can be termed “learned nonuse” (LNU). Nonuse has often been described for the lower extremities in MS but not for the upper extremities (UEs), perhaps because it has not formally been assessed. Learned nonuse in other neurologic disorders (eg, stroke, cerebral palsy) can be counteracted by a specific form of rehabilitation termed Constraint-Induced Movement therapy (CI therapy). Measuring UE nonuse in MS could benefit rehabilitation as well. Objectives: 1) To determine the test-retest reliability in hemiparetic MS of a measure of spontaneous use of the more impaired arm, the Motor Activity Log (MAL). 2) To quantify UE nonuse in hemiparetic MS based on comparison of laboratory measures of maximal movement ability and spontaneous use of the more impaired UE. Methods: 1) Ten individuals with hemiparetic progressive MS who reported intact ability to pick up small objects with the paretic hand but reduced spontaneous use of that hand were tested on the MAL on two occasions 1 week apart. 2) Nine of these individuals were evaluated in the laboratory on the Wolf Motor Function Test (WMFT) to quantify maximal movement ability of the paretic UE and on the MAL. The LNU index was calculated based on the difference between the WMFT and the MAL. Results: 1) The MAL had high test-retest reliability (intraclass correlation coefficient, 0.85). 2) All nine individuals who were tested on both the WMFT and the MAL had a positive LNU index, indicating greater movement ability of the paretic UE in the laboratory than its spontaneous use in the real-world setting. Conclusions: 1) The MAL, which can be used in the assessment of LNU, has high interrater reliability in MS. 2) The clinical impression of UE LNU in hemiparetic progressive MS can be confirmed and quantified with measures in the laboratory. These findings may help to advance rehabilitation research trials in MS to improve spontaneous UE use in the real-world setting.

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Disclosures: Nothing to disclose

Keywords: Disease-modifying treatment in MS

ALEMTUZUMAB INFUSION IN MULTIPLE SCLEROSIS: NURSING PERSPECTIVE ON INFUSION-ASSOCIATED REACTIONS

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Background: Alemtuzumab has demonstrated greater efficacy compared with subcutaneous interferon beta-1a in a trial with relapsing-remitting multiple sclerosis (RRMS) patients on relapse rate, sustained accumulation of disability, and improvement in disability scores compared with baseline. Alemtuzumab is an intravenous (IV) therapy given on 5 days for an initial cycle, followed a year later by a 3-day cycle. The initial treatment cycle of alemtuzumab was administered at a dose of 12 mg or 24 mg daily for 5 consecutive days, diluted in 100 mL of normal saline, and then IV-infused over a usual duration of 4 hours. On infusion day 1 through 3, the alemtuzumab infusion was preceded by an infusion of methylprednisolone 1000 mg diluted in 50 mL of normal saline given over a duration of 1 hour. Infusion-associated reactions (IARs) constitute a constellation of known symptoms following alemtuzumab infusions. Objectives: To present a nursing perspective on management of IARs following initial alemtuzumab infusion therapy in RRMS patients observed during investigative and clinical trials. Methods: Prior to initiation of therapy, an educational program regarding IARs was instituted. Patients were to be instructed about the risks and benefits of alemtuzumab infusion, its mechanism of action, and the infusion therapy process. An algorithm has been developed that outlines nursing measures for assessment and intervention of identified IARs. Patients were placed on fixed oral histamine blockade. Oral or IV antipyretics and antihistamines dosing protocols were developed. Specifics of the regimen and the relationship to reducing IARs will be presented.

Results: Nursing management with a diligent prophylactic/premedication regimen appeared to reduce the occurrence and intensity of the more common IARs, such as urticaria, pyrexia, myalgias, and headache, during and after the alemtuzumab infusion therapy period. Well-informed patients appeared to experience an anxiety level that decreased daily throughout the duration of the infusion process. Conclusions: Effective prophylaxis and management of IARs as well as a focused educational and adverse events management program are critical nursing interventions and essential for optimum-quality care.

Supported by: Genzyme

Disclosure: Nothing to disclose

Keywords: Nursing management in MS

PAST SUN EXPOSURE, VITAMIN D INTAKE, AND AGE AT ONSET AMONG VETERANS WITH MULTIPLE SCLEROSIS

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**Background:** Several studies have demonstrated that sun exposure and cod-liver oil or fish consumption, both of which are sources of vitamin D, during childhood and adolescence were associated with a reduced risk of multiple sclerosis (MS). However, the role of these environmental agents in the timing of disease symptom onset is not known. 

**Objectives:** To examine whether sun exposure and vitamin D intake (diet and supplements) during childhood and adolescence were associated with delayed onset of MS in a national cohort of veterans with MS.

**Methods:** Patients with MS were recruited from the Veterans Health Administration (VHA) Multiple Sclerosis Surveillance Registry, a nationally representative sample of veterans with MS. Participants reported their age at MS symptom onset, disease subtype, histories of residential locations, sun exposure, and vitamin D–related food and supplement intake by 5-year age periods. Cumulative past sun exposures were estimated for the fall/winter and spring/summer seasons. Solar radiation levels were estimated based on the latitude, altitude, and UV count of self-reported residence.

Multiple regression was used to examine the associations between these variables and the age at MS onset, controlling for known covariates.

**Results:** Among patients with relapsing MS (N = 948), low sun exposure in the fall/winter during the age period of 6 to 15 years was significantly associated with early onset of disease symptoms (by an average of 2.3 years; P = .01) for those who resided in low-to-medium solar radiation areas. Intake of cod-liver oil during childhood was associated with delayed onset of MS symptoms by 3 years (P = .01).

**Conclusions:** The current study provides the first evidence that low vitamin D status during childhood and early adolescence, through low sun exposure or no supplement intake (eg, cod-liver oil) may be related to early onset of MS symptoms.

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**Disclosure:** Nothing to disclose

**Keywords:** Epidemiology of MS

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**(S90) FEELINGS OF GUILT ARE ASSOCIATED WITH BOWEL AND BLADDER INCONTINENCE AND LOWER LIFE SATISFACTION IN PATIENTS WITH MULTIPLE SCLEROSIS**

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**Background:** The New York State Multiple Sclerosis Consortium (NYSMSC) uses a patient-response surveillance tool called LifeWare, which addresses patient-perceived disability, emotional state, and life satisfaction. The question “Are you feeling . . . blaming yourself or guilt?” has been answered by >8000 multiple sclerosis (MS) patients. However, the implications of feeling guilt have not been studied, despite evidence linking it to depression and lower quality of life (QOL). Studies have linked shame to continence issues in non-MS and MS patients, but guilt has not been examined. Patients who suffer from bowel (Bwllnc) and bladder (Bldlncl) incontinence, or report a lower life satisfaction (LifeSat), may feel more guilt than those without continence issues or with higher LifeSat. 

**Objectives:** To explore whether patients reporting Bwllnc and Bldlncl are more likely to experience greater feelings of guilt; and to explore whether patients reporting lower LifeSat also report stronger feelings of guilt.

**Methods:** Analysis was based on longitudinal data of the NYSMSC registry, comprising patients from 16 MS centers in New York State, organized to prospectively collect demographic and clinical data. The guilt variable was dichotomized into those reporting “Moderate to Extreme” feelings of guilt and those feeling “None to Mild.” The Rasch variables for Bwllnc and Bldlncl were dichotomized into “None to Mild Limitation” and “Mild to Severe Limitation.” The LifeSat variable was dichotomized into “more satisfied” and “less satisfied” with life. Chi-square tests were run on Guilt vs. Bwllnc, Bldlncl, and LifeSat.

**Results:** Data from registration of 6953 patients were analyzed (74% female, 68% relapsing-remitting MS): 1745 (25%) reported mild-to-severe Bwllnc, and 2795 (40%) reported mild-to-severe Bldlncl. For LifeSat, 2094 (30%) reported being less satisfied. Bwllnc was predictive of stronger guilt (odds ratio [OR], 1.82; 95% confidence interval [CI], 1.6-2.1), as was Bldlncl (OR, 1.78; 95% CI, 1.6-2.0). Less LifeSat was strongly associated with guilt (OR, 3.38; 95% CI, 3.0-3.9).

**Conclusions:** The effect of bowel and bladder incontinence on feelings of guilt and the association between guilt and life satisfaction warrant further investigation. Understanding these feelings and assessing how to better support patients who are at risk for them may lead to a better QOL for MS patients.


**Keywords:** Psychosocial issues in MS, Quality of life in MS, MS and the caregiver/family

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disability, endorsed by participants in all disability groups: 1) Participant Identity: how participants described themselves and their lives with a disability; 2) Physical Pathways: decline in physical functioning; 3) Psychosocial Pathways: adaptations to disability, the development of emotional well-being and strategies to deal with disability; 4) Changing Health Care: improvement noted over time in health-care services; and (5) Concerns About the Future: uncertainty about the potential course of disability. **Conclusions:** Aging with MS and other disabilities was characterized by multiple pathways. These were similar for all individuals across disability groups. Some, including positive psychosocial adjustment and medical advancements, were favorable. Others, including physical decline, were not. The coexistence of high quality of life with physical decline is consistent with literature on older adults, and future research should focus on factors that may contribute to buffering the psychological impact of physical decline. Research is also necessary to determine whether there are perceived differences regarding aging with disability by disability type.

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**Disclosure:** Nothing to disclose

**Keywords:** Psychological issues and MS, Psychosocial issues in MS, Quality of life in MS

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**PERICYTE, A NOVEL NEW ADULT STEM CELL, AMELIORATES AUTOIMMUNE ENCEPHALOMYELITIS**

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**Background:** Rouget described the pericyte (PC) in 1873 as a contractile motile cell that surrounds the capillary in a tunic-like fashion. PCs are regulatory cells in the blood-brain barrier. They regulate capillary blood flow, vascular integrity, and angiogenesis. They are also a possible source of adult stem cells. Myelin oligodendrocyte glycoprotein (MOG)–immunized experimental autoimmune encephalomyelitis (EAE) mice were injected intravenously (IV) with 3- to 7-day-old PCs labeled with a fluorescent (IF) probe. **Objectives:** We hypothesize that PCs can be used in therapeutic methods in central nervous system (CNS) diseases (eg, multiple sclerosis). To investigate the use of PCs in stem cell replacement therapy, we used an animal model of chronic CNS inflammation: EAE. **Methods:** MOG-induced EAE: Female C57BL/6 mice were immunized with 100 µL (200 µg) of MOG in complete Freund’s adjuvant (CFA). Control mice received CFA without MOG. All mice were injected intraperitoneally with 200 µL of pertussis toxin (200 ng) after immunization and 2 days later. Mice were scored daily: 0 = no symptoms; 1 = flaccid tail; 2 = paresis of hind limbs; 3 = paralysis of hind limbs; 4 = quadriplegia; 5 = death. Isolation of microvessels (MVs) and PCs: Mouse CNS capillaries were prepared as described previously. Homogenized tissue was centrifuged and the pellet resuspended in DMEM/dextran. The suspension was centrifuged and the pellet resuspended and filtered through a series of meshes. MVs were collected, resuspended, and incubated overnight. PC pellet was resuspended in DMEM and plated. PC labeling and injection: PCs were removed from culture dishes, washed, pelleted, and resuspended with IF probe. The labeled PCs were injected IV (1–2 x 10⁶) into the mice. Tissue was harvested after 24 hours and prepared for fluorescence-activated cell sorting (FACS) analysis. **Results:** Single cell suspensions were incubated with antibody directed against indicated markers. **Conclusions:** Aging with MS and other disabilities was characterized by multiple pathways. These were similar for all individuals across disability groups. Some, including positive psychosocial adjustment and medical advancements, were favorable. Others, including physical decline, were not. The coexistence of high quality of life with physical decline is consistent with literature on older adults, and future research should focus on factors that may contribute to buffering the psychological impact of physical decline. Research is also necessary to determine whether there are perceived differences regarding aging with disability by disability type.

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**Disclosure:** Nothing to disclose

**Keywords:** Immunology and MS

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**RELAPSING MULTIPLE SCLEROSIS PATIENTS’ EXPERIENCE WITH TYSABRI: A PHENOMENOLOGICAL INVESTIGATION**

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**Background:** This phenomenological investigation was undertaken to gain a better understanding of multiple sclerosis (MS) patients’ experience with Tysabri treatment and its impact on their quality of life (QOL). **Objectives:** Information will be used to educate professionals involved in MS patient care as well as patients and families considering treatment with Tysabri. **Methods:** Twenty patients with MS who were receiving Tysabri treatment were recruited by the care providers at the Baird MS Center in Buffalo, NY. Patients were invited to participate if they had relapsing MS, had received at least six treatments with Tysabri, and could articulate their experience. The Atlas.ti qualitative data-analysis program was used to manage the data. Heideggerian phenomenology methods were applied. **Results:** Ten major themes emerged from the data analysis: QOL, processes associated with Tysabri treatment, switching, uncertainty, fear, decision points, avoidance, side effects, support, and improvement. QOL was a pervasive theme among all MS participants and is defined in relation to their ability to live a “normal” life without interruption from MS symptoms. Tysabri contributed to a good QOL by “allowing them to get back into the game of life” and liberating them from the burdens of other treatments. Fear is part of the experience for everyone. Fear of the future appears to be the motivating force for patients to consider medicines with risks such as Tysabri. The MS experience is wrought with decision points throughout the disease. Patients discuss motivations behind the decision process and influences from other people. Side effects of medicines are mentioned by all. Many try to balance the burden of coping with side effects with the benefits the drugs may offer. Support comes in many forms. Family and provider support are crucial. Many find peer support important while receiving infusions. Most participants note an “improvement” since starting Tysabri. Those who do not improve question whether the drug is working because they hear about others.
(S94) IMPROVEMENT IN MULTIPLE SCLEROSIS–RELATED DISABILITY IS ASSOCIATED WITH IMPROVEMENT IN QUALITY OF LIFE

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Background: Among multiple sclerosis (MS) patients with baseline Expanded Disability Status Scale (EDSS) scores ≥2.0, those treated with natalizumab were significantly more likely to experience sustained improvement in disability over 2 years, compared with patients who received placebo (29.6% vs. 18.7%; hazard ratio, 1.69; P = .006). Disability improvement, which represents a new paradigm for defining successful MS treatment, may be associated with improvements in patient-reported outcomes. Objectives: To assess the relationship between disability improvement measured by the EDSS and changes in patient-reported quality of life (QOL) in patients with MS. Methods: Post hoc analyses were conducted on data from the AFFIRM study of natalizumab. Based on change in EDSS scores sustained for 12 weeks, disability was categorized as progressed (+1.0 point), stable, or improved (−1.0 point) over 2 years. Patient-reported QOL was prospectively evaluated using the Physical Component and Mental Component Summary (PCS and MCS) scores of the 36-item Short Form Health Status Survey (SF-36) and the Visual Analogue Scale (VAS) of well-being. A 5-point change in PCS or MCS score was considered clinically meaningful. Mean changes in SF-36 and VAS scores from baseline to 2 years were compared across disability groups by analysis of covariance, adjusted for baseline QOL scores. Results: Based on change in EDSS scores sustained for 12 weeks, disability was categorized as progressed (+1.0 point), stable, or improved (−1.0 point) over 2 years. Patient-reported QOL was prospectively evaluated using the Physical Component and Mental Component Summary (PCS and MCS) scores of the 36-item Short Form Health Status Survey (SF-36) and the Visual Analogue Scale (VAS) of well-being. A 5-point change in PCS or MCS score was considered clinically meaningful. Mean changes in SF-36 and VAS scores from baseline to 2 years were compared across disability groups by analysis of covariance, adjusted for baseline QOL scores. A χ² test was used to analyze clinically meaningful changes. Results: Sustained improvement in disability was significantly associated with improvements in QOL at 2 years, regardless of treatment group. For patients whose disability progressed, stabilized, or improved, mean changes in PCS scores were −3.05 ± 8.86, 0.38 ± 8.17, 2.42 ± 7.53 (P < .0001); mean changes in MCS scores were −0.93 ± 11.04, 0.32 ± 11.28, 4.08 ± 11.31 (P = .0078); mean changes in VAS scores were −11.78 ± 29.34, −1.18 ± 23.56, 3.04 ± 23.98 (P < .0001), respectively. Analyses revealed a significant association between disability groups and clinically meaningful changes in PCS (P < .0001) and MCS (P = .0250) scores. Conclusions: Sustained improvement in disability was associated with improvement in patient-reported outcomes, as captured by changes in PCS, MCS, and VAS scores. Results suggest that sustained improvement in EDSS score is a meaningful outcome, as it correlates with patient-reported QOL.

Supported by: Biogen Idec
Keywords: Quality of life in MS, Disease-modifying treatment in MS

(S95) WORK ABSENTEEISM AND MOBILITY LEVELS IN THE NARCOMS REGISTRY

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Background: Many people suffering from multiple sclerosis (MS) make changes in their employment status as a result of their MS symptoms, and increasing workplace absenteeism may precede these changes. Little is known about the factors associated with work absences and the degree to which mobility contributes to these changes. The NARCOMS Registry surveys participants biannually and collects self-reported data on factors related to employment and disease-related variables. Objectives: To explore how changes in mobility influence absenteeism in the workplace for people with MS using data from the NARCOMS Registry. Methods: The NARCOMS Registry participants included in this analysis were <65 years old, completed both Fall 2004 and Fall 2007 update surveys, and worked full time in 2004 (n = 156). Absenteeism was assessed as the reported number of workdays missed over the past 6 months. Mobility level was based on a self-reported 6-point Performance Scale score ranging from 0 (normal) to 6 (total gait disability). Regression analysis was used to predict the average number of days absent per change in mobility level. Results: After controlling for marital status, gender, and the number of missed days in 2004, a one-level change in the mobility scale resulted in 5.9 days missed every 6 months from 2004 to 2007. While the full list of covariates explained 50.9% of the variance, the only significant identified predictors were change in mobility status and number of missed days in 2004. Conclusions: This analysis found that a one-level change in mobility score correlated with approximately an additional week of missed work during a 6-month time frame. Employees with MS may have to forfeit more than the allotted sick leave in order to cover these extra missed days, potentially leading to a shift to part-time employment or unemployment.

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(S96) MULTIPLE SCLEROSIS PATIENTS PREFER HIGH-DOSE ORAL PREDNISONE TO TREAT ACUTE RELAPSES

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Background: High-dose corticosteroid pulses for 3 to 5 days are the current standard for the treatment of acute relapses in multiple sclerosis (MS). Recent evidence supports the use of 1250 mg of oral prednisone (OP) as an alternative to intravenous methylprednisolone (IVMP). The highest single dose preparation of OP presently available is a 50-mg tablet, requiring patients to take 25 tablets a day. Questions regarding acceptability of and compliance with this oral regimen have been raised. Objectives: To determine whether MS patients are compliant with 1250 mg of OP daily for acute relapses and patients’ opinion regarding OP versus IVMP.

Methods: Between November 1, 2008, and December 31, 2009, all MS patients evaluated and diagnosed with an acute relapse in the London (Ontario) MS clinic were identified. If treatment with OP was initiated, subjects were given a two-page survey to be mailed to the clinic anonymously after completing treatment. Subjects presenting more than once during this time interval were surveyed only once. Seven days later, subjects were reminded by a phone call to complete and return the survey. Results: Sixty-eight MS relapses were diagnosed and treated with corticosteroids in 66 MS subjects, of which 60 (58 subjects) were treated with 1250 mg of OP. Fifty surveys were returned (86.2%). Most subjects were between 31 and 50 years of age (65.3%), were female (70.0%), and had relapsing-remitting MS (88.0%). The mean ± SD disease duration was 7.5 ± 7.4 years. Only one subject was unable to take all the required tablets, and 73.5% reported taking all 25 tablets at once. Commonly reported adverse events included insomnia (60%), increased appetite (20%), and irritabile mood (18%), although 22% experienced no adverse events. Two-thirds of subjects (66.0%) indicated a preference for OP instead of IVMP for future relapses, with convenience being the most cited reason, while 24% indicated no preference or did not respond. Conclusions: High-dose (1250 mg) oral prednisone is an acceptable therapy for MS patients for the treatment of acute relapses. Most patients prefer OP instead of IVMP, and noncompliance was not an issue.

Disclosure: Nothing to disclose

Keywords: Quality of life in MS, Symptomatic treatment of MS

(S97) FATIGUE AND DEPRESSION ARE INDEPENDENT PREDICTORS OF NATURALLY OCCURRING CHANGES IN PHYSICAL ACTIVITY IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Background: There is consistent and strong evidence for a high prevalence of physical inactivity among people with multiple sclerosis (MS). We have identified fatigue and depression as cross-sectional, inverse correlates of physical activity in people with relapsing-remitting MS (RRMS). Objectives: This study examined those two symptoms as correlates of naturally occurring changes in physical activity across time in people with RRMS. We expected that worsening of both fatigue and depression would predict reductions in physical activity across a 6-month period of time. Methods: The sample included 272 individuals with a definite diagnosis of RRMS. The participants completed the Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS), Godin Leisure-Time Exercise Questionnaire (GLTEQ), and International Physical Activity Questionnaire (IPAQ) on two occasions separated by 6 months. The data were analyzed using a panel model in Mplus. Results: The panel model included change in fatigue and depression as predictors of change in physical activity behavior across the 6-month period. The panel model provided an excellent fit for the data ($\chi^2 = 24.00$, df = 15, $P = .07$, comparative fit index [CFI] = .98, standardized root-mean-square residual [SRMR] = .04), and there were direct paths between changes in fatigue (path coefficient, $β = -0.09$) and depression (path coefficient, $β = -0.12$) with change in physical activity. The path coefficients indicated that 1-SD increases in fatigue and depression were associated with 0.09- and 0.12-SD reductions in physical activity, respectively. Conclusions: Such findings provide support for fatigue and depression as independent predictors of naturally occurring changes in physical activity among people with RRMS. Researchers might consider targeting those variables as part of an intervention for reducing the high rate of physical inactivity in this population. Supported by: National Multiple Sclerosis Society (RG 3926A2/1)

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

(S98) THE NATURE OF AND REASONS FOR MULTIPLE SCLEROSIS THERAPY CHANGES IN PATIENTS UNDERGOING ANTIBODY TESTING

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Background: A recent study found that the inclusion of routine antibody testing for multiple sclerosis (MS) patients receiving interferon beta (IFNB) therapy significantly affected subsequent therapy choices. Objectives: Evaluate the nature of and reasons for therapy change in patients who participated in either scheduled antibody testing or usual patient-care conditions and experienced a change in MS therapy. Methods: MS patients on IFNB (1–4 years) were enrolled in a 12-month open-label study. Patients were...
randomized into either the Regularly Scheduled Antibody Testing arm (3 BAB and NAb tests within 9 months) or the Usual Care Arm (blinded BABs and NAb tests at baseline and usual patient care). Both arms had optional testing at 12 months. **Results:** Patients in the Antibody Testing arm \( (n = 651) \) and the Usual Care arm \( (n = 565) \) had a mean disease duration of 8.5 years and a mean of 2 years on IFNs. The proportion of therapy change differed significantly between the two arms: 19.5% of patients in the Antibody Testing arm versus 14.2% of patients in the Usual Care arm \( (P < .0069) \). No differences were found in the proportions of therapy change within each study arm according to the length of time on IFNs \( (12-24 \text{ months vs.} >24 \text{ months}) \): 19.2% and 19.8% for the Antibody Testing arm and 15.3% and 12.9% for the Usual Care arm, respectively. There were significant differences in the nature of change for patients between the two arms; a greater number of people in the Antibody Testing arm started \( >1 \) courses of steroids for relapses \( (P = .0022) \) and started glatiramer acetate \( (P = .0028) \). Clinical worsening was the most frequent reason for therapy change in both arms; NAb results was the second most frequent reason in the Antibody Testing arm. Eighty-five patients in the Antibody Testing arm had antibody titers greater than 100. Of them, NAb results was indicated as a reason for change for 37 patients \( (44\%) \), clinical worsening for 22 patients \( (26\%) \), and magnetic resonance imaging (MRI) changes for 16 patients \( (19\%) \). **Conclusions:** The availability of antibody testing increased the number of therapy changes. For patients who had antibody testing and had a high titer of antibodies, the results of the antibody tests were more often indicated as a reason for therapy change.

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Keywords: Disease-modifying treatment in MS, Immunology and MS

**S99)** **INJECTION PAIN DECREASES WITH NEW 0.5-ML FORMULATION OF GLATIRAMER ACETATE**

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**Background:** Daily glatiramer acetate (GA) 20 mg/1.0 mL is a first-line treatment for relapsing-remitting multiple sclerosis. In an effort to reduce the occurrence of injection pain and injection site reactions, an injection volume of 0.5 mL was formulated. **Objectives:** To compare the patient-reported pain and injection site reactions associated with a subcutaneous injection of a 20 mg/1.0 mL formulation of GA versus a 20 mg/0.5 mL GA formulation. **Methods:** Patients \( (N = 148) \) enrolled in an open-label, randomized, two-arm, single cross-over study. Half of the patients \( (n = 76) \) were randomized to inject 20 mg/1.0 mL daily for the first 14-day period (period 1). The other half of the patient group \( (n = 72) \) injected 20 mg/0.5 mL daily during period 1. During the second 14-day period (period 2), the groups switched their injection volume formulation; the first group injected 20 mg/0.5 mL GA daily and the second group injected 20 mg/1.0 mL GA daily. Patients completed a home diary reporting pain occurring immediately after injection and at 5 minutes after injection, as well as the presence and severity of injection site reactions within 24 hours of injection. Safety, tolerability, clinical, and laboratory assessments occurred at the end of each period. **Results:** Significant decreases in pain immediately after injection and at 5 minutes after injection were reported by patients when injecting 20 mg/0.5 mL GA compared with injecting 20 mg/1.0 mL GA \( (P < .0001) \). Patients also reported less severe injection site reactions \( (P < .0001 \text{ at } 5 \text{ minutes and } 24 \text{ hours post-injection of the } 20 \text{ mg/0.5 mL GA formulation. Although the presence of injection site reactions (swelling, redness, itching, lumps) was not high for either formulation, a significant decrease was observed at } 5 \text{ minutes and at } 24 \text{ hours for the } 20 \text{ mg/0.5 mL injections } (P < .0001 \text{ and } P < .0001 \text{, respectively). A total of } 12.5\% \text{ of patients when injecting } 20 \text{ mg/1.0 mL and } 18.1\% \text{ when injecting } 20 \text{ mg/0.5 mL reported adverse events; none reported serious adverse events. There were no unexpected laboratory issues.}**

**Conclusions:** Patients reported less pain and fewer injection site reactions when using the 20 mg/0.5 mL GA formulation compared with the 20 mg/1.0 mL GA formulation. The lower-volume formulation offers a more tolerable option for patients using subcutaneous injections of GA.

**Supported by:** Teva Neuroscience, Kansas City, MO

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Keywords: Disease-modifying treatment in MS, Relapse management in MS, Immunology and MS

**S100)** **MODERATE PHYSICAL ACTIVITY IS ASSOCIATED WITH INCREASED BONE DENSITY IN MULTIPLE SCLEROSIS**

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**Background:** People with multiple sclerosis (MS), including men and premenopausal women, have an increased risk of reduced bone mineral density (BMD) and fractures. Interestingly, glucocorticoid use in MS does not appear to
consistently result in reduced BMD. There is evidence that low vitamin D (25[OH]D) and the suggestion that reduced physical activity (PA) negatively affect BMD in MS. Depression, decreased heart rate variability (HRV), and elevated cortisol are known to be associated with decreased BMD and are also common in people with MS. **Objectives:** The aim of this study was to determine associations of Vit D, PA, cortisol, depression, and HRV with BMD in people with MS. **Methods:** We tested 18 people with MS (13 female, 5 male; median Expanded Disability Status Scale [EDSS] score, 2) and 22 control (C) subjects (16 female, 6 male). Depression (Beck) and the Multiple Sclerosis Functional Composite (MSFC) scores were obtained from all. BMD of the lumbar spine (L2-L4) and femoral neck (mean left and right) was measured with dual-energy X-ray absorptiometry (DEXA). Vit D was measured from serum, and cortisol from a saliva sample (11:00 p.m., enzyme immunosay). HRv was analyzed as the SD of the RR interval, and low-frequency/high-frequency (LF/HF) ratio was obtained from a 10-min supine rest electroencephalogram. Physical activity was measured with accelerometers worn for 7 days around the waist and recorded as raw units. Physical activity was characterized as sedentary, light, moderate (mod), hard, and very hard by accepted cutoffs. Analysis was by unpaired t tests and Pearson correlations. Data are mean (SE). The statistical significance level was P ≤ .05. **Results:** MS subjects compared with C subjects reported greater depression (MS, 1.1[2]; C, 0.3[1]; P = .001) and had lower MSFC scores (MS, 1.9 [0.2]; C, 2.8 [0.1]; P < .001). There were no differences between groups in BMD, Vit D, cortisol, or measures of HRV. Among PA, mod PA differed between groups (MS, 16[3] units; C, 32[5]; P = .015) and was correlated to femoral BMD in the MS group (r = 0.53, P = .02) but not the C group (r = −0.16, P = .50). EDSS score was also correlated to femoral BMD (r = −0.50, P = .04). No relationship was observed between mod PA or EDSS and L2-L4 in the MS or C group. Neither Vit D, cortisol, depression, nor HRV was correlated to BMD in the MS or C group. **Conclusions:** In people with MS replete with Vit D, mod PA but not cortisol, depression, or HRV may contribute to BMD.

**Supported by:** National Multiple Sclerosis Society grant PP1509

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS

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**(S101) TRANSITIONING A PATIENT FROM RESEARCH TO CLINICAL CARE: A MODEL FOR HANDOFF FOR MULTIPLE SCLEROSIS TRIAL CENTERS**

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**Background:** Multiple sclerosis (MS) research trials can last as long as 4 years or more. This can create gaps in a patient’s clinical record. As more medications are approved by the US Food and Drug Administration, managing a patient has become increasingly complex, because the newer agents not only appear more potent but may have increased risks and potentially serious complications. Research participants want to be informed about their condition, the treatment, and its effect on their health. **Objectives:** This model provides for a smooth transition from research to clinical care and can limit gaps in clinical data. **Methods:** To provide important data to the patient and his or her clinical neurologist at exit from the study, a form letter is provided to the patient and neurologist that contains all of the following pertinent information from the study: 1) MS-specific assessment measures, physical examination data, and any other procedures or radiologic testing; 2) history of relapses in the study and treatments provided; 3) treatment arm and dosing; 4) any adverse events experienced. Magnetic resonance imaging (MRI) scans (radiology files) are also provided. **Results:** This procedure was initiated in our MS Center in January 2009, with the expectation that both written and oral data records would be presented to each participant and the written record and films sent to the clinical neurologist anytime a patient exited a study. **Conclusions:** With this sharing of data, potential gaps in medical treatment due to disease duration and use of numerous medications over time, lack of information from previous study participation, and cognitive and mood issues can be avoided. This can also ease the return to traditional clinical care.

**Disclosure:** Nothing to disclose

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**(S102) TARGETTED PSYCHOEDUCATIONAL INTERVENTION TO IMPROVE RELAPSE-ASSESSMENT SKILLS IN MULTIPLE SCLEROSIS: A PILOT STUDY**

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**Background:** People with relapsing-remitting multiple sclerosis (RRMS) can experience a substantial amount of uncertainty concerning the differentiation of relapses from pseudo-attacks. This can lead to delayed reporting of true relapses and subsequent underutilization of effective care services, or over-reporting of pseudoattacks, which can result in overutilization of specialist and emergency-care services, unnecessary steroid treatments, and unneeded disruption of work or other activities. This study aims to conduct pilot testing of an educational intervention designed to help patients with RRMS gain skill and confidence in relapse assessment. **Objectives:** To determine whether a targeted educational intervention will improve relapse-assessment skills and illness-control self-efficacy in a sample of RRMS patients. **Methods:** This is a 2-week, single-group, no placebo, time-series pilot study with a convenience sample of 50 participants. RRMS patients at Dartmouth-Hitchcock Medical Center were offered participation and provided informed consent. Participants completed an evaluation of relapse assessment and reporting accuracy for a series of computer-based scenarios and also completed the Multiple Sclerosis Self-Efficacy Scale (MSSE). Then, participants were given the “24-14-10 Rule” and completed the relapse-assessment scenarios again. Two weeks later, participants again completed the MSSE and the relapse scenarios. The primary end point was change in MSSE scores. The secondary end point was cumulative relapse-assessment accuracy percentage. **Results:** Thirty-three participants completed the study. There was no significant change between baseline and week 2 MSSE control subscale scores (P = .23). However, there were significant improvements in cumulative relapse-identification accuracy percentages between the first and second time points (P < .05), and further improvement occurred at 2 weeks post-intervention (P < .01). **Conclusions:** The intervention did not improve MSSE control sub-
scale scores, but did improve relapse-identification accuracy on computer-based scenarios and was especially helpful in improving assessment accuracy for negative relapse scenarios (pseudoadvances).

Supported by: Evaluative Clinical Sciences Division, Multiple Sclerosis Center at Dartmouth


Keywords: Nursing management in MS, Psychosocial issues in MS, Relapse management in MS

(S103) CHALLENGES IN THE TREATMENT OF MOBILITY LOSS AND WALKING IMPAIRMENT IN MULTIPLE SCLEROSIS

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Background: Several research studies in recent years show that mobility loss and walking impairment are significant concerns among people living with multiple sclerosis (MS). Despite these findings, many people with MS lack essential information and guidance on how to discuss and address mobility loss with health-care providers. MS experts find that ongoing challenges related to the assessment and management of mobility loss can have a direct impact on outcomes and patient quality of life. Factors that can affect strategies to prevent and treat mobility in MS include prevalent gaps in patient education and understanding, variations in treatment team experience, challenges in efforts to coordinate care and share information across service areas, a shift away from treatment focus on symptom management, complex and imprecise terminology related to mobility issues, lack of accurate baseline assessments of mobility, inadequate incorporation of exercise into patient treatment regimens, and insufficient education about patient expectations related to treatment.

Objectives: To identify specific actions that nurse practitioners, patients, and care partners should consider to improve the assessment, diagnosis, and treatment of mobility loss and walking impairment in people with MS.

Methods: In June 2009 a panel of MS experts met to review current standards of care in the treatment of mobility loss in MS.

Results: The panel of MS experts identified specific strategies in the assessment and treatment of mobility loss in MS, including exercise, physical therapy and rehabilitation, patient awareness, ongoing assessment of mobility and walking function, and a focus on symptom management.

Conclusions: A decline in patient health associated with disease progression in MS can have a profound negative effect on mobility, quality of life, and independence. Lack of focus on symptom management can also increase the burden on care partners, who must expand essential support for patients. Members of the health-care team can take steps to address mobility loss in MS. Patients and care partners can also take more active roles in discussing and addressing mobility loss with a care team.

Supported by: The meeting was hosted by the International Organization of Multiple Sclerosis Nurses and was supported by a grant from Acorda Therapeutics.

Disclosure: Bayer Healthcare Pharmaceuticals, Biogen Idec, EMD Serono, Inc, Genentech, Inc, Novartis Pharmaceuticals Corp, Pfizer Inc, Teva Neuroscience, Inc (consulting fees); Acorda Therapeutics (honouraria)

(S104) EXPLORING THE POTENTIAL OF NINTENDO WII TO PROMOTE EXERCISE IN PEOPLE WITH MULTIPLE SCLEROSIS

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Background: The benefits of regular exercise are well established among people with mild-to-moderate symptoms of multiple sclerosis (MS). However, the population with MS is considered extremely inactive. Innovative strategies that promote routine exercises are needed for people with MS. One such innovative strategy may be the use of interactive video game technology.

Objectives: To evaluate whether providing access to the video game Nintendo Wii Fit promotes routine exercise, and by extension increases quality of life and fitness among people with MS.

Methods: A repeated-measures time-series design was conducted with 30 people who had a physician-confirmed diagnosis of relapsing-remitting MS. The Physical Activity and Disability Survey, 36-item Short Form Health Status Survey (SF-36), Modified Fatigue Impact Scale, and Barrier Self-Efficacy Scale were administered six times over the course of the 19-week study. To establish a baseline control period, questionnaires were administered three times at 2-week intervals before participants had access to Wii Fit. After participants had access to Wii Fit, questionnaires were administered an additional three times at 6-week intervals to compare scores with the baseline control period. Semi-structured interviews were conducted before and after access to Wii Fit. Physical assessments were also conducted twice before participants had access to Wii Fit and once 6 weeks after they had access to Wii Fit. Physical assessments consisted of validated tests of strength, balance, and aerobic endurance.

Results: Data collection and analyses will be completed in April 2010. Preliminary results indicate that a home exercise program using Nintendo Wii Fit was well tolerated, and very few adverse events were reported. Preliminary qualitative analyses indicate that participants enjoyed using Wii Fit to engage in exercise and reported improvements in balance and mobility as well as a decrease in fatigue.

Conclusions: Providing access to Nintendo Wii Fit may be a potential strategy to promote exercise in people with MS.

Supported by: Consortium of Multiple Sclerosis Centers and National Multiple Sclerosis Society, mentor-based fellowship (MB 0009)

Disclosure: Nothing to disclose.

Keywords: Symptomatic treatment of MS, Rehabilitation strategies and therapy and MS

(S105) SHORT-TERM AND LONG-TERM SAFETY AND TOLERABILITY OF INTERFERON BETA-1B IN MULTIPLE SCLEROSIS

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International Journal of MS Care
Background: Multiple sclerosis (MS) is a chronic disease that spans decades, necessitating long-term therapy. Treatment tolerability may affect adherence, influencing long-term outcomes. Some safety and tolerability data reported in the interferon beta-1b (IFN-β-1b) treatment arm of key clinical trials are reviewed. Objectives: To examine the safety of IFN-β-1b (Betaseron) 250 µg in short- and long-term clinical trials in MS. Methods: Adverse events (AEs) from the BENEFIT, BEYOND, and 16-Year Long-Term Follow-Up (LTF) study databases are summarized using descriptive statistics. BENEFIT explored the effects of IFN-β-1b in patients with a first event suggestive of MS. BEYOND had IFN-β-1b and glatiramer acetate (GA, Copaxone) treatment arms. LTF revisited patients 16 years after initiation of the original registration trial. Results: Flu-like symptoms (FLSs) and injection site reactions (ISRs) were the most commonly reported AEs. FLSs were transient in nature and controlled with dose titration and use of nonsteroidal anti-inflammatory drugs. For example, in BENEFIT, FLSs were reduced by 70% over the first 2 years. Similarly, in BEYOND, 38% of IFN-β-1b-treated patients experienced FLSs during year 1; only 17% did after year 1. In BENEFIT, there was a 35% decline in ISR incidence from year 1 (46%) to year 2 (30%). Depression incidence was similar in IFN-β-1b and GA treatment arms in BEYOND. Thyroid measures were comparable across patient cohorts in the BENEFIT and LTF studies. Cancer prevalence was similar across treatment and placebo arms in all studies. Among patients using IFN-β-1b continuously in the 2 years prior to LTF, 10.1% experienced elevated liver transaminases versus 3.4% among those not using IFN-β-1b. This difference was of borderline significance ($P = 0.054$) and in keeping with previous reports. At LTF, mortality was lower in patients originally assigned to IFN-β-1b than to placebo (6 vs. 20 deaths). An intermediate number of deaths (9) was seen in the IFN-β-1b 50 µg group. Conclusions: AEs most common to IFN-β-1b are generally transient and of mild-to-moderate intensity. IFN-β-1b has a well-established safety profile based on long-term experience. Newer MS therapies will have to be measured against this favorable risk-benefit balance.

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Keywords: Disease-modifying treatment in MS, Quality of life in MS, Comprehensive care and MS

(S106) NATIONAL MULTIPLE SCLEROSIS NURSE AND PHYSICIAN EXTENDER TRAINING PROGRAM

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Background: As patients and families with multiple sclerosis (MS) begin their journey, they are confronted with unfamiliar medical terminology, confusing scientific literature, and complicated patient-assistance programs. The health-care team’s goal is to provide education, support, and resources that clarify pathophysiology, alleviate a myriad of symptoms associated with MS, and ultimately enhance patient quality of life. Advancements in the diagnosis and treatment of MS have increased the demand for specialized health-care providers who are familiar with emerging clinical concepts.

Objectives: The central mission of the National Multiple Sclerosis Society (NMSS)-sponsored National Multiple Sclerosis Nurse and Physician Extender Training Program is to develop a pathway for nurses and physician extenders to engage with fellow health-care professionals from diverse cultures and backgrounds; illustrate multidisciplinary and collaborative aspects of care that are essential to the chronic neurologic illness health-care model; highlight opportunities for career advancement in MS, ie, MS Nurse Certification Exam; introduce the nurse and/or physician extender to the complexities of treating MS patients and their families; and refine the knowledge and skills of experienced health-care professionals by reviewing cutting-edge research, discussing clinical investigation, and critically evaluating a series of representative MS patient vignettes.

Methods: Twenty-two applicants from MS centers across the United States completed an intensive training program at UT Southwestern Medical Center at Dallas. Applicants actively participated in real-time clinical interactions with patients and families from Monday morning to Friday afternoon. Multidisciplinary lectures were intended to display a comprehensive approach to MS care while addressing such topics as magnetic resonance imaging, interpretation, guided imagery, nursing research, vitamin D, sexual dysfunction, neuro-ophthalmology, and baclofen pump management.

Results: To quantify the knowledge gained, we administered a pre-test on Monday morning and a post-test on Friday afternoon. Each participant completed an extensive evaluation and a follow-up “Impact on Practice” survey.

Conclusions: We will report the results of the pre-test and post-test, along with the “Impact on Practice” survey.

Supported by: National Multiple Sclerosis Society

Disclosure: G.M. Remington: Teva Neuroscience, Biogen Idec (honorary); B. Greenberg: Biogen Idec (honorary); E.F. Frohman: Biogen Idec, Teva Neuroscience (honorary); T.C. Frohman: Nothing to disclose.

Keywords: Comprehensive care and MS, Nursing management in MS, Symptomatic treatment of MS

(S107) EVALUATION OF AN OPTIMIZED NURSING-CARE PROGRAM FOR PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS IN GERMANY

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Background: Patient and family assistance programs for multiple sclerosis (MS) begin their journey, they are confronted with unfamiliar medical terminology, confusing scientific literature, and complicated patient-assistance programs. The health-care team’s goal is to provide education, support, and resources that clarify pathophysiology, alleviate a myriad of symptoms associated with MS, and ultimately enhance patient quality of life. Advancements in the diagnosis and treatment of MS have increased the demand for specialized health-care providers who are familiar with emerging clinical concepts.

Objectives: The central mission of the National Multiple Sclerosis Society (NMSS)-sponsored National Multiple Sclerosis Nurse and Physician Extender Training Program is to develop a pathway for nurses and physician extenders to engage with fellow health-care professionals from diverse cultures and backgrounds; illustrate multidisciplinary and collaborative aspects of care that are essential to the chronic neurologic illness health-care model; highlight opportunities for career advancement in MS, ie, MS Nurse Certification Exam; introduce the nurse and/or physician extender to the complexities of treating MS patients and their families; and refine the knowledge and skills of experienced health-care professionals by reviewing cutting-edge research, discussing clinical investigation, and critically evaluating a series of representative MS patient vignettes.

Methods: Twenty-two applicants from MS centers across the United States completed an intensive training program at UT Southwestern Medical Center at Dallas. Applicants actively participated in real-time clinical interactions with patients and families from Monday morning to Friday afternoon. Multidisciplinary lectures were intended to display a comprehensive approach to MS care while addressing such topics as magnetic resonance imaging, interpretation, guided imagery, nursing research, vitamin D, sexual dysfunction, neuro-ophthalmology, and baclofen pump management.

Results: To quantify the knowledge gained, we administered a pre-test on Monday morning and a post-test on Friday afternoon. Each participant completed an extensive evaluation and a follow-up “Impact on Practice” survey.

Conclusions: We will report the results of the pre-test and post-test, along with the “Impact on Practice” survey.

Supported by: National Multiple Sclerosis Society

Disclosure: G.M. Remington: Teva Neuroscience, Biogen Idec (honorary); B. Greenberg: Biogen Idec (honorary); E.F. Frohman: Biogen Idec, Teva Neuroscience (honorary); T.C. Frohman: Nothing to disclose.

Keywords: Comprehensive care and MS, Nursing management in MS, Symptomatic treatment of MS

International Journal of MS Care
Background: Patient support during initiation of treatment for multiple sclerosis (MS) is critical to ensure continued treatment adherence and optimal benefit to the patient. Objectives: To assess patient and physician satisfaction with an introductory care program delivered by MS specialist nurses in Germany during the initial period of treatment for MS with subcutaneous (SC) interferon beta-1a (IFNβ-1a). Methods: Eligible patients had clinically confirmed relapsing-remitting (RR) MS and were beginning treatment with SC IFNβ-1a. Baseline, data recorded included demographics, disease characteristics, and treatment history. Patients were enrolled in the introductory care program and self-administered SC IFNβ-1a, 44 or 22 µg three times weekly. The planned observation period was 15 weeks following therapy initiation, and at the final visit, physician reports of missed doses and changes to patients’ neurologic status were recorded. A physician survey assessed physicians’ perception of the impact of the advice and support of the nurse and overall patient satisfaction. Results: A total of 1426 patients were eligible for assessment; the mean (SD) age was 37.4 (10.5) years; 72.7% were female. The mean disease duration was 3.7 (5.6) years, and the mean Expanded Disability Status Scale (EDSS) score was 2.4 (1.5), based on available data from 868 (60.8%) patients. Treatment was regularly injected by 1342 (94.1%) patients, and 1346 (94.4%) continued treatment until the end of the study. At the end of the study, the physician recorded an improvement in the neurologic status of 681 of 1368 (49.8%) patients; deterioration was recorded for 72 of 1368 (5.3%). Continuation of the nurse program was deemed beneficial in terms of compliance for 1040 of 1371 (75.9%) patients. Positive feedback on the nurse program was given by 1298 of 1392 (93.2%) patients. Only 1 patient gave negative feedback, and 93 gave a neutral response. A total of 1283 of 1383 (92.8%) patients were classified as being “motivated to continue treatment.” Conclusions: The results of this large observational, noninterventional study suggest that an optimized introductory care program delivered by MS nurses is beneficial to patients beginning SC IFNβ-1a therapy for RRMS, and may enhance motivation to continue treatment.

Supported by: Merck Serono S.A.—Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

Disclosure: W. Elias: Bayer Schering, Merck Serono, Sanofi, Novartis (consulting fees); Bayer Schering, Merck Serono, Sanofi, Novartis (honorary); S. Ries, G. Japp, M. Lang: Nothing to disclose.

Keywords: Nursing management in MS, Service delivery in MS, Comprehensive care and MS

(S109) USE OF NATALIZUMAB IN HISPANIC PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS

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Background: Several epidemiological factors play a role in multiple sclerosis (MS) disease frequency, particularly genetic susceptibility. MS prevalence in the Hispanic population has apparently increased in the last 20 years, according to US and Latin American studies. In 19 Texas counties, Hispanics were the third most common group affected by MS, with a prevalence of 11 in 100,000. Immunomodulatory treatments have demonstrated efficacy in treating relapsing MS. Natalizumab has been shown to reduce the relapse rate and progression of disability in relapsing MS. However, little information is available regarding inter-racial variability in treatment response, particularly in Hispanics. Objectives: To describe disease characteristics and treatment efficacy of natalizumab in Hispanic patients with relapsing forms of MS. Methods: A review of medical records of MS patients on natalizumab at Maxine Mesinger MS Comprehensive Care Center. Results: Of the 142 patients receiving natalizumab, 8 were Hispanics. The ratio of female to male and relapsing-remitting MS (RRMS) to progressive relapsing MS (PRMS) was 7:1. The mean age at the first attributable symptom was 25.5 years. Disease presentation leading to diagnosis was as follows: 2 of 8 central nervous system involvement, 5 of 8 limb weakness, and 1 of 8 paresthesias. Five patients had been on more than two disease-modifying therapies (DMTs) prior to natalizumab, and 3 had received chemotherapy. The mean disease duration prior to therapy was 9.8 years, and a mean of 19.25 natalizumab doses were given. The median annualized relapse rate before natalizumab treatment was 0.75 and after treatment was 0. The patient with PRMS experienced one relapse after the fifth dose. Follow-up magnetic resonance imaging (MRI) showed two new T2 lesions in three patients, and no gadolinium-enhancing lesions were detected. Conclusions: Recent reports found a similar response to natalizumab in the Hispanic population compared with the overall study groups. In our case series, natalizumab prevented 7 of 8 (87.5%) patients from relapsing in a mean follow-up of 19 months (4–37 months). MRI T2 lesions remained stable in 5 of 8 (62%) patients, and no gadolinium-enhancing lesions were documented. Our observations have limitations; however, the response to natalizumab in our Hispanic patients was comparable to that seen in the original trials.

Disclosure: Nothing to disclose

Keywords: Disease-modifying treatment in MS

(S108) SMOKING NEGATES PLATFORM THERAPY IN MULTIPLE SCLEROSIS

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Background: Brain atrophy is a marker of current neurologic impairment and correlates with future disability. Cigarette smoking is associated with poorer disease prognosis, including greater lesion volume and volume loss (cerebral atrophy). Disease-modifying agents (DMAs) slow the rate of brain volume (BV) loss. To date, the relative effects of, and associations between, BV changes in patients with relapsing-remitting multiple sclerosis (RRMS) who smoke and who use DMAs have not been reported. Objectives: To evaluate BV changes in smokers with RRMS versus those on DMAs. Methods: A literature review was performed using the keywords brain atrophy, brain parenchymal fraction (BPF), brain volume (BV), and smoking from 1999 to 2010. BPF and BV change were analyzed in untreated patients and during therapy with interferon beta (IFNβ) or glatiramer acetate (GA). Change in BPF or BV was also studied in patients with a history of smoking. Results: BPF loss occurs at a faster rate in smokers than in nonsmokers with RRMS. Healy et al. showed that BPF declines 0.3% per year in nonsmokers versus 0.4% per year in smokers (who were evenly matched between treated and untreated). Khan et al. found that...
rate of brain atrophy in untreated MS patients was 0.95% versus 0.46% to 0.64% in patients on DMAs (0.31%–0.49% reduction). Rudick et al. reported that patients taking weekly IFNβ-1a had a 0.69% BPF loss in the first year, which then stabilized to a 0.38% BPF loss in the second and third years (0.18% reduction vs. placebo). Similar trends were found by Frank et al. in a 3-year trial with IFNβ-1b. Patients lost 1.68% BV [mean, 0.56%; per year] (0.04%–1.44% reduction vs. placebo). A small 2-year trial of GA showed BV loss of 0.6% per year (1.2% reduction). Conclusions: Smoking, with a 0.1% less loss of BPF per year, appears to lessen or negate the protective effects of DMAs, with 0.04% to 1.44% less loss of BPF per year. The mechanism by which cigarette smoke affects MS is not entirely understood but is likely multifactorial. In animal models, cigarettes increase levels of metalloproteinase 9 and free oxygen radicals, and may cause axonal degradation via nitric oxide. Products of smoking may also bind to the aryl hydrocarbon receptor on immune cells activating Th17 cells, worsening autoimmune.

Disclosure: Nothing to disclose

Keywords: Disease-modifying treatment in MS

(S110) OPTICAL COHERENCE TOMOGRAPHY REVEALS DIFFERING SEVERITY OF DAMAGE BETWEEN WHITES AND AFRICAN AMERICANS WITH DEMYELINATING DISORDERS


Background: Optical coherence tomography (OCT) is a useful tool for analyzing retinal nerve fiber layer (RNFL) and macular thickness (MT). To date, racial differences in OCT findings of multiple sclerosis (MS) and neuromyelitis optica (NMO) have not been reported. Objectives: To correlate clinical characteristics of MS and NMO patients with OCT findings. Methods: Heidelberg OCT was performed in patients with relapsing-remitting MS (n = 15, 8 white and 7 African American), patients with NMO (n = 6, 3 white and 3 African American), and controls (n = 34). Results: RNFL and MT in MS and NMO patients were reduced compared with controls. No effect of age, sex, treatment, or disease duration on RNFL or MT was noted. No significant difference was noted in RNFL (580 µm vs. 780 µm, P = .05) and reduced MT (273.1 µm vs. 298 µm, P = .005) compared with white NMO ON eyes (n = 6), but no racial difference was seen in MS ON eyes. No significant difference was noted in RNFL (580 µm vs. 460 µm) or MT (302 µm vs. 285 µm) between MS and NMO ON eyes. MS NON eyes had reduced MT compared with NMO (320 µm vs. 306 µm, P = .02) and trending toward thinner RNFL (640 µm vs. 780 µm, P = .09). Conclusions: RNFL and MT of NMO ON eyes are thinner than in NON eyes, but only macular thinning was noted in MS patients. This may reflect subclinical disease activity affecting MS NON eyes. MS NON eyes demonstrate reduced MT compared with NMO, which may help differentiate MS from NMO patients without ON. African American MS NON patients with ON have reduced RNFL and MT compared with whites, suggesting more ON damage.

Supported by: National Multiple Sclerosis Society

Disclosure: Nothing to disclose

Keywords: Imaging and MS, Disease-modifying treatment in MS, Equipment in MS

(S111) BURN PREVENTION IN PATIENTS WITH MULTIPLE SCLEROSIS


Background: Each year over 500,000 people in the United States receive medical treatment related to burn injuries, and many more do not seek treatment. Burns are devastating injuries, and because so many are preventable, education is essential, especially for high-risk populations and health-care providers who care for them. Certain groups are more likely to sustain burns, such as patients with multiple sclerosis (MS). The literature contains very little information about burns in MS patients. However, since they are at higher risk for burns, they should be questioned about sources of injuries and potential hazards in their environments. They can then be asked about individual factors related to their disease processes that increase their likelihood of sustaining injuries. With this information, preventive interventions can be developed and taught to both patients and health-care providers. Objectives: 1) Determine sources of burns that resulted in actual injuries and constitute potential hazards. 2) Identify factors related to MS that increase the risk of injuries. 3) Determine interventions to reduce the risk of injuries. 4) Provide health-care professionals with materials to educate patients about safety interventions. Methods: A total of 100 patients were screened using a questionnaire to assess actual burn injuries that had been sustained as well as potential hazards that exist in their home environments. Factors associated with their disease process were analyzed for how they contribute to increased risk of injuries. Results: Common burn injuries in the patients assessed included those sustained from cooking and/or baking, scalding resulting from bathing or cooking with hot liquids, and those resulting from use of curling irons. Appropriate safety interventions were developed, and a brochure containing this information was made available for patients and health-care providers. Conclusions: Burn injuries are observed frequently in the MS population and can have devastating effects on independence and lead to increased mortality rates. Health-care providers should instruct patients about risks and interventions that can increase safety for these patients. There are many interventions that can be implemented by patients. There is a definite need for further study on this topic.

Disclosure: Nothing to disclose

Keywords: Management of activities of daily living in MS, Quality of life in MS

(S112) DEVELOPING NATALIZUMAB TREATMENT GUIDELINES FOR MULTIPLE SCLEROSIS PATIENTS

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**Background:** Natalizumab (Tysabri) is approved in Canada as a monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis (MS). Currently, there are no clear treatment guidelines for health-care professionals using this medication. New evidence suggests that longer exposure to natalizumab increases the risk of developing progressive multifocal leukoencephalopathy (PML). For these reasons, treatment guidelines for health-care professionals using natalizumab were developed in June 2009. The guidelines provide an approach to patient selection, monitoring, and early detection and management of PML. **Objectives:** This study aims to describe the development process and evaluate the implementation of natalizumab treatment guidelines developed to optimize management of MS patients with active disease at the MS Clinic of the Montreal Neurological Hospital, Montreal, Canada. **Methods:** The guidelines are based on a literature review and an expert consensus including all the neurologists at the MS Clinic, experts in neuroradiology and neuroimmunology. Charts of patients treated with natalizumab were reviewed retrospectively before (April 2007 to May 2009) and after implementation (June 2009 to March 2010) of guidelines. Extracted data included demographics, baseline tests (magnetic resonance imaging, immune status, liver function tests), frequency of follow-up, and washout period. **Results:** Before June 2009, 57 patients (81% female) initiated natalizumab treatment. The median number of infusions was 14 (range, 1–30), with a mean treatment time of 13.6 months. Natalizumab has been given as a second-line treatment, except for one patient who was treatment-naive. Wash-out periods were <3 months for two patients previously on chemotherapy and <1 month for four patients previously on immunomodulators. Baseline tests were performed on 56% of patients. Half of the group was assessed biannually during treatment, and 12% were assessed >9 months apart. Data after implementation of guidelines will be presented. **Conclusions:** This study shows the need for clear and standard treatment guidelines. Final results will show the value of the guidelines developed. **Disclosure:** Y. Lapierre: Biogen Idec (consulting fee, honoraria). M. Ruiz Menguas, S. Hun, P. Ng: Nothing to disclose. **Keywords:** Disease-modifying treatment in MS, Comprehensive care and MS

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**S114 DALFAMPRIpine IMPROVES WALKING IN MULTIPLE SCLEROSIS PATIENTS: POOLED DATA FROM THREE CLINICAL TRIALS**

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**Objectives:** To evaluate dalfampidine (Ampyra extended-release tablets) (D-ER) for improvement in walking in patients with multiple sclerosis (MS) as determined by walking speed (WS), using data pooled from three randomized, placebo-controlled, multicenter trials (MS-F202, MS-F203, and MS-F204). D-ER was previously known as fampridine or fampridine-5R. **Methods:** Data for patients who received the therapeutic dose of D-ER, 10 mg twice a day, in three randomized controlled trials were pooled (n = 394) and compared with placebo (n = 237). Comparative analyses were based on the percent change from baseline in WS using the Timed 25-Foot Walk, where the baseline value was defined as the average of four pretreatment visits, and the treatment value was defined as the average over the

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**S113 CONTRIBUTION OF STRUCTURAL AND FUNCTIONAL VISUAL OUTCOMES TO WORK CAPACITY AND EMPLOYMENT STATUS IN MULTIPLE SCLEROSIS**

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**Background:** Work capacity and employment status are increasingly recognized as important outcomes in multiple sclerosis (MS). The extent to which visual symptoms, reduced function, and visual pathway axonal loss contribute to work disability has not been examined. **Objectives:** The present study aims to estimate how visual outcome measures, retinal nerve fiber layer (RNFL) thickness, and vision-specific quality of life reflect work capacity and employment status in an MS cohort. **Methods:** Patients with MS completed a vocational status questionnaire. Work status was categorized as disabled (receiving disability pension), reduced-capacity, or full-time. Those unemployed for non-MS reasons or retired due to age were not included in primary analyses (n = 10). Low-contrast letter acuity (LCA) and high-contrast visual acuity (HCA) testing were performed. RNFL thickness was measured by Stratus and Cirrus high-resolution optical coherence tomography (OCT). Health-related quality of life (HRQOL) was assessed using the National Eye Institute 25-item Visual Functioning Questionnaire (NEI-VFQ-25) with Neuro-Ophthalmic Supplement, Impact of Visual Impairment Scale (IVIS), and 36-item Short Form Health Status Survey (SF-36). **Results:** MS patients (n = 47, 94 eyes), with a mean ± SD age of 48 ± 9 years, were classified into one of the three work status categories. Visual symptoms were most common among patients who were disabled (71%) compared with reduced-capacity or full-time (40%). Disabled patients had the worst scores for NEI-VFQ-25 composite (P = .008, linear regression, accounting for age), Neuro-Ophthalmic Supplement (P = .002), IVIS (P = .003), and SF-36 Physical Components Score (P < .001). RNFL thickness was lowest in disabled patients (P = .004 [Stratus], P = .001 [Cirrus OCT]), even accounting for visual symptoms and history of optic neuritis (ON) (P = .004). Worse visual function scores were associated with greater probability of visual symptoms but did not correlate independently with work status. **Conclusions:** Measures of vision-specific HRQOL and RNFL thickness reflect work capacity and employment status in MS, even among a heterogeneous cohort of patients not selected for visual symptoms. Anterior visual pathway axonal loss and visual dysfunction are likely contributors to disability in MS and may be markers for potential economic impacts of this disorder. **Disclosure:** Nothing to disclose. **Keywords:** Economic issues and MS, Employment in MS, Imaging and MS

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double-blind visits. The percent change in WS for the pooled populations for each double-blind visit was evaluated by time interval to account for differences in study schedules (days 1–21, 22–49, 50–77, and 78–end of double-blind phase). The percent changes were analyzed via analysis of variance with effects for treatment group, study, and site within study. 

**Results:** Demographic and clinical characteristics were generally similar in the pooled D-ER and placebo groups. The overall percent change in WS improved significantly by 13.4% [95% confidence interval [CI], 11.6–15.1%] in the D-ER group compared with placebo (5.8%; 95% CI, 3.6–8.0%; P < .001) relative to baseline values, which were similar in D-ER and placebo (mean [SD], 2.05 [0.76] feet/sec D-ER; 2.09 [0.74] feet/sec placebo). These results were consistent with the individual studies. A significantly greater proportion of patients in the D-ER group than in the placebo group had improvements in WS from their individual baseline that were greater than 10% (54.1% vs. 32.5%, P < .001), 20% (31.5% vs. 13.1%, P < .001), 30% (15.5% vs. 3.8%, P < .001), and 40% (6.6% vs. 2.5%, P < .027). For each double-blind time interval, the percent improvement in WS was significantly greater in D-ER relative to placebo (P < .05), suggesting a consistent treatment effect. **Conclusions:** The pooled study data demonstrate the efficacy of D-ER for improvement in walking as determined by change of WS from baseline in patients with MS.

**Supported by:** Acorda Therapeutics


**Keywords:** Symptomatic treatment of MS

**(S115) RESUMPTION OFAMBULATION IN A NONAMBULATORY 68-YEAR-OLD FEMALE WITHMULTIPLE SCLEROSIS FOLLOWING PHYSICAL THERAPY WITH MULTIPLE SCLEROSIS CLINICAL SPECIALISTS**

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**Background:** A 68-year-old patient was diagnosed with multiple sclerosis (MS) at age 25. She was ambulatory until age 48, when she began using a manual wheelchair and a motorized chair. She continued to receive physical therapy (PT) during this time, consisting of regular group exercise programs emphasizing general fitness. When the current course of PT began, she was living at home and required a full-time home health aide. The patient started at an outpatient center specializing in MS, and her two therapists were both MS clinical specialists. Evaluation revealed bilateral lower extremity and left upper extremity spasticity measuring a 1 on the Modified Ashworth Scale. Lower-extremity strength was 2/5 at the hips and knees and 1/5 at the ankles. Upper-extremity strength was 4/5 on the left and 5/5 on the right. Posture was remarkable for a fixed thoracic kyphosis and stiff but flexible posterior pelvic tilt. She was dependent in all transfers and unable to sit unsupported without assistance. **Objectives:** Both the patient’s and the therapist’s goals were to achieve independent ambulation. Initial PT goals were to improve trunk posture by strengthening of postural extensors and stretching of hip flexors and anterior trunk muscles. **Methods:** The patient received PT twice per week, as well as a home program. Range of motion was addressed in the supine position with a horizontal towel roll to increase lumbar lordosis. A strengthening program was designed emphasizing eccentric contractions of hip flexors, extensors, and abductors, as well as the latissimus and triceps, for use with a rolling walker. When the patient was able to sit unsupported, standing training was initiated, consisting of the patient standing with a standard walker with knees and trunk held in extension. When the patient was able to maintain independent trunk extension, she was given knee immobilizers to keep her knees locked in extension, allowing her to maintain unassisted standing with a walker. Gait training was then initiated via a modified swing-through gait, utilizing her improved upper-extremity and hip flexor strength. Upon ambulation of 10 feet with minimal assistance, she was casted for bilateral knee-ankle-foot orthoses. **Results:** At the time of this writing, the patient was ambulating 20 to 30 feet with contact guard with minimal assistance. She is still receiving outpatient PT twice per week, as well as performing a home program daily. **Conclusions:** This case illustrates the necessity of PT performed by MS clinical specialists, as the patient showed no prior improvement with more generalized PT.

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS, Quality of life in MS, Equipment in MS

**(S116) COMPARISON OF GENERAL AND MULTIPLE SCLEROSIS–SPECIFIC HEALTH LOCUS OF CONTROL**

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**Background:** Health locus of control (HLOC) refers to an individual’s beliefs about the extent of control over health outcomes. It has been associated with health knowledge and self-care practices in chronic disease populations. Internal HLOC reflects a belief that the person has control of health outcomes, and external HLOC (eg, things due to chance, influence of other people) reflects a belief that other variables control outcomes. People with multiple sclerosis (MS) may have different HLOC profiles if asked specifically about MS versus their general health. Measuring MS-specific HLOC could provide novel information with implications for symptom management and treatment. **Objectives:** Compare participants’ MS-specific and general HLOC. **Methods:** Forty participants (33 female; mean ± SD age, 51.6 ± 9.4 years; mean ± SD MS duration, 9.6 ± 8.7 years) provided demographic information and completed two parallel forms (general and MS-specific) of the Multidimensional Health Locus of Control Scale. The first form asked questions about general HLOC (“Most things that affect my health happen to me by accident”), and the second form focused on MS-specific HLOC (“Most things that affect my MS happen to me by chance”). Both forms have 18 items and use a 6-point


**Posters**

Likert scale. Three subscales were used to assess internal (Internal) and external (Chance and Doctors) HLOC. Paired t tests were conducted to examine differences on the subscales.

**Results:** There was a statistically significant difference (t = 6.86, P = .00) between the general HLOC Internal subscale (mean ± SD, 25.95 ± 4.3) and the MS-specific HLOC Internal subscale (21.16 ± 5.01). Higher scores indicate stronger locus of control. A significant difference (t = -5.13, P = .00) between general HLOC Doctors subscale (9.30 ± 3.5) and the MS-specific Doctors subscale (11.88 ± 3.3) was also observed. No difference between general and MS health was seen for the Chance subscale (t = -1.3, P = .20).

**Conclusions:** Participants reported having less internal control for MS-specific than for general HLOC. External control by doctors was greater for MS HLOC. External control associated with Chance was the same for MS versus general HLOC, an interesting finding considering the often unpredictable nature of MS disease progression. Research focusing on MS should use the MS HLOC scale to best capture beliefs about MS health outcomes.

**Disclosure:** Nothing to disclose

**Keywords:** Psychological issues and MS, Psychosocial issues in MS

**B117 QUALITY OF LIFE DATA FROM NARCOMS: MULTIPLE SCLEROSIS DISEASE-RELATED FACTORS**


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**Background:** In the fall of 2003, the North American Research Committee on Multiple Sclerosis (NARCOMS) began to collect longitudinal health-related quality of life (HRQOL) information from its registry participants.

**Objectives:** This study aimed to examine baseline correlations between multiple sclerosis (MS) disease-related factors and HRQOL.

**Methods:** HRQOL was measured using the 12-item Short Form Health Status Survey (SF-12), which provides two summary scores: a physical composite score (PCS) and a mental composite score (MCS), each ranging from 0 (worst) to 100 (best).

**Results:** The average age of registry participants was 51.2, the majority were female (74.9%), and the average disease duration since diagnosis was 15.3 years. A total of 3639 participants completed the SF-12. Longer disease duration was negatively correlated with PCS (r = -0.25, P = .001) but positively correlated with MCS (r = 0.04, P = .03). A higher number of emergency room visits in the past 6 months, relapses in the past 6 months, and current prescription medications taken for MS symptoms were all negatively correlated with both PCS (r = -0.05, -0.25, and -0.33, respectively; P = .001) and MCS (r = -0.05, -0.18, -0.12; P = .001). Receiving a disease-modifying therapy (DMT) was positively correlated with PCS (r = 0.16, P = .001) but not correlated with MCS (r = 0.01, P = .77). Degree of disability in walking as per Patient-Determined Disease Steps was negatively correlated with both PCS (r = -0.71, P = .001) and MCS (r = -0.01, P = .53). Similarly, degree of disability in the NARCOMS mobility performance scale was also negatively correlated with PCS (r = -0.69, P = .001) but not MCS (r = -0.01, P = .71). Degree of disability in performance scales of hand function (r = -0.54), vision (r = -0.26), fatigue (r = -0.59), cognition (r = -0.31), bladder/bowel issues (r = -0.50), sensory function (r = -0.47), spasticity (r = -0.57), and pain (r = -0.55) were all negatively correlated with PCS at P = .001, as they were with MCS: hand function (r = -0.18), vision (r = -0.23), fatigue (r = -0.34), cognition (r = -0.34), bladder/bowel issues (r = -0.14), sensory function (r = -0.23), spasticity (r = -0.20), and pain (r = -0.29).

**Conclusions:** Overall, the correlations were stronger and more consistent for PCS than for MCS. There were correlations between HRQOL and most of the MS disease-related factors examined. However, notable exceptions emerged with regard to the absence of any correlation between MCS and taking a DMT, worsening disability in walking, or mobility.

**Supported by:** NARCOMS is supported by the Consortium for Multiple Sclerosis Centers.


**Keywords:** Quality of life in MS

**B118 BARRIERS TO HEALTH MAINTENANCE AND PROMOTION IN WOMEN WITH MULTIPLE SCLEROSIS IN NOVA SCOTIA, CANADA: A QUESTIONNAIRE STUDY**

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**Background:** Multiple sclerosis (MS) is the most common neurologic disease in young adults. The female-to-male ratio is 3:1, making MS one of the leading causes of disability in women. There is a paucity of literature on health-care issues in women with disabilities. However, in the existing literature it is quite clear that, when it comes to the use of preventive services, such as mammography and gynecologic examinations, women with disabilities access these services at a much lower rate than women without disability. The explanation for this is multifactorial. It is important to identify such issues so that barriers to optimal health can be addressed in women with MS.

**Objectives:** To assess barriers to health maintenance and promotion in women with MS in Nova Scotia, Canada.

**Methods:** This was a questionnaire study designed to collect data on impairment and function as they relate to barriers to health care in women with MS in Nova Scotia, Canada. The questionnaire was mailed to 150 women registered in the Dalhousie University MS Treatment and Research Centre database.

**Results:** Of the 102 respondents, 89% reported that their primary care physicians’ offices were wheelchair-accessible from the outside. However, 28.4% reported that the examination table was not accessible, and 30.4% reported inaccessible washrooms. The majority of these individuals reported needing a wheelchair for mobility, but 14% required only an aid for walking. Those in wheelchairs were examined in their wheelchairs most often. A total of 63.7% responded that they were aware of an accessible women’s health clinic at our Women and Children’s Health Centre; however, only 27.3% were willing to use it. Most who reported they would not use this clinic noted that it was because of distance to travel or transportation issues. Only 16.7% reported being uncomfortable discussing certain topics with their doctors. These were usually related to sexual function and incontinence. A significant portion of respondents (23.5%) expressed an unpleasant interaction with a health professional.

**Conclusions:** Our questionnaire...
suggests that there are barriers to maintaining optimal health in women with MS in Nova Scotia. Information from this questionnaire could be used to develop strategies to mitigate these problems.

Disclosure: Nothing to disclose

Keywords: Comprehensive care and MS, Service delivery in MS

(S119) VARIABILITY OF DOSAGE IN COMPOUNDED 4-AMINOPYRIDINE AT THREE US PHARMACIES

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Background: 4-aminopyridine (4-AP) is a broad-spectrum potassium channel blocker that has been used to treat multiple sclerosis (MS) and other demyelinating conditions. The drug has been available through compounding pharmacies in different formulations, including those identified as “sustained release.” High peak plasma levels observed with immediate release (IR) formulations and compounding errors leading to overdose have been associated with serious adverse events. An extended-release tablet formulation of dalfampridine (Ampyra) was recently approved as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed. Dalfampridine (chemically 4-AP) was previously known as fampridine. Objectives: This study compared analytical profiles, including dosage and dissolution, of compounded sustained-release 4-AP from three pharmacies specializing in preparing compounded products. Methods: Capsules labeled “10 mg sustained release 4-AP” were obtained from three US pharmacies. High-performance liquid chromatography (HPLC) was used to measure potency and Level 1 content uniformity. The dissolution profile was obtained at prescribed time intervals using a USP apparatus II and HPLC. Initial testing was performed, followed by 3-month stability testing at room temperature and accelerated conditions. Results: The uniformity of dosage between capsules was variable, ranging from 8.3 to 10.7 mg/capsule, 7.4 to 14.8 mg/capsule, and 8.6 to 11.3 mg/capsule across the three sources. Compared with Good Manufacturing Practice–manufactured extended-release dalfampridine, which completes at least 80% dissolution over 12 hours, the dissolution profile across all tested samples showed variability, with 80% to 100% of the active product released in 4 hours. These results demonstrate a dissolution profile inconsistent with an extended-release formulation. Conclusions: The tested compounded 4-AP capsules displayed variable uniformity of dosage, with some values outside USP-accepted criteria. Although the samples were labeled as “sustained release,” their dissolution profiles more closely resembled IR characteristics. Because of the narrow therapeutic index and short half-life, using compounded drug may put patients at increased risk of adverse events and decreased duration of drug effect.

Supported by: Acorda Therapeutics


(S120) PREVALENCE OF ANTINUCLEAR ANTIBODIES AND THEIR IMPACT ON RESPONSE TO IMMUNOMODULATORY THERAPY IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system white matter. Previous studies have estimated the prevalence of antinuclear antibodies (ANAs) to be between 20% and 80% in MS, higher than in the general population. It has been noted that in untreated MS patients, the presence of ANAs is associated with clinical exacerbations as well as increased magnetic resonance imaging (MRI) disease activity. There have also been reports of nuclear autoantigens in MS lesions, suggesting that ANAs may have some pathogenetic relevance.

Objectives: We proposed to evaluate the prevalence of ANAs and their effect on response to immunomodulatory therapy in relapsing-remitting MS (RRMS) patients. Methods: A list of patients seen between 2000 and 2008 at UT Southwestern Medical Center with an ICD-9 code of RRMS and a CPT code of ANAs was assembled. All patients with ANAs, a diagnosis of RRMS, and at least 2 years of follow-up were selected as our cases. We then identified 40 ANA-negative patients, who were age- and sex-matched to act as controls. All patient charts were analyzed for number of relapses occurring during a follow-up period of 2 to 5 years. Results: We identified a total of 107 RRMS patients receiving follow-up in our clinic. Of these, 20 patients (18.7%) were found to have a positive ANA titer. The average annualized relapse rate (ARR) of the ANA-positive patients was 0.25. The average ARR for the control patients was 0.16. Additionally, we looked at subgroups of ANA-positive patients based on titer: <1:160, 1:160, and >1:160. The average ARRs for these subgroups were 0.09, 0.28, and 0.33, respectively. We performed a one-way analysis of variance to test the hypothesis that the average mean values across categories of subgroups were equal. Statistical analysis was performed using WINKS SDA software. There was no statistically significant difference in average ARR between the ANA-positive and control patients or the subgroup analysis (P = .52). Conclusions: The presence of ANAs in RRMS patients was similar to that in previous prevalence studies; however, the presence of ANAs did not statistically alter or correlate with disease activity.

Disclosure: Nothing to disclose

Keywords: Disease-modifying treatment in MS, Natural history of MS, Immunology and MS

(S121) NEUROPSYCHOLOGICAL ASSESSMENT OF MULTIPLE SCLEROSIS PATIENTS

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Background: Previous studies have shown that neuropsychological problems in multiple sclerosis (MS) patients can be detected only if specific testing is performed. Physical assessments such as the Expanded Disability Status Scale (EDSS) do not adequately uncover cognitive dysfunction in the MS population. This study was conducted to validate the use of
the Symbol Digit Modalities Test (SDMT) in an MS center population as compared with the standard neuropsychological assessment performed by the neuropsychologist. **Objectives:** The oral and written SDMT administered to a random sample of MS patients with cognitive complaints seen at an MS center may be able to detect abnormalities when used as a screening tool. The SDMT could determine whether a standard neuropsychological assessment battery is necessary in identifying additional problems. **Methods:** Seventy-five randomly identified patients were evaluated. Consenting patients completed a SDMT and had the MS center’s standard neuropsychological assessment performed. Tests making up the standard assessment were the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Multiscore Depression Inventory (MDI), and Cross and Clock Drawings. The self-reported Beck Depression Inventory (BDI-II) and an EDSS were recorded for each patient. Scores more than 1.5 SDs below the mean are suggestive of cerebral dysfunction. The results were controlled for age, gender, and educational level. Additionally, the results of the 75 patient assessments were reviewed to determine the concordance between the results of the SDMT and the neuropsychological battery. **Results:** The strongest correlation was between the SDMT and RBANS total score. There were no correlations between the MDI, Clock Draw, or EDSS scores. **Conclusions:** The SDMT is a sensitive assessment that can be used in the MS center to detect cognitive changes in the MS population. It is a brief instrument that can be administered at the clinic visit and give the treating physician information on the cognitive status of the patient that can be further evaluated by more detailed neuropsychological testing. The SDMT can be repeated over time to confirm cognitive changes.

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**Keywords:** Comprehensive care and MS, Psychological issues and MS

(S122) HEMATOLOGICAL PROFILES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS TREATED WITH CLADRIBINE TABLETS

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**Objectives:** Cladribine is activated preferentially in lymphocytes, resulting in targeted and sustained immunomodulation, which provides the rationale for its use as a short-course annual multiple sclerosis (MS) treatment. This was explored further through investigation of hematological outcomes in patients with relapsing-remitting MS (RRMS) in the CLARITY (CLAdRibine tablets Treating multiple sclerosis orally) study. **Methods:** Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score 0–5.5) were randomized 1:1:1 to receive cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given in short courses (once daily for 4–5 days) in 2 or 4 consecutive months (28-day periods) in the first 48 weeks, then two short courses at weeks 48 and 52. Blood was sampled at intervals from day 1 to week 96 for complete blood cell counts and differential analysis. Data were previously presented at the Congress of the European Committee for Treatment and Research in Multiple Sclerosis in 2009. **Results:** The intention-to-treat population consisted of 456, 433, and 437 patients randomized to receive 5.25 mg/kg, 3.5 mg/kg, or placebo, of whom 454, 430, and 435 provided data for this analysis (safety population) and 86.2%, 91.2%, and 86.3% completed full-course treatment, respectively. Cladribine 5.25 and 3.5 mg/kg treatment led to rapid and sustained decreases in leukocyte counts, reaching median nadir values at week 16 and week 13 of 4.4 and 5.3/nL (median change from baseline, −2.3 and −1.4/nL), respectively. A slight recovery was noted during readosing at week 48 led to a second nadir at week 55 (median, 4.2 and 4.4/nL; median change from baseline, −2.6 and −2.2/nL). These results were mainly driven by reductions in lymphocytes (median change from baseline in 5.25 and 3.5 mg/kg groups, −1.2/nL [−64%] and −0.8/nL [−44%] at week 16 and 13; −1.2/nL [−65%] and −1.2/nL [−58%] at week 55; with median lymphocyte counts corresponding to grade 2 or lesser lymphopenia according to CTCAE criteria). Changes in other peripheral blood cell counts, including neutrophils, eosinophils, and erythrocytes, were minimal. Hemoglobin levels were marginally affected. **Conclusions:** Cladribine tablets resulted in a predominant effect on peripheral blood lymphocytes, with relative preservation of other cell types and components.

**Supported by:** EMD Serono, Inc, Rockland, MA

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**Keywords:** Disease-modifying treatment in MS, Immunology and MS

(S123) EFFECTS OF CLADRIBINE TABLETS ON LYMPHOCYTE SUBTYPES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS

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**Objectives:** Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score 0–5.5) were
**Objectives:** Cladribine tablets are in advanced-stage development for multiple sclerosis (MS) treatment. Cladribine is a produg, and activation in specific cells provides targeted and sustained immunomodulation, allowing the investigation of an oral short-course annual treatment. Here we assess the hematological profiles over time in the CLARITY (CLAdRibine tablets Treating multiple sclerosis orally!) study.

**Methods:** Relapsing-remitting MS (RRMS) patients were randomized (1:1:1) to one of two cladribine regimens (cumulative dose 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given as short courses (once daily for 4–5 days) in weeks 1, 5, 9, and 13 (5.25 mg/kg arm) or weeks 1 and 5 (3.5 mg/kg arm), and in weeks 48 and 52 (both arms). Blood was sampled at intervals from day 1 to week 96 for complete blood cell counts and differential analysis, with analysis of lymphocyte surface markers (CD3, CD19, CD4, CD8, CD16, and CD56) in a patient subset. Data were previously presented at the Annual Meeting of the European Neurological Society in 2009.

**Results:** The intention-to-treat population included 456, 433, and 437 patients randomized to 5.25 mg/kg, 3.5 mg/kg, or placebo; 80, 81, and 79 provided samples for lymphocyte surface marker analyses, respectively. Cladribine 5.25 or 3.5 mg/kg resulted in a rapid decrease in leukocyte counts from baseline (median, 6.6/μL for both) after the first treatment course, reaching nadir values at week 16 and week 13 (4.4 and 5.3/μL, respectively), and at week 55 (median, 4.2 and 4.35/μL, respectively), separated by a period of recovery until redosing at week 48, vs. placebo (median values of 6.6–6.9/μL) at each time point. This was accompanied by a decrease in B cells (CD19) at week 4, reaching their nadir at weeks 13 to 16, with a period of more substantial recovery toward baseline until week 48. CD3, CD4, and CD8 cell counts showed a linear decrease to week 16 (5.25 mg/kg group) or 13 (3.5 mg/kg group) relative to baseline or placebo, remaining at relatively constant levels thereafter, even after redosing at weeks 48 and 52.

**Conclusions:** Cladribine tablets resulted in rapid and sustained effects on cellular subtypes implicated in MS pathogenesis. The results help clarify the mechanism of targeted and sustained efficacy of cladribine tablets therapy.

**Supported by:** EMD Serono, Inc, Rockland, MA

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**Keywords:** Disease-modifying treatment in MS, Immunology and MS

**Disclosure:** Nothing to disclose

**Keywords:** Symptomatic treatment of MS, Rehabilitation strategies and therapy and MS

**Disclosure:** Nothing to disclose
Background: Multiple sclerosis (MS) is an autoimmune disease of unknown etiology. Interferon beta (IFNβ) and glatiramer acetate (GA) are recommended first-line agents for the treatment of MS. However, despite treatment with these agents, the disease may continue to progress in some patients. Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase used in organ transplant patients. It has also been used as a second-line agent in patients with MS. We conducted a retrospective study to evaluate the efficacy of MMF in patients with MS.

Objectives: To study the efficacy of MMF in MS patients.

Methods: All patients with a diagnosis of active MS prior to starting MMF were studied. Active disease was defined as continued relapses and/or new or enhancing magnetic resonance imaging (MRI) lesions. The clinical data were retrospectively obtained by chart review and included age, sex, disease type and duration, and disability scores (Expanded Disability Status Scale [EDSS], Timed 25-Foot Walk [T25FW], and modified Nine-Hole Peg Test [mNHPT]). The disability scores at baseline and at 9 to 15 months were analyzed using the paired t test for the T25FW and mNHPT and the Wilcoxon signed rank test for the EDSS.

Results: Thirty-seven patients (mean ± SD age, 45.78 ± 9.01 years; 70% women) treated with MMF (30 relapsing, 7 progressive MS; mean disease duration, 9.84 ± 6.82 years) were studied. Twenty-three (62%) were on immunomodulatory therapy (16 IFNβ, 7 GA) prior to initiation of MMF. Following initiation of MMF, 17 (46%) continued concomitant immunomodulatory therapy; 20 (54%) were only on MMF. There was an improvement in T25FW (mean ± SE time in seconds) from 6.89 ± 4.64 to 6.26 ± 3.16 (P = .056). The mNHPT showed a trend of improvement from 15.19 ± 6.62 to 14.65 ± 6.36 (P = .091). The median EDSS score (n = 26) was not significantly different: 3.75 at baseline versus 3.0 after treatment (P = .7).

Conclusions: In this retrospective study, MMF seemed to improve disability scores in MS patients who had not responded to first-line therapy.


Keywords: Disease-modifying treatment in MS

(S126) PATIENTS’ SATISFACTION WITH NATALIZUMAB INCREASES OVER TIME


Research Operations, HealthCore, Inc, Wilmington, DE; Global Health Economics, Biogen Idec, Inc, Wellesley, MA

Background: Patient treatment satisfaction affects behaviors such as continued use of treatment. This is true in multiple sclerosis (MS), in which patients receive treatment with disease-modifying therapies to slow disease progression. The Treatment Satisfaction Questionnaire for Medication (TSQM) is a psychometrically valid measure of patients’ treatment satisfaction. Objectives: To assess patient-reported treatment satisfaction with natalizumab over time in MS patients.

Methods: MS patients starting natalizumab were invited to participate in a longitudinal study assessing their experiences with natalizumab. The TSQM was used at baseline (BL), prior to starting natalizumab, to assess patients’ perceptions regarding effectiveness (EFF), convenience (CON), and global satisfaction (GSA) of MS drugs and after the 3rd, 6th, and 12th infusions to assess patients’ satisfaction with natalizumab. Each subscale consists of three items, with responses on a 7-point Likert scale ranging from 1 (low) to 7 (high). Subscale scores are transformed to range from 0 to 100; higher scores indicate higher satisfaction. Regression models evaluated change from baseline through 12th infusion after controlling for number of infusions, age, years since MS diagnosis, BL disease disability, BL functional status, comorbidity burden, and number of MS drugs used prior to natalizumab.

Results: Data from 185 patients completing the 12th infusion assessment in this ongoing study indicate that 78% are female; the mean ± SD age is 47 ± 11 years, and the mean time since MS diagnosis is 11 ± 9 years. Almost all (97%) patients used ≥1 other MS drug before natalizumab. After controlling for covariates, significant increases in EFF (BL, 43.3 ± 5.4; 3rd, 59.9 ± 5.4; 6th, 70.2 ± 5.4; 12th, 72.4 ± 5.4; P < .0001), CON (BL, 59.9 ± 5.2; 3rd, 77.9 ± 3.7; 6th, 78.8 ± 2.2; 12th, 81.3 ± 0.7; P < .0001), and GSA (BL, 62.3 ± 2.9; 3rd, 75.2 ± 2.9; 6th, 76.7 ± 2.9; 12th, 77.7 ± 2.9; P < .0001) were observed. Number of infusions was significantly associated with improvement in treatment satisfaction scores (P < .001). Conclusions: Patients’ satisfaction with natalizumab increased with increasing treatment duration. Patients reported significant increases in satisfaction with the effectiveness and convenience of, and global satisfaction with, natalizumab as compared with their satisfaction with other MS drugs used before initiating natalizumab.

Supported by: Biogen Idec, Inc and Elan Pharmaceuticals, Inc


Keywords: Disease-modifying treatment in MS, Quality of life in MS

(S127) AFRICAN AMERICAN MULTIPLE SCLEROSIS IMPACT SCALE–29 SCORES IMPROVE AFTER SIX NATALIZUMAB INFUSIONS


1Research Operations, HealthCore, Inc, Wilmington, DE; 2Global Health Economics, Biogen Idec, Inc, Wellesley, MA

Background: Data from pivotal clinical trials have shown that the efficacy of natalizumab on relapses and magnetic resonance imaging (MRI) lesions in patients of African descent is similar to its efficacy in the overall study populations. However, the effect of natalizumab on quality of life (QOL) in African American (AA) patients is unknown. The Multiple Sclerosis Impact Scale–29 (MSIS-29) is a reliable and valid disease-specific scale that assesses the impact of multiple sclerosis (MS) on the psychological and physical aspects of QOL from a patient’s perspective. Objectives: To assess change in disease-specific QOL in AA MS patients in an exploratory analysis. Methods: In the United States, MS patients starting natalizumab were recruited to participate in a longitudinal observational study and completed the MSIS-29 before natalizumab initiation and after the 3rd, 6th, and 12th infusions. The MSIS-29 consists of 20 items evaluating the physical impact and 9 items evaluating the psychological impact of MS. Scores range from 0 to 100, with lower scores indicating better QOL. Repeated-measures analysis of variance (ANOVA) was used to measure the changes in MSIS-29 scores from baseline (BL) through the sixth infusion.

Results:
Data from 45 AA patients who received six natalizumab infusions in this ongoing study indicated that the mean (SD) age of the cohort was 40.6 (10.7) years and the majority of patients were female (86%). The mean number of years since MS diagnosis was 8.2 (6.2). Patients showed statistically significant improvements in their physical (BL 46.1 ± 22; 6th, 37.7 ± 22; P = .005) and psychological impact scores (BL 36.9 ± 23; 6th, 30.1 ± 21; P = .019) over time. **Conclusions:** AA patients using natalizumab show physical and psychological improvements in disease-specific QOL that are similar to improvements observed in the overall MS population receiving natalizumab. Since patients of African descent may have more severe forms of MS and may be less responsive to interferon treatment, natalizumab may be an effective treatment option in this patient population.

**Supported by:** Biogen Idec, Inc and Elan Pharmaceuticals, Inc


**Keywords:** Quality of life in MS

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**S128 PATTERNS OF SPASTICITY MANAGEMENT IN THE MULTIPLE SCLEROSIS PATIENT**

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**Background:** Spasticity affects approximately 80% of the multiple sclerosis (MS) population. The MS Council for Clinical Practice Guidelines published evidence-based recommendations for the management of spasticity in MS. **Objectives:** To evaluate self-reported spasticity in MS patients enrolled in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, and to identify current spasticity management patterns. **Methods:** The NARCOMS Registry is a self-report registry. Semi-annual surveys capture sociodemographic and clinical information and disability status (Patient Determined Disease Steps [PDDS], Performance Scales). In October 2008, participants were asked questions regarding spasticity. **Results:** A total of 10,200 US residents responded (66%). Spasticity affected more than 80% of participants (30.1% reported moderate to totally disabling spasticity). More severe spasticity was associated with greater PDDS scores (r = 0.54), mobility impairment (r = 0.53), bladder dysfunction (r = 0.46), higher levels of fatigue (r = 0.47) and pain (r = 0.50), and longer disease duration (r = 0.19) (all P < .0001). Over 80% of participants reported receiving at least one spasticity treatment. Oral medications were the most common treatment used overall. The mean number of medications increased with the severity of spasticity. Close to 7% of participants reported ever using botulinum toxin (BT). The odds of using BT increased as the severity of spasticity increased. Participants receiving care from a neurologist had a twofold increase in use of BT (fourfold increase with a physiatrist). A total of 310 participants reported currently using intrathecal baclofen (ITB). The use of ITB increased with levels of disability and spasticity severity. Receiving care from a physiatrist was associated with fivefold increased odds of using ITB. Severity of spasticity was the only predictive factor in treatment satisfaction in a logistic regression model. **Conclusions:** Most patients received at least one treatment modality for spasticity. Oral medications were the most commonly used treatment, closely followed by stretching. There was evidence of treatment escalation as the reported spasticity severity increased. The type of provider had a strong impact on the use of BT and ITB therapies.


**Keywords:** Symptomatic treatment of MS, Service delivery in MS, Rehabilitation strategies and therapy and MS

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**(S129) ADHERENCE TO FIRST-LINE IMMUNOMODULATORY DRUGS IN MULTIPLE SCLEROSIS**

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**Background:** First-line immunomodulatory drugs (IMDs) used for the treatment of multiple sclerosis (MS) include the beta-interferons and glatiramer acetate. If patients are unable to comply with therapy, then potential gains from treatment will not be optimized. **Objectives:** 1) Characterize duration of uninterrupted use of a) the initial IMD, and b) all first-line IMDs combined; 2) examine baseline predictors of adherence: sex, age, baseline disability, disease duration, and IMD type; and 3) determine whether adherence changed over time. **Methods:** This was a retrospective analysis of 2051 MS patients prescribed an IMD in British Columbia, Canada, from 1995 to 2009. Time to cessation of drug was determined using survival analysis; potential baseline predictors of adherence (sex, age, disease duration, and baseline disability as measured by Expanded Disability Status Scale [EDSS] score) were examined via univariate (Kaplan-Meier) and multivariable (Cox proportional hazards) models. **Results:** Patients adhered to their initial first-line IMD for a median of 4.2 years (95% confidence interval [CI], 3.8-4.7), and to any first-line IMD for a median of 6.9 years (95% CI, 6.4-7.4) before ceasing IMD therapy, taking a break from therapy for greater than 3 months, or switching to a second-line therapy. However, one-quarter of patients stopped their initial IMD within 1.2 years (95% CI, 1.1-1.4) and any first-line IMD within 2.2 years (95% CI, 1.9-2.4). Factors associated with poor adherence included greater disability (higher EDSS score) and younger age. **Conclusions:** Given the chronic nature of MS, long-term adherence to IMDs in MS is likely suboptimal for many patients. The reasons why younger patients, who may have the most to gain from IMD treatment, were the least adherent require further investigation.

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**Disclosure:** Nothing to disclose.

**Keywords:** Disease-modifying treatment in MS
posters

(S130) IMPACT OF TREATMENT ADHERENCE ON CLINICAL AND ECONOMIC OUTCOMES
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Background: The goals of treating multiple sclerosis (MS) with disease-modifying therapies (DMTs) are to slow the rate of disease progression and reduce relapses. Medication adherence in chronic diseases like MS plays an important role in long-term disease management. However, there are limited data on the impact of treatment adherence on MS-related clinical and economic outcomes in the real-world setting. Objectives: To assess the impact of treatment adherence on MS-related hospitalizations (INP), emergency department (ED) visits, relapses, and medical costs. Methods: Patients with ≥1 DMT (intramuscular or subcutaneous interferon beta-1a, interferon beta-1b, or glatiramer acetate) between July 1, 2004, and June 30, 2008, were identified from an administrative claims database. The first DMT received during the study period was defined as the index treatment, and ≥12-month pre- and ≥12-month post-index continuous health-plan enrollment were required. Adherence was assessed using medication possession ratio (MPR), defined as total number of days’ supply of the index treatment divided by a 1-year period; patients with an MPR >80% were defined as adherent. Multivariate analyses were used to evaluate the impact of adherence on MS-related clinical and economic outcomes after controlling for baseline demographic and clinical characteristics. Results: Among 2446 MS patients, 54.6% were adherent to their index DMT. Compared with the adherent group, nonadherent patients were significantly more likely to have MS-related INP visits (odds ratio [OR], 1.70; 95% confidence interval [CI], 1.28-2.26), ED visits (OR, 1.49; 95% CI, 1.12-1.98), and relapses (OR, 1.71; 95% CI, 1.43-2.05), and incurred higher annual medical costs ($3199; 95% CI, $2870-$3564 vs. $4485; 95% CI, $3982-$5052; P < .001, respectively). Conclusions: Adherent patients had statistically significantly better clinical and economic outcomes compared with nonadherent patients. Medication adherence is important in improving disease outcomes and should be considered an important factor in selecting the appropriate treatment.

Supported by: Biogen Idec, Inc and Elan Pharmaceuticals, Inc

Keywords: Economic issues and MS, Disease-modifying treatment in MS

(S131) EFFECTS OF TRAINING AND EDUCATION IN PEOPLE WITH MULTIPLE SCLEROSIS
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Background: People with multiple sclerosis (MS) exhibit a wide range of symptoms, often including reduced mobility and decreased quality of life. Objectives: The purpose of this study was to evaluate the effects of a 12-week guided wellness program including upper- and lower-extremity resisted strengthening exercises; cardiorespiratory fitness training; and interactive wellness education, including nutrition, sleep hygiene, energy conservation, and stress management. We hypothesized that participation would improve overground gait function, lower-extremity torque production, strength, and quality of life. Methods: The target population consisted of six subjects diagnosed with MS in a stable disease process. The program was offered twice a week for 12 weeks with the guidance of a licensed occupational therapist. The following outcome assessments were completed before and after the 12-week period: Multiple Sclerosis Quality of Life–54 (MS-QOL-54) interview physical (PHC) and mental health (MHC) composite scores, 6-minute and 10-m timed walk, Timed Up and Go (TUG) test, Box & Blocks test (BBT), Expanded Disability Status Scale (EDSS), manual upper-extremity strength testing (MMT), isometric torque measurements, and dynamometer grip strength testing. Results: Five subjects completed the 12-week course. One subject dropped out because of transportation issues after 2 weeks. The program was well tolerated by all subjects and for the majority resulted in improved overground gait function corresponding to improvements in isometric torque production. Changes exceeded the minimal detectable change in the 10-m timed walk (three subjects) and TUG test (one subject). All subjects experienced improved upper-extremity function in at least one hand as measured by the BBT, which did not directly correspond to improvements in grip strength. Improvements in the MS-QOL-54 were demonstrated for both composite scores. No changes were observed in EDSS score. Conclusions: This small pilot study demonstrates that a wellness program for people with MS in a community-based fitness center may be beneficial in maintaining or improving quality of life and overground walking ability. Further studies are needed to discern efficacious dosing and intensity for the disease process.

Disclosure: Nothing to disclose

Keywords: Rehabilitation strategies and therapy and MS

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(S132) PATIENT-PERCEIVED SEVERITY OF STRESS DECREASES BETWEEN BASELINE AND FIFTH-YEAR INTERVAL
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Background: A link between stress and multiple sclerosis (MS) has been widely accepted for decades, and modern views hold that stress is related to exacerbations and progression. However, research has been limited to existing...
studies based on small sample sizes. **Objectives:** To examine patient-perceived stress levels over a 5-year period by duration from symptom onset, disability, and disease types. **Methods:** The study design was a retrospective cohort study of 1250 patients with MS. Clinical, demographic, and patient reports using the LIFEware instrument, which measures patient-perceived disability and emotional states, were extracted from the New York State Multiple Sclerosis Consortium registry for patients aged 18 to 60, with complete data at baseline and fifth-year interval. **Results:** Of the patients, 75.1% were female and 94% white; the mean (SD) age at symptom onset was 31.5 (9.0) years, and the mean duration from symptom onset to registration was 11.5 (8.7) years. There was an overall reduction in stress levels from baseline to fifth-year interval for all subgroups. Stress levels did not significantly differ by disease type at registration, Expanded Disability Status Scale (EDSS) score, duration from symptom onset, sex, or age. The proportion of patients reporting moderate-to-high levels of stress at baseline was 42.9% of relapsing-remitting MS (RRMS) patients and 41.6% of patients with progressive disease types. The proportions decreased over the fifth-year interval to 35.3% of RRMS patients and 31.3% of RMS patients with DMT use. There was a decrease in the progressive disease group, with 28.4% reporting high stress levels at the fifth-year interval. **Conclusions:** It appears that the proportion of MS specialty-care patients who perceive high levels of stress at baseline abates over a 5-year interval, with the greatest decrease for RRMS patients occurring with DMT use. Because this study includes only patients of MS-care specialists without comparison with patients of other provider types, we cannot rule out the potential effect of the care environment and likelihood of drug treatments related to stress reduction. Further study is warranted to understand how stress reduction is related to progressive disease types, as well as investigation of the effect of high or moderate chronic stress.

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**Keywords:** Psychosocial issues in MS, Comprehensive care and MS, Quality of life in MS

**(S133) COMPUTER-ASSISTED COGNITIVE REHABILITATION FOR MULTIPLE SCLEROSIS: UPDATED FINDINGS**

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**Background:** Preliminary data from our clinic have been presented that were encouraging for the cognitive rehabilitation of people with multiple sclerosis (MS). Since then, we have recruited additional participants, and the data lend conclusive evidence to our hypotheses. **Objectives:** Cognitive deficits are common in individuals with MS, with a prevalence of 50% to 60%. Currently, options for treatment are limited. Therefore, we are evaluating the effectiveness of a computer-assisted cognitive rehabilitation (CACR) program. This intervention has been shown to improve neuropsychological processes in individuals with cognitive deficits unrelated to MS, thus showing promise for this study. **Methods:** Twenty-two individuals with MS demonstrating mild-to-moderate cognitive deficits on formal neuropsychological testing were recruited to participate in a 30-week study. Subjects completed 1 hour of CACR days a week at home, and their progress was monitored using a log and recorded data. Patients completed pre and post MicroCog neuropsychological assessment. **Results:** Pre/post MicroCog test analyses demonstrated statistically significant changes in general cognitive functioning and proficiency, attention and mental control, memory, reasoning, spatial processing, and reaction time. In addition, information processing speed and accuracy approached significance. **Conclusions:** In general, these preliminary results suggest that participating in this online cognitive rehabilitation program produced improvements in cognitive functioning.

**Supported by:** Maxine Mesinger Clinic, Baylor College of Medicine

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS

**(S134) BELIEFS ABOUT BREAST CANCER SCREENING AMONG WOMEN WITH MULTIPLE SCLEROSIS**

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**Background:** Breast cancer is a leading cause of cancer-related death among women. Although limited research suggests that women with multiple sclerosis (MS) have a slightly higher risk of developing breast cancer than the general population, little is known about specific attitudes and beliefs of women with MS regarding breast cancer screening (mammography, breast self-exam [BSE]). **Objectives:**
The purpose of this study was to explore beliefs about breast cancer screening and mammography among women with MS. **Methods:** A sample of 273 women (mean ± SD age, 59.6 ± 9.8; mean time since diagnosis, 22 years) completed a modified version of Champion’s Breast Cancer Screening Belief Scale (BCBSB) as part of a longitudinal survey of health promotion and quality of life among people with MS. The original BCBSB was adapted for use with women with MS using qualitative data from interviews with 36 women with MS. The modified BCBSB includes 29 items that measure beliefs about the perceived benefits and barriers to mammography and BSE, self-efficacy in performing BSE, and perceived susceptibility to breast cancer. This instrument uses a Likert-type response scale ranging from 1 to 5 (strongly disagree to strongly agree). **Results:** The women most frequently reported feeling “good about taking care of my health” (83.7%) and that mammograms “help . . . find lumps early” (81.5%). The most frequent barriers included pain (30.2%) and difficulty in positioning (23.2%) for mammography and decreased finger sensation (27.2%) and remembering (44.3%) for BSE. Most of the women (64.5%) felt confident in their ability to perform BSE, but only half reported being able to identify the difference between abnormal and normal breast tissue. Interestingly, 27% reported not thinking about developing breast cancer because they have “enough to deal with.” **Conclusions:** Since beliefs and behavior related to breast cancer screening have been linked in other populations, future research should focus on identifying factors influencing behaviors reflecting participation in breast cancer screening among women with MS as well as their beliefs.

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**Disclosure:** Nothing to disclose

**Keywords:** Imaging and MS

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**(S135) QUALITY OF LIFE DATA FROM NARCOMS: DIFFERENCES BY SOCIO DEMOGRAPHIC FACTORS**

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**Background:** In the fall of 2003, the North American Research Committee on Multiple Sclerosis (NARCOMS) began to collect longitudinal health-related quality of life (HRQOL) information from its registry participants. **Objectives:** This study aimed to describe the baseline HRQOL of the registry participants and to determine whether differences exist by sociodemographic factors. **Methods:** HRQOL was measured using the 12-item Short Form Health Status Survey (SF-12), which provides two summary scores: a physical composite score (PCS) and a mental composite score (MCS), each ranging from 0 (worst) to 100 (best). The US general population mean for both the PCS and MCS is 50.0, with a standard deviation (SD) of 10.0. **Results:** The average age of the registry participants was 51.2, and the majority were female (74.9%). A total of 3639 participants completed the SF-12, with an overall mean (SD) PCS of 39.8 (10.4) and an overall mean MCS of 51.7 (9.2). Participants ≤50 years of age had a higher PCS than those >50 (42.6 vs. 37.2, P = .001). However, participants ≤50 had a lower MCS than participants >50 (51.0 vs. 52.4, P = .001). Females had a higher PCS than males (40.6 vs. 37.6, P = .001) but a similar MCS (51.6 vs. 52.3, P = .09). Participants who were married had a higher MCS than those who were not (52.1 vs. 50.9, P = .001) but a similar PCS (39.8 vs. 39.5, P = .47). Participants with postsecondary education had a higher PCS than those without (41.1 vs. 37.4, P = .001) and also a higher MCS (52.1 vs. 51.0, P = .001). Those who were employed had a higher PCS than those who were not (45.7 vs. 36.0, P = .001) and a higher MCS (52.6 vs. 51.1, P = .001). Finally, participants with a steady income had a higher PCS than those who did not (41.3 vs. 39.7, P = .001) and a higher MCS (52.4 vs. 50.9, P = .001).

**Conclusions:** The overall mean PCS of the participants was lower than their overall mean MCS, suggesting that MS may have more impact on physical than on mental HRQOL. There were differences in PCS and MCS by all sociodemographic factors examined, but the most consistent pattern was both lower physical and mental HRQOL scores among participants who had less education, were unemployed, and had no steady income. The results suggest that women and younger people may have better physical HRQOL than men and older people, and that being married may have a positive impact on mental HRQOL.

**Supported by:** NARCOMS is supported by the Consortium of Multiple Sclerosis Centers.


**Keywords:** Quality of life in MS

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**(S136) DURABLE EFFICACY OF ALEMTUZUMAB TREATMENT: CLINICAL EFFICACY AT FOUR YEARS**

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**Background:** Alemtuzumab demonstrated efficacy superior to that of subcutaneous interferon beta-1a (IFNβ-1a) in a 3-year safety and efficacy trial with relapsing-remitting multiple sclerosis (RRMS) patients, significantly reducing the relapse rate and risk for 6-month sustained accumulation of disability (SAD) [all comparisons P < .001]. Notable alemtuzumab-related adverse events included infusion reactions, predominantly mild-to-moderate infections, and secondary autoimmunity, principally immune thrombocytopenic purpura and thyroid disorders. In an extension study, a subset of patients has been followed for 4 years. **Objectives:** To summarize the clinical efficacy of alemtuzumab treatment for relapse and 6-month SAD after 4 years of follow-up. **Methods:** A total of 334 early, active RRMS patients were randomized 1:1:1 to receive IFNβ-1a (44 μg subcutaneously [SC] 3 times/week), or 12 mg/day or 24 mg/day alemtuzumab. Alemtuzumab was administered intravenously at months 0 and 12. Some patients (21%) received an optional third cycle at month 24. Subcutaneous IFNβ-1a was provided through month 36. Analyses of patients with 4-year follow-up data (47% of the original sample) compared treatment groups on the primary efficacy end points of time to 6-month SAD and relapse rate, as well as the proportion of patients who are relapse-free and the proportion of patients who do not experience 6-month SAD. **Results:** At 4 years, pooled alemtuzumab data demonstrated a 73% reduction in risk for
SAD (P < .0001). The annualized relapse rate for pooled alemtuzumab was 0.10 (95% confidence interval [CI], 0.08-0.12) versus 0.33 (95% CI, 0.28-0.41) for IFNβ-1a. At year 4, 77% of alemtuzumab-treated patients were relapse-free, compared with 49% of IFNβ-1a-treated patients; 91% of alemtuzumab patients were 6-month SAD-free versus 68% of IFNβ-1a patients (P < .001). Updated safety results will be reported. Conclusions: Alemtuzumab-treated patients maintained a better efficacy profile for 6-month SAD and relapses compared with IFNβ-1a-treated patients among patients followed for 4 years. Alemtuzumab treatment for the majority of patients had occurred 3 years earlier, indicating a durable treatment effect.

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CAMMS223 Study Group: Genzyme (other financial benefit).

Keywords: Disease-modifying treatment in MS

(S137) EARLY ONSET OF EFFECT WITH CLADRIBINE TABLETS IN THE CLARITY STUDY

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Objectives: Cladribine is activated preferentially in lymphocyte subtypes resulting in targeted and sustained immunomodulation, which provides the rationale for use of cladribine tablets as a short-course annual multiple sclerosis (MS) treatment. We investigated the time of onset of treatment effect with cladribine tablets relative to placebo in the CLARITY (CLAdRibine tablets Treating multiple sclerosis orally) study in patients with relapsing-remitting MS (RRMS). Methods: Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score, 0–5.5) were randomized 1:1:1 to receive cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given in short courses (once daily for 4–5 days) in 2 or 4 consecutive months (28-day periods) in the first 48 weeks, then two short courses at weeks 48 and 52 for both groups. Qualifying relapses were evaluated serially throughout the study, and magnetic resonance imaging (MRI) parameters (T1-Gd+, active T2, and combined unique [CU] lesions per patient per scan) were evaluated at 24, 48, and 96 weeks post-randomization. Results were previously presented at the Congress of the European Committee for Treatment and Research in Multiple Sclerosis in 2009. Results: The intention-to-treat (ITT) population included 456, 433, and 437 patients randomized to the 5.25 mg/kg, 3.5 mg/kg, and placebo groups, respectively. Differences in qualifying relapse rate between active treatment groups versus placebo were apparent as early as 4 weeks after the first treatment course (5.25 and 3.5 mg/kg vs. placebo: 0.27 and 0.23 vs. 0.42, respectively). Statistically significant differences for all three MRI parameters were also evident at the first assessment (mean number of lesions per patient per scan in the 5.25 and 3.5 mg/kg vs. placebo groups at week 24: 0.07 and 0.07 vs. 0.97 for T1 Gd+ lesions, 0.33 and 0.45 vs. 1.59 for active T2 lesions, and 0.38 and 0.49 vs. 1.91 for CU lesions, respectively). Conclusions: Treatment with cladribine tablets resulted in early onset of effect in clinical and MRI outcomes. These results support the potential role of cladribine tablets in the treatment of MS.

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Keywords: Disease-modifying treatment in MS

(S138) MANUAL WHEELCHAIR PROPULSION PATTERN USE BY PEOPLE WITH MULTIPLE SCLEROSIS

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Background: The symptoms of multiple sclerosis (MS) vary considerably and may include sensory deficits, cognitive problems, weakness, tremor, and spasticity. These symptoms and, in particular, fatigue, poor trunk control, and deficits in upper-limb functioning, may influence efficiency in wheelchair self-propulsion. As a result, a manual wheelchair may be considered an inappropriate mobility aid for people with MS. In the literature four propulsion patterns have been identified; contrary to findings for wheelchair users with spinal cord injury, it has been reported that people with MS commonly use the least effective pattern. Objectives: To determine the most commonly used manual wheelchair propulsion pattern by people with MS and assess which factors influence the preference. Methods: Sixty manual wheelchair users with MS were clinically assessed for upper-limb active range of motion and trunk stability in order to determine whether these factors or demographic factors, disease factors, or wheelchair use history influence the choice of wheelchair propulsion pattern. Video documentation of each subject during propulsion was analyzed in order to identify propulsion pattern. Results: Fifty-four (90%) subjects used the “arcing” propulsion pattern, the least efficient pattern as reported in the literature. Sixteen (26.7%) subjects had impaired trunk stability, and 38 (63.3%) subjects demonstrated some deficit in either

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extremity for active range flexion-extension. Twenty (33.3%) subjects had no deficits on active range flexion-extension and had normal trunk control. Upper-limb range of motion and trunk stability were not significant in determining preference for propulsion pattern ($P = 1.03$ and $P = .38$, respectively). Demographic and disease factors and wheelchair use history were also not significant in determining propulsion pattern.

**Conclusions:** The person with MS uses the least efficient pattern overall, requiring frequent repetitions, although with a smaller range of movement. This may be an energy-conservation technique due to neurologic fatigue, a problem that other groups of wheelchair users do not generally face.

**Supported by:** Foundation of the Italian Multiple Sclerosis Society (FISM)

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**Keywords:** Rehabilitation strategies and therapy and MS

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**S139** VASCULOPATHIES MIMICKING MULTIPLE SCLEROSIS

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**Background:** Rare conditions that may mimic multiple sclerosis (MS) in their clinical course and radiologic findings continue to pose a challenge in accurately diagnosing MS. We report two women presenting with relapsing neurologic symptoms that raised suspicions of MS. **Objectives:** To demonstrate the importance of considering rare cerebrovascular diseases in the differential diagnosis of central nervous system (CNS) demyelination. **Methods:** Case presentation. **Results:** We present two women who had been incorrectly diagnosed with MS based on transient neurologic symptoms and T2 hyperintensities on brain magnetic resonance imaging (MRI). A 50-year-old woman presented at age 41 with dizziness, nausea, and headaches. She subsequently developed numbness and stiffness in her left leg, transient diplopia, several months of fatigue, urinary urgency, depression, and cognitive problems. Brain MRI showed multiple periventricular and juxtacortical T2-hyperintense lesions, some of which were enhancing. She was seen by different neurologists and diagnosed with MS. Vessel imaging including a cerebral angiogram, however, revealed multiple significant intracranial stenoses, occlusions, and aneurysms. The second patient is a 52-year-old woman who was diagnosed with relapsing–remitting MS at age 31 after she had presented with several episodes of right hand weakness and left face numbness, brief episodes of loss of consciousness, and fatigue and depression. She received disease-modifying treatment with Avonex. She then presented to us with acute-onset severe global aphasia as well as moderate right arm weakness after losing consciousness. Magnetic resonance angiography showed several high-grade stenoses of the intracranial vessels with normal extracranial vasculature, suggestive of moyamoya disease, which was confirmed by cerebral angiography. **Conclusions:** We report on two women presenting with transient relapsing neurologic symptoms that raised suspicions of MS but ultimately showed vascular etiology. Moyamoya disease is rare, and significant intracranial cerebrovascular disease is uncommon in young women, but vasculopathies are important differential diagnoses in patients presenting with first symptoms suggestive of MS, particularly because the treatments are substantially different.

**Disclosure:** Nothing to disclose

**Keywords:** Etiology of MS, Epidemiology of MS

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**S140** CENTRAL NERVOUS SYSTEM DEMYELINATION AND ANTI–TUMOR NECROSIS FACTOR ALPHA THERAPY

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**Background:** Tumor necrosis factor alpha (TNF-α) inhibitors have gained more importance in the treatment of Crohn’s disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis. An association between anti-TNF-α therapy and peripheral and central nervous system (CNS) demyelination has been described, although the extent of this association and its impact on clinical practice have not been fully evaluated. However, anti-TNF-α therapy may need to be included in differential diagnosis considerations when assessing patients for possible demyelinating disease. **Objectives:** To assess the relevance of TNF-α inhibitor treatment in the differential diagnosis of possible CNS demyelination. **Methods:** Case presentation and literature review. **Results:** A 35-year-old man with severe Crohn’s disease since age 12 was placed on infliximab (Remicade) at age 30. At age 33 years, he developed urinary urgency and incontinence and was found to have detrusor overactivity classified as neurogenic bladder by an experienced urologist, although no other neurologic symptoms or signs were found on history or clinical examination. Magnetic resonance imaging (MRI) of the brain showed minimal white matter disease; MRI of the cervical and thoracic spine was unremarkable. The second patient is a 39-year-old woman with severe psoriatic arthritis who has been on etanercept (Enbrel) since age 34. She presented with right-sided optic neuritis. Brain MRI showed very few punctate T2 signal abnormalities within the bilateral frontal white matter as well as along the deep surface of the corpus callosum without contrast enhancement. **Conclusions:** We present two cases of possible CNS demyelination and relevant literature review. Although the cases we present demonstrate that it is difficult to prove a causal relationship between TNF-α inhibitors and the development of CNS demyelination, it appears that patients treated with TNF-α inhibitors need to be assessed more frequently for neuropathic side effects. Providers in neurologic practices and multiple sclerosis (MS) clinics should be aware of this possible consideration. As discontinuation of the anti-TNF-α therapy has led to improvement of neurologic symptoms in most cases reported in the literature, other disease-modifying treatments to prevent future attacks of MS may not be necessary.

**Disclosure:** Nothing to disclose

**Keywords:** Etiology of MS, Epidemiology of MS

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**S141** DYNAMIC BALANCE PREDICTS WALKING SPEED AND ENDURANCE IN ADULTS WITH MULTIPLE SCLEROSIS

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**Background:** Dynamic balance is not routinely assessed in multiple sclerosis (MS) clinical practice and may be a significant contributor to both a decline in ambulation and self-perception of walking limitation. **Objectives:** The purpose of this study was to determine whether dynamic
balance impairment is predictive of walking speed, walking endurance, and self-reported limitations in walking in adults with MS. **Methods:** Seventeen adults with MS (8 male, 9 female; mean ± SD age, 47.2 ± 8.4 years) and moderate clinical disability (mean Expanded Disability Status Scale [EDSS] score, 4.2 ± 1.1; range, 3–6) were assessed on dynamic balance using the Dynamic Gait Index (DGI) and Four Square Step Test (FSST). In addition, the Timed 25-Foot Walk Test, the distance walked during the 6-Minute Walk Test, and the self-report Multiple Sclerosis Walking Scale–12 were measured. The relationship of dynamic balance impairment with walking speed, endurance, and self-reported limitations in walking was assessed by forward stepwise multiple linear regression. **Results:** Performance on the two dynamic balance measures was moderately correlated \( r = -0.56, P < .05 \). Dynamic balance impairment was predictive of walking speed \( R^2 = 0.67, P < .001 \) and walking endurance \( R^2 = 0.51, P = .01 \). Of the two dynamic balance tests, the FSST was the stronger predictor of walking speed \( R^2 = 0.62 \) and walking endurance \( R^2 = 0.51 \). Dynamic balance impairment was not predictive of self-reported limitation in walking \( R^2 = 0.02, P = .16 \). **Conclusions:** These preliminary data suggest that dynamic balance impairment, as measured by the FSST, helps to predict walking speed and walking endurance. Despite the high correlations with accepted measures of ambulation in MS, dynamic balance did not correlate with self-report limitations of walking. Additional research is needed to determine whether dynamic balance training improves walking speed and endurance in adults with MS, and the factors that predict self-reported limitations in walking in adults with MS.

**Supported by:** National Institutes of Health grant K12-HD055931-02


**Keywords:** Rehabilitation strategies and therapy and MS

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**S142 ACCELEROMETERY: FREE-LIVING MEASURE OF AMBULATORY IMPAIRMENTS IN MULTIPLE SCLEROSIS**

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**Background:** Accelerometers are motion sensors that might provide a direct, objective, unobtrusive, and cost-effective measure of ambulatory impairments under free-living conditions among people with multiple sclerosis (MS). Indeed, total daily movement counts from accelerometers have been strongly and negatively correlated with scores from self-report measures of walking impairment such as the Patient Determined Disease Steps (PDDS) scale and Multiple Sclerosis Walking Scale–12 (MSWS-12). One limitation of previous research is that researchers have not correlated total daily movement counts from an accelerometer with objective measures of ambulatory impairment such as the 6-Minute Walk (6MW) or Timed Up and Go (TUG). **Objectives:** The present study examined the correlation of total daily movement counts from an accelerometer with both self-report and objective measurements of ambulatory impairment in people with MS. **Methods:** The sample included 31 individuals with a definite diagnosis of MS. The participants filled out the PDDS and MSWS-12, completed the 6MW and TUG, and then wore an Actigraph model 7164 accelerometer during the waking hours of a 7-day period. The data were analyzed using Spearman rho rank-order correlations (\( \rho \)) in SPSS for Windows, version 17.0. **Results:** The mean ± SDs were 180,724 ± 107,427 for accelerometer counts, 2.1 ± 1.7 (PDDS), 31.5 ± 26.2 (MSWS-12), 1,540 ± 462 (6MW), and 8.8 ± 6.1 (TUG). Total daily movement counts from the accelerometer had large, statistically significant correlations with PDDS scores \( \rho = -0.53, P < .005 \), MSWS-12 scores \( \rho = -0.57, P < .001 \), 6MW distance \( \rho = 0.78, P < .0001 \), and TUG \( \rho = -0.67, P < .0001 \). Moreover, there were large correlations between PDDS and MSWS-12 scores \( \rho = 0.79, P < .0001 \) and 6MW distance and TUG \( \rho = -0.78, P < .0001 \). **Conclusions:** This study provides additional, stronger evidence that accelerometry provides a measure of ambulatory impairment that can be assessed in the context of daily living. This suggests that accelerometry might have value as a marker of free-living mobility impairment for inclusion in clinical research and practice.

**Disclosure:** Nothing to disclose

**Keywords:** Equipment in MS, Disease-modifying treatment in MS, Rehabilitation strategies and therapy and MS

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**S143 THE IMPACT OF GAIT DISABILITY ON THE CALIBRATION OF ACCELEROMETER OUTPUT IN ADULTS WITH MULTIPLE SCLEROSIS**

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**Background:** Accelerometer activity counts have been correlated with energy expenditure during treadmill walking among minimally impaired, independently ambulatory adults with multiple sclerosis (MS). This association yielded cut-points for computing time spent in moderate-to-vigorous physical activity (MVPA) based on the accelerometer output. **Objectives:** The current study examined the impact of gait disability on 1) the association between accelerometer activity counts and energy expenditure during overground walking in people with MS, and 2) the calibration of accelerometer output for computing cut-points that correspond with time spent in MVPA. **Methods:** The sample included 24 individuals with a definite diagnosis of MS, and 10 people reported gait disability based on Patient-Determined Disease Steps (PDDS) scores. The participants undertook three 6-minute periods of overground walking while wearing an Actigraph accelerometer (model 7164) and a portable metabolic unit (K4b2 Cosmed, Italy). The first period of walking involved the participants walking at a self-selected, comfortable speed, and this was followed by two consecutive walking periods that were either ½ mph above or below the comfortable walking speed. **Results:** Strong linear relationships were observed between activity counts and energy expenditure during overground walking in the overall sample \( R^2 = 0.90 \) and in the subsamples with and without gait disability \( R^2 = 0.88 \) and \( R^2 = 0.91 \), respectively. The slope of the relation-
ship was significantly steeper in the subsample with gait disability ($\beta = .0049$) compared with those without gait disability ($\beta = .0026$). The difference in slopes yielded a significantly lower cut-point for MVPA in those with gait disability (1886 vs. 2717 counts/min). Conclusions: Such findings provide evidence for a strong linear relationship between activity counts and energy expenditure during overground walking in people with and without gait disability. The findings verify that cut-points for quantifying time spent in MVPA are significantly lower in people with MS who have gait disability.

Disclosure: Nothing to disclose

Keywords: Equipment in MS, Rehabilitation strategies and therapy and MS

(S144) OBSERVATIONAL STUDY OF MULTIPLE SCLEROSIS IN THE IRANIAN POPULATION IN FRASER HEALTH, BRITISH COLUMBIA

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Background: Canada and the northern United States have some of the highest reported rates of multiple sclerosis (MS). In contrast, the prevalence of MS was found to be significantly lower in the Middle East. Although genetic susceptibility has been well demonstrated in twin and family studies, the geographic distribution of MS suggests a strong environmental contribution as well. Various environmental contributing factors have been proposed, including infections, immunizations, climate, diet, and stressors. Objectives: To study the effects of migration from Iran (a low-prevalence area) to British Columbia (a high-prevalence area) on MS onset; and to investigate how MS presents in this poorly studied population and the effect that various environmental factors may have. Methods: A standardized questionnaire form assessing factors such as age at migration, exposure to sunlight, and others was created for the study. Interviews and chart reviews were performed for Iranian MS patients. Information was collected on 22 patients (with all patients being diagnosed in Canada and 17 of 22 experiencing their first onset of symptoms in Canada as well). Results: The rate of MS in the Iranian population in Fraser Health was found to be 110 in 100,000. The male:female ratio was 1:1. Relapsing-remitting MS was present in 20 of the patients, and two having tumefactive MS. Patients experiencing MS onset in Iran took an average (±SD) of 15.2 (±6.32) more years to be diagnosed, as compared with those experiencing the onset in Canada. The most commonly reported onset symptoms were sensory impairment (59%), motor weakness (32%), and visual deficits (23%). Smoking half a pack or more of cigarettes a day predisposed to an earlier age of MS onset than that for the rest of the patients: 25.2 (±3.33) years versus 35.1 (±1.94) years. Conclusions: The results suggest that Iranians do not have genetic protection from acquiring MS and that when taken out of their native environment are as likely as other Canadians to get MS. The difference in the health-care systems may contribute to the shorter time from onset to diagnosis in Canada. Increasing sample size by collecting data from other MS centers will allow for a better understanding of whether smoking in the Iranian population has a robust effect. The final analysis of the data will be presented at the conference.

Supported by: Consortium of Multiple Sclerosis Centers

Disclosure: Nothing to disclose

Keywords: Epidemiology of MS

(S145) DEVELOPMENT OF A SCALE TO MEASURE BARRIERS TO DISEASE-MODIFYING THERAPY ADHERENCE IN MULTIPLE SCLEROSIS

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Background: Patients with multiple sclerosis (MS) have a number of options when it comes to choosing a disease-modifying therapy (DMT) with their health-care professional. All currently available therapies approved for the treatment of MS are injection-based. Objectives: To develop a survey to investigate the factors underlying poor adherence to MS therapies. Methods: A review of the scientific literature was undertaken, in parallel with a qualitative review of an online discussion forum from the MS community on the website PatientsLikeMe.com. From this analysis, items were generated to create a questionnaire to quantify issues related to barriers to adherence and treatment burden. Cognitive debriefing was used to refine the items. An online sample was recruited from the PatientsLikeMe MS site for purposes of exploratory analysis and psychometric validation. The questionnaire was administered via online survey through PatientsLikeMe.com. Results: A total of 445 respondents completed the online survey, yielding a response rate of 37%. Most respondents were female (n = 353, 79%), with a mean (SD) age of 46 (10) years. Thirty-one percent of patients reported missing at least one dose of their DMT. The number of patients reporting missing a dose of their medication in the past 28 days varied significantly between DMTs (P < .001). The barriers to adherence most likely to be rated as either “moderately” or “extremely” important to patients who missed a dose were “Did not feel like taking my medication” (38%), “Memory problems” (35%), “Tired of taking my medication” (33%), “Too busy” (32%), and “Side effects of the injection” (27%). Twenty-nine percent of patients reported difficulty in grasping or holding their DMT injector. Conclusions: A number of factors affecting adherence to DMTs were identified by the questionnaire. Our tool identifies these and could be used in clinical practice to improve adherence and maximize the benefit of DMTs. Further research is needed to establish the validity of the instrument.

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Keywords: Disease-modifying treatment in MS

(S146) EFFECTS OF NATALIZUMAB ON FATIGUE IN MULTIPLE SCLEROSIS: FINDINGS FROM THE ENER-G STUDY

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Background: Fatigue is a major quality of life problem for people living with MS. The purpose of this study was to assess the effects of Natalizumab (natalizumab) on subjective and objective measures of fatigue in people with relapsing-remitting MS. Objective: To quantify the effects of Natalizumab (natalizumab) on fatigue in people with relapsing-remitting MS. Methods: Data were extracted from a retrospective chart review of people with relapsing-remitting MS who were treated with Natalizumab (natalizumab) for at least 1 year. The data included baseline and post-treatment data on fatigue, quality of life, and functional status. Results: The results suggest that Natalizumab (natalizumab) significantly reduced subjective and objective measures of fatigue in people with relapsing-remitting MS. Conclusions: Natalizumab (natalizumab) is an effective treatment for fatigue in people with relapsing-remitting MS.
Background: Natalizumab treatment has demonstrated a positive impact on quality of life for patients with multiple sclerosis (MS). Fatigue is a common and disabling symptom of MS and may also contribute to cognitive difficulties experienced by patients. Objectives: To determine the effects of natalizumab treatment on fatigue in patients with relapsing MS. Methods: ENER-G is a 12-month, multicenter, open-label, single-arm study. The primary end point is change in Visual Analog Scale for Fatigue (VAS-F) 12 weeks (3 months) after initiating natalizumab. Secondary end points include changes in the Modified Fatigue Impact Scale (MFIS) and the Fatigue Severity Scale (FSS) at 3, 6, and 12 months, as well as in VAS-F at 6 and 12 months. Patients who exhibited fatigue (defined as an average VAS-F ≥60 across three visits) were selected for enrollment. Cognition data are also being collected as a tertiary end point. Results: A total of 89 patients were enrolled; 28 have completed the study. The mean ± SD age was 41.3 ± 7.72 years; 89.9% of patients were female. The median disease duration was 8 years (range, 1–39); the median Expanded Disability Status Scale (EDSS) score was 3.0 (range, 0.0–5.5); and the mean number of relapses during the past year was 1.6 ± 1.18. All patients had received prior therapy for MS, with 51% receiving at least two prior therapies. At the time of this analysis, the median number of natalizumab infusions was 6 (range, 1–13). A significant improvement in VAS-F scores was observed from baseline (mean, 77.7 ± 10.19) to week 12 (mean change, −14.8 ± 17.16; P < .0001). Significant improvements were also seen for changes in FSS scores from baseline (median, 6.3; range, 3.9–7.0) to week 12 (median change, −0.4; range, −2.9 to 1.4; P < .0001) and in total MFIS scores from baseline (median, 59.1 ± 12.21) to week 12 (mean change, −7.3 ± 11.82; P < .0001), as well as in all individual components of the MFIS (all P ≤ .0002). Conclusions: Fatigue, as determined by patient-reported VAS-F, MFIS, and FSS, was significantly improved 12 weeks after initiating natalizumab therapy. Building upon earlier presentations of preliminary results, data up to 1 year and findings from analyses exploring the association between baseline characteristics and changes in fatigue will be presented.

Supported by: Biogen Idec, Inc, and Elan Pharmaceuticals, Inc


Keywords: Disease-modifying treatment in MS, Quality of life in MS, Symptomatic treatment of MS

(S147) QUALITY ASSURANCE/PERFORMANCE IMPROVEMENT BY A REHABILITATION TEAM: IMPACT ON MULTIPLE SCLEROSIS CARE

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Background: The MS Clinic at the Denver VA Hospital has been in existence for over 20 years. It is staffed by a physiatrist, nurse practitioner/clinic coordinator, psychologist, physical therapist, occupational therapist, speech/language pathologist, social worker, dietitian, and licensed practical nurse. Objectives: The purpose of this poster presentation is to describe the quality assurance/performance improvement (QA/PI) process undertaken to achieve Council on Accreditation of Rehabilitation Facilities (CARF) accreditation in 2009 for a Veterans Affairs rehabilitation-based multiple sclerosis (MS) clinic. Methods: In preparation for the CARF survey, a Microsoft Access database was developed to capture data on demographics, Expanded Disability Status Scale (EDSS) scores, functional status, activity limitations, participation restrictions, care needs, treatments and equipment offered, referrals made, and other variables. Satisfaction surveys from staff, patients, and stakeholders were also collected and analyzed. QA/PI projects addressed the following areas: identification of demographics, timeliness of consultation completion, analysis of audiology referrals, analysis of driving evaluations, analysis of neuropsychological assessment referrals. Results: Analysis of audiology referrals (N = 111); initiated for 25% of individuals assessed, 71% completed, 90% of those with abnormal findings, and 61% with hearing aid recommendations. Analysis of driving evaluations (N = 12): 9 for safety assessment, 4 for equipment evaluation. Of the 9 consultations for safety assessment, 78% of individuals (7) were provided with recommendations or training to improve safety. In both groups, when training was recommended, 75% (3 of 4) were deemed able to drive safely when training was completed. Analysis of neuropsychological assessment referrals in 2008 (N = 56): 78.5% completed, 79.5% with abnormal cognitive findings, 75% with identified psychiatric problems, and 79.5% total interventions recommended.

(S148) TREATMENT OF MULTIPLE SCLEROSIS WITH INTERFERON BETA-1A ASSOCIATED WITH AUTOIMMUNE HEMOLYTIC ANEMIA

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Background: Autoimmune hemolytic anemia (AIHA) is a rare condition that has been associated with interferon therapy, hepatitis C, and lupus. Although it is more often seen with interferon alpha (IFNa) treatment, there has been one documented case with interferon beta-1b (IFNb-1b) therapy in a patient with multiple sclerosis (MS). This case involves a 47-year-old patient with a 19-year history of MS who presented with generalized weakness, dyspnea on exertion, and fatigue for 2 months. Development of substernal chest pain prompted an emergency room evaluation. Laboratory evaluation revealed anemia with a hemoglobin level of 4 g/dL, and Coombs’ test was positive for warmautoantibodies. The patient had been on interferon beta-1a (IFNb-1a) therapy for 4 years prior to symptom onset. IFNb-1a was discontinued, and treatment with intravenous corticosteroids, oral steroid taper, and intravenous Rituxan resulted in resolution of symptoms. The patient remains stable at 6-month follow-up. The findings suggest that autoimmune hemolytic anemia should be considered if an MS patient experiences an unexplained decrease in hematocrit while taking IFNb-1a.

Disclosure: M.J. Williams: Teva Neuroscience, Pfizer (honoraria); Biogen Idec (consulting fee). R.J. Rahn, S.D. Williams, S.M. Wilson: Nothing to disclose.
**Conclusions:** Findings of the QA/PI projects will be summarized, including changes made to our practice as a result. Additionally, 2010 QA/PI projects in progress will be presented: 1) cooling products and factors affecting use/nonuse, 2) identification of community exercise/physical activity resources, 3) evaluation of timeliness and clinical relevance of renal studies.

**Supported by:** Denver VA Medical Center PMRS Department

**Disclosure:** Nothing to disclose

**Keywords:** Comprehensive care and MS, Rehabilitation strategies and therapy and MS, Service delivery in MS

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**($149$) PHARMACOKINETICS OF BG-12 ALONE AND WITH INTERFERON-beta-1A OR GLATIRAMER ACETATE**

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Biogen Idec, Inc, Cambridge, MA

**Background:** BG-12 is an oral therapy that exhibits anti-inflammatory and potentially neuroprotective mechanisms of action. It is currently being tested in phase 3 clinical trials for relapsing-remitting multiple sclerosis (RRMS). Two drugs commonly used to treat RRMS are interferon beta-1a (IFNβ-1a) and glatiramer acetate (GA). It is possible that BG-12 could be given with IFNβ-1a or GA.

**Objectives:** To assess the potential drug interaction for co-administration of BG-12 + intramuscular (IM) IFNβ-1a or subcutaneous (SC) GA.

**Methods:** Two phase 1, open-label, single-center, randomized, crossover studies each enrolled 26 healthy volunteers. Dosing sequences comprised two dosing periods separated by 7 days. Treatment consisted of BG-12, 240 mg twice a day, for 2 or 3 days alone (GA and IFNβ-1a studies, respectively) or given with a single IM IFNβ-1a 30-µg or SC GA 20-mg injection administered on day 2. Pharmacokinetic (PK) parameters, vital signs, electrocardiographic findings, and adverse events (AEs) were assessed.

**Results:** Twenty-five subjects completed the BG-12 + GA study, and 24 subjects completed the BG-12 + IFNβ-1a study. BG-12 metabolite (monomethyl fumarate [MMF]) concentrations in all treatment groups were comparable, suggesting no clinically significant effect of IM IFNβ-1a or GA on BG-12 disposition. The most common AEs were flushing with BG-12 alone (both studies) and BG-12 + GA, and flu-like symptoms with BG-12 + IM IFNβ-1a. There were no serious AEs or deaths. One subject with a transient, moderate increase in liver enzymes and neutropenia following BG-12 + IM IFNβ-1a treatment withdrew from the study. In the BG-12 + GA study, 1 subject discontinued after receiving BG-12 alone because of a mild erythematous facial nodule; 1 subject discontinued because of mild nausea after receiving BG-12 + GA. A mild increase in temperature and pulse was observed only following IM IFNβ-1a administration; no subject withdrew for these reasons. Hematologic shifts were observed in subjects receiving BG-12 alone and BG-12 + GA (mild neutropenia and anemia); no subject withdrew for these reasons. No clinically significant abnormalities on physical examination or ECG were observed.

**Conclusions:** The PK profile of BG-12 was not altered by co-administration with IM IFNβ-1a or GA, indicating no drug interaction. No safety profile change or new safety signals were identified.

**Supported by:** Biogen Idec, Inc

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**($150$) DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTINATIONAL STUDY OF AVP-923 FOR PSEUDOBULBAR AFFECT IN MULTIPLE SCLEROSIS**


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**Background:** Pseudobulbar affect (PBA) is characterized by uncontrollable outbursts of laughter or crying incongruent with the patient’s emotional state. Although it results in considerable distress for patients and caregivers, it is often underrecognized and undertreated. DMq is a combination of dextromethorphan (an NMDA receptor antagonist/sigma receptor agonist) and quinidine (a CYP2D6 inhibitor) that has demonstrated efficacy in PBA.

**Methods:** Adults with PBA in conjunction with multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS) were recruited in the United States and Latin America. Center for Neurologic Studies-Lability Scale (CNS-LS) score ≥13 was required. Eligible patients were randomized (1:1:1) to receive 1 of 2 doses of DMq (dextromethorphan 20 mg/quinidine 10 mg or dextromethorphan 30 mg/quinidine 10 mg) or placebo twice a day for 12 weeks. The primary outcome was change in number of laughing or crying episodes per day, analyzed using longitudinal negative binomial regression. Secondary outcomes included change in CNS-LS score and on a Pain Rating Scale (PRS). Safety/tolerability assessments included adverse event reports.

**Results:** Of 326 subjects, 129 had underlying MS. At baseline, they suffered, on average, >3 PBA episodes per day and had an average CNS-LS score of approximately 20. In the longitudinal analysis of PBA rate, the therapeutic effect relative to placebo was significant in the higher-dose group (P = .0280). A generalized estimating equation analysis showed a trend for superiority in both DMq groups (P = .0647 and P = .0527). Reductions in mean CNS-LS score were demonstrated for both DMq groups (vs. placebo) but did not reach statistical significance. In the higher-dose group, mean pain scores across time and means at days 15 and 29 showed trends for superiority over placebo (P = .0512 and P = .0859). The most common adverse events more frequent in the DMq groups than in the placebo group were dizziness, diarrhea, and somnolence. One patient in the higher-dose group and two in the placebo group reported nonfatal serious adverse events.

**Conclusions:** At both doses, efficacy results resembled those in previous studies of DMq containing quinidine at a higher dose, and safety and tolerability were improved.

**Supported by:** Avanir Pharmaceuticals

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Background: The role of diet in reducing the severity of multiple sclerosis (MS) has long been of interest. Past observational studies suggest that a diet low in total fat and saturated fat can reduce disease activity and disability progression. However, this study is the first randomized controlled study to examine the potential benefits and safety of a very-low-saturated-fat, plant-based diet in the management of relapsing-remitting MS. Objectives: The primary objective is to compare new T2 lesion formation on brain magnetic resonance imaging (MRI) of the low-fat diet group with that of the control group. The secondary objectives are 1) to assess the effects of the study diet on clinical activity of MS as assessed by relapse rate and disability progression as well as effects on fatigue, depression, and quality of life; 2) to study the effects of the study diet on serum markers of inflammation, soluble intercellular adhesion molecule–1, matrix metalloproteinase–1, tumor necrosis factor, and interferon; and 3) to assess compliance, safety, and tolerability of the study diet for 12 months. Methods: The study is a randomized controlled two-arm trial. Subjects (N = 54) are randomly assigned to the low-fat diet group or the control group, which follows their regular diet. Both groups will be instructed to exercise for 30 minutes a day, 5 days a week. Subjects are followed for 12 months and are evaluated at baseline and at 1, 3, 6, 9, and 12 months. They undergo brain MRI at baseline and at 12 months. Blood samples are collected for safety and immune assays at baseline and at 6 and 12 months. All visits include a physical examination, Expanded Disability Status Scale, Multiple Sclerosis Functional Composite, and self-administered questionnaires to assess MS-related quality of life, fatigue, depression, and level of physical activity. Medications, compliance, and adverse events are monitored by means of monthly follow-up calls. Results: Study is ongoing.

Supported by: The McDougall Research and Education Foundation


Keywords: Complementary/alternative therapies in MS, Quality of life in MS, Comprehensive care and MS
WHITAKER RESEARCH TRACK

Dr. John N. Whitaker was a world-famous researcher in multiple sclerosis. Not only did Dr. Whitaker engage in research himself, he encouraged budding scientists to enter the field and develop their skills and talents in this important work. The Consortium of Multiple Sclerosis Centers is proud to honor Dr. Whitaker’s memory by presenting the Whitaker Research Track each year as part of its annual meeting.

TH1 AND TH17 PATHWAYS DETERMINE OPPOSITE RESULTS OF INTERFERON BETA TREATMENT OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS AND RELAPSING-REMITTING MULTIPLE SCLEROSIS


Interferon beta (IFNβ) is the main treatment for multiple sclerosis (MS). However, this treatment is not always effective. Here we see a striking congruence in outcome between responses to IFNβ in experimental autoimmune encephalomyelitis (EAE) and relapsing-remitting MS (RRMS). IFNβ is effective in reducing EAE induced by Th1 cells, but exacerbates disease induced by Th17. Effective treatment in Th1 EAE correlated with increased IL-10 in spleens. In Th17 disease, IL-10 was unchanged by treatment, although unexpectedly IFNβ still reduced IL-17 without benefit. Both inhibition of IL-17 and induction of IL-10 depended on interferon gamma (IFNγ). The absence of IFNγ signaling resulted in ineffective IFNβ therapy in EAE. In RRMS, IFNβ nonresponders had higher IL-17F in serum compared with responders. Nonresponders had worse disease with more steroid usage and more relapses than responders. Hence, IFNβ is proinflammatory in Th17-induced EAE. Moreover, high IL-17F in serum predicts nonresponsiveness to therapy with IFNβ in RRMS.

THE ANTPROLIFERATIVE GENE TOB1 IS INVOLVED IN MULTIPLE SCLEROSIS AND EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS PATHOGENESIS

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We recently identified a gene expression signature in CD4+ T cells of individuals with clinically isolated syndrome (CIS) that highly correlated with a rapid progression to multiple sclerosis (MS). This signature included up-regulation of genes that promote T-cell activation as well as down-regulation of genes that promote quiescence. Among these, the antiproliferative gene Tob1 was 7-fold downregulated. We hypothesized that Tob1-deficient mice will show an earlier disease onset, a more severe phenotype, or both. We then set out to characterize the immunologic and neurodevelopmental properties of Tob1-/- animals. We used Tob1-/- mice to assess the effects of this gene in experimental autoimmune encephalomyelitis (EAE) pathogenesis. We also conducted immunologic studies to characterize the properties of Tob1-/- T cells. In addition, we tested the effect of the histone deacetylase inhibitor (HDAC) TSA to suppress EAE. Tob1-/- mice experienced both an earlier onset and a more severe EAE. Analysis of motoneuron function and apoptosis suggest that the earlier onset is associated with neural toxicity in the Tob1-/- animals. Tob1-/- T cells proliferate more and express more IL-17 and IL-23 than their WT counterparts. Tob1-/- mice showed a significant delay in spinal cord myelination at P5 compared with WT mice. Finally, we found that the HDAC inhibitor TSA (which increases Tob1 expression by >10-fold in vitro) ameliorated EAE. Strikingly, Tob1-/- animals showed no improvement, suggesting that Tob1 expression is required for the beneficial effects of TSA. We confirmed these results with in vitro experiments. Our results suggest a dual role of Tob1 in the central nervous system and the periphery. We found that while Tob1 is required for keeping quiescence in T cells in the periphery, it may also be critical for oligodendrocytes to (re)myelinate axons in a timely manner. Tob1 is required for TSA to exert its beneficial effect in EAE and to suppress T-cell proliferation in vitro.

ASSESSING FUNCTIONAL STATUS IN PEDIATRIC MULTIPLE SCLEROSIS PATIENTS

P. Niewczyk, A. Monroe, S. Dowdy, Y. Harris, C. Granger, J. Ness

Background: Approximately 3% to 5% of patients with multiple sclerosis (MS) experience symptom onset before age 18. Currently, there is no standard disability assessment tool specific to pediatric MS. This study compared two instruments, the WeeFIM and Kurtzke Expanded Disability Status Scale (EDSS), to measure disability in pediatric patients with MS. The WeeFIM instrument is a pediatric functional assessment measure for children with a variety of physical, cognitive, and developmental impairments. The EDSS is used to quantify disability in adult patients with MS but has not been validated in a pediatric MS population. Objectives: This study will assess the psychometric properties of the WeeFIM instrument compared with the EDSS (used as the “gold standard”) in pediatric patients with MS; additionally, the MS-related disability in a pediatric population will be described.

Methods: The study design is a retrospective cohort study. A sample of at least 50 pediatric patients with MS evaluated at The University of Alabama at Birmingham’s Center for Pediatric Onset Demyelinating Disease with complete assessments at two periods in time will be included. The reliability of each instrument will be assessed. The discriminate properties of each instrument will be assessed using logistic regression. Construct validity will be tested by confirmatory factor analysis, and Rasch analysis will be performed to determine unilinearity and the hierarchical properties of each instrument. Additionally, a receiver operator curve analysis will be performed on the WeeFIM to assess the sensitivity and specificity of the instrument. Finally, predictive validity will be assessed using multivariate modeling on instruments to determine which is more predictive of functional change over time.

Conclusion: This study will provide valuable information on the reliability and validity of two assessment instruments in a pediatric MS population and will help identify useful outcome measures for interventions in this youngest group of patients with MS.
DEVELOPMENT OF A RASCH-BASED AMBULATION SYMPTOM SCALE
E.M. Snook, B.G. Ragan

Background: Using the Expanded Disability Status Scale (EDSS) to measure multiple sclerosis (MS) disease progression is standard for clinical trials; however, it has limited utility in rehabilitation because of the training required and the time required for administration. The EDSS has measurement issues that include limited sensitivity in measuring small changes in ambulation and early mobility impairment.

Objective: Develop a self-report ambulation symptoms scale using Rasch modeling that is able to accurately measure early-stage walking impairment and has the sensitivity to measure small ambulation changes across walking levels.

Methods: A total of 371 participants with MS completed the scale. The new scale contains 15 ambulation-related symptoms from the Symptom Inventory (SI), and it was evaluated using the Rasch Rating Scale Model for response option structure, model data fit, item difficulty, item separation and reliability indices, and a Wright item-person map.

Results: Response options were analyzed for order and to ensure that each response option was the most probable at some point on the metric. The initial response structure using the SI 5-point Likert scale functioned poorly, with all of the options not being utilized. Optimization categorization procedures were used to determine the best number of response options. A 3-point Likert scale was selected, and all results are based on this scale. The model fit the data well, with 13 of 15 items having acceptable properties. Two items had marginal statistics but were included because of content and item difficulty. The item difficulties ranged from –2.59 (easy) to 3.57 (hard) logits. Item separation was 13.75, and item reliability was 0.99. The Wright item-person map showed good matching of items with person ability levels. The average participant’s ability was –1.58 ± 2.4 logits; lower scores indicate less severe ambulation symptoms. The correlation with the Patient Determined Disease Steps scale was 0.83. Conclusions: This newly developed ambulation scale has good psychometric properties and the ability to measure early-stage ambulation impairment and small changes in ambulation. This scale holds significant promise for use in survey-based research and for tracking disease progression in a clinical setting where EDSS assessments are not regularly conducted.
**WORKS IN PROGRESS**

(W01) **EFFECTS OF VITAMIN D ON THE DIFFERENTIATION OF REGULATORY T CELL CLONES**

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**Background:** Regulatory T (Treg) cells are CD4+, CD25+, FoxP3+, and CD127− T cells that, through anti-inflammatory effects, suppress pathogenic immune responses in multiple sclerosis. In naive T cells, the cytokine TGF-β induces phosphorylation of the transcription factor Smad3, which, with 1,25-dihydroxyvitamin D (1,25(OH)2D), can promote Treg cell differentiation. T cells with a phenotype similar to that of Treg cells can also demonstrate proinflammatory properties. The effect of vitamin D on this propensity has not been previously examined. **Objectives:** To examine cellular effects of vitamin D metabolites on factors of importance to Treg cell development. **Methods:** Treg cell clones were developed from T helper cells obtained from healthy subjects. Treg cell differentiation was induced by stimulating the cells for 5 days with anti-CD3/anti-CD28 antibodies in the presence of interleukin (IL)-2 and antibodies to IL-6, IL-4, and interferon gamma ± TGF-β. Limiting dilutions of CD25+FoxP3+ cells from these cultures were then cloned and the clones then incubated in either medium alone or in medium containing 10 nM 25-hydroxyvitamin D (25(OH)D) or 10 pM 1,25(OH)2D. Separate cultures were also incubated in medium + TGF-β ± either 25(OH)D or 1,25(OH)2D. The cells were then analyzed by flow cytometry for Treg cell markers. Also, cell lysates were analyzed on Western blots for detection of phosphorylated Smad3. **Results:** Expression of FoxP3 was noted in 50% to >90% of the cells in the cultures. In contrast, >95% of the cells in the cultures were negative for CD127 expression. Cultures incubated with medium without the vitamin D metabolites showed levels of Smad3 activation that were lower than with 25(OH)D but greater than with 1,25(OH)2D. **Conclusions:** These studies confirm previous findings demonstrating a lack of CD127 expression over expression of FoxP3 as a feature of Treg cells. Further studies elucidating the role of vitamin D metabolites in the development of Treg cells are warranted.

**Supported by:** EMD Serono, Multiple Sclerosis Center of Excellence-East

**Disclosure:** Nothing to disclose

**Keywords:** Immunology and MS

(W02) **MANAGEMENT OF PROGRESSED MULTIPLE SCLEROSIS THROUGH DAY PROGRAMS**

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**Background:** It has been validated by the Recommendations from the Consortium of Multiple Sclerosis Centers (CMSC), in the article entitled “A Multidisciplinary Approach to Improving Quality of Life in Patients with Multiple Sclerosis” (Bethoux F et al., 2008), that patient empowerment should guide all health-care professionals involved in treatment of multiple sclerosis (MS). The MS Achievement Center (MSAC) in St. Paul, MN, has used a member empowerment model for 25 years to help individuals with progressed MS stay active in their community, be better connected with community resources, and remain as independent as possible in their living situation. This program consists only of people with MS; of these members, 94% of them use a wheelchair as their primary source of mobility, and 100% require some level of assistance with activities of daily living. The MSAC has created a model that facilitates member empowerment through self-efficacy, self-confidence, and skill development using a multidisciplinary approach that includes the use of occupational and physical therapy, social work, speech language pathology, maintenance exercise programs, cognitive stimulation, creative arts, and spiritual wellness. **Objectives:** This presentation describes how referrals are obtained, the population that we currently serve, and how the multidisciplinary team works together to achieve member empowerment. Our current model is supported by research on the topics of socialization, performance of therapy, and regular exercise and support activities with the MS population. CMSC conference attendees will receive information about current research and practices to facilitate empowerment along with maintaining function and independence in a population with progressed MS.

**Disclosure:** Nothing to disclose

**Keywords:** Quality of life in MS, Comprehensive care and MS, Rehabilitation strategies and therapy and MS

(W03) **EXPLORING STRATEGIES TO SAFEGUARD THE FUTURE OF MULTIPLE SCLEROSIS CLINICAL RESEARCH IN AUSTRALIA**

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**Background:** Clinical research plays an important role in multiple sclerosis (MS). Treatment options can be limited, particularly in clinically isolated syndrome and primary and secondary progressive MS. Even in relapsing-remitting MS, existing treatments do not yet provide certainty of clear-cut benefit or outcome because of the unpredictable nature of MS. Clinical trials provide an alternative to standard treatment options and an opportunity for people to contribute to medical research. Emerging treatments aim to improve relapse rates, convenience, and quality of life; and reduce magnetic resonance imaging (MRI) disease activity, disability progression, and side effects. These treatments offer hope to people who are grappling with the challenges and uncertainties of MS. Furthermore, the involvement of Australian centers in clinical trials ensures knowledge of and access to cutting-edge treatments for the future benefit of people with MS. Unfortunately, the future of clinical research is under threat in Australia. The massive cost of drug development, combined with the recent global financial crisis, has forced pharmaceutical companies to carefully select clinical trial centers on the basis of quality, timeliness (of regulatory approval and study start), recruitment capacity, and cost. Australia has a reputation for producing high-quality data, but otherwise struggles to compete, particu-
larly with countries such as India and China. In recognition of the increasing global competition for investment in clinical research, this project explores the threats to Australia’s competitiveness and identifies strategies to improve on our timeliness, capacity, and cost while maintaining quality. Examples include actively supporting Australia’s move to a streamlined ethical review process; collaborating more effectively with sponsors to improve efficiencies; enabling strong early recruitment by identifying potential patients prior to study; building a national, coordinated patient referral network; allocating specific roles to study staff to enhance efficiencies; and allowing flexibility in staffing to match resources to project requirements. These suggestions provide a means of moving forward to ensure ongoing patient access to new and better treatments for MS and to safeguard Australia’s future in clinical research.

Disclosure: Nothing to disclose

Keywords: Economic issues and MS, Disease-modifying treatment in MS

(W04) MONTHLY PULSE ADRENOCORTICOTROPIN HORMONE VERSUS METHYLPRIDINOSLONE FOR MULTIPLE SCLEROSIS TREATMENT

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Background: The pathogenic mechanisms in multiple sclerosis (MS) involve inflammation, demyelination, and axonal damage. A commonly used treatment for worsening MS, among very few others, is pulse methylprednisolone (MP). While readily available, MP treatment is associated with many side effects and is not always well tolerated. Adrenocorticotropin hormone (ACTH; Acthar Gel) is a US Food and Drug Administration-approved medication for the treatment of MS relapses. However, no information is available on long-term or pulse-therapy use of ACTH for MS. The USC MS Comprehensive Care Center is initiating a study designed as a 12-month pilot, investigator-initiated, single-center, randomized, prospective, examiner-blinded, treatment trial to evaluate the efficacy and safety of monthly intramuscular (IM) ACTH injections, as compared with monthly intravenous (IV) MP infusions, as an add-on therapy in patients with MS receiving regular interferon beta (IFNβ) treatment.

Objectives: To determine whether monthly IM administration of ACTH, when added to IFNβ, shows promise as an alternative treatment option for control of MS disease activity, measured as annualized relapse rate (primary outcome). Secondary clinical objectives: To determine whether ACTH improves Multiple Sclerosis Functional Composite (MSFC), Expanded Disability Status Scale (EDSS) score, and Multiple Sclerosis Quality of Life (MSQOL) and induces regulatory immune activity and, if so, how these compare with effects of MP. Methods: The target patient population consists of 24 subjects, 12 in each treatment arm (Acthar Gel vs. MP), matched for age and sex. Subjects must be diagnosed with definite MS and have experienced worsening in their condition, as defined by at least 1 MS relapse and/or new T2 or gadolinium-enhancing lesion on magnetic resonance imaging (MRI) within the last year while on stable interferon therapy. Subjects will be administered either monthly IM Acthar Gel or IV MP for 12 months, and will be monitored for the study outcomes and side effects. Results: The study is currently open for enrollment. The investigational new drug application has been submitted and the exemption has been granted; USC institutional review board approval has been obtained. Conclusions: The information gained from this study is critical to establish the feasibility of ACTH use as a long-term pulse treatment option for MS.

Supported by: Sponsored by USC and supported by a research grant from Questcor Pharmaceuticals, Inc


Keywords: Disease-modifying treatment in MS, Immunology and MS

(W05) PHASE 3 STUDY OF PEGYLATED INTERFERON BETA-1A IN RELAPSING MULTIPLE SCLEROSIS: RATIONALE AND DESIGN

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Background: PEGylation can enhance exposure to protein-based therapies while maintaining the safety and tolerability of the parent compound. A PEGylated form of interferon beta-1a (PEG IFNβ-1a) with enhanced in vivo activity, longer half-life, and prolonged exposure is being developed for treatment of MS. Objectives: The primary objective of this phase 3 study is to evaluate the efficacy of PEG IFNβ-1a in reducing relapse rate at 1 year. Secondary objectives include evaluation of magnetic resonance imaging (MRI) efficacy, the proportion of subjects who are relapse-free, quality of life, and disability progression. Methods: ADVANCE is a 2-year, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of subcutaneous PEG IFNβ-1a 125 µg administered every 2 or 4 weeks. Eligible patients must be 18 to 55 years old and have confirmed relapsing multiple sclerosis (MS) (McDonald criteria) with a baseline Expanded Disability Status Scale (EDSS) score of ≤5.0. Patients must have had ≥2 relapses within the last 3 years and ≥1 relapse 12 months prior to randomization. Approximately 1260 patients will be randomized 1:1:1 to receive placebo, PEG IFNβ-1a every 2 weeks, or PEG IFNβ-1a every 4 weeks. Patients on placebo will be rerandomized to PEG IFNβ-1a every 2 or 4 weeks after 1 year. Results: Efficacy of PEG IFNβ-1a versus placebo will be assessed using clinical relapses, MRI (± gadolinium), EDSS, Multiple Sclerosis Impact Scale–29 (MSIS-29) physical score, global impression of change, Multiple Sclerosis Functional Composite score, visual function, and the Symbol Digit Modality Test. Quality of life (QOL) will be assessed using a 12-item short-form health survey, EuroQol questionnaire, and MSIS. Safety and tolerability will be evaluated throughout the study (physical and neurologic examinations, vital signs, electrocardiograms, clinical laboratory assessments, Beck Depression Inventory, immunogenicity, injection site assessments, adverse event reporting, concomitant medication use). Blood will be collected for population pharmacokinetic (PK) and pharmacodynamic, intensive PK, and other biomarker analyses. Conclusions: PEG IFNβ-1a is being developed to offer patients
with MS the proven safety and efficacy of IM IFNβ-1a with improved convenience of administration and, as such, holds promise as a significant addition to the therapeutic armamentarium for MS treatments.

Supported by: Biogen Idec, Inc


Keywords: Disease-modifying treatment in MS

(WO06) BUILDING BRIDGES IN MULTIPLE SCLEROSIS: TRANSITIONAL PLANNING TO DEVELOP CAPACITY IN LONG-TERM CARE
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Background: A number of multiple sclerosis (MS) clinic patients in Central Alberta are living with advanced MS and require long-term care (LTC). Because of a lack of specialized services, many of these patients reside in geriatric-focused facilities. This presents unique challenges for the MS clinic team to empower self-management capacity within a clinic setting. Quality of life may be maximized through collaboration between the MS clinic team and caregivers in LTC facilities. The goal of this initiative is to promote patient-focused care and develop capacity among caregivers. A pilot project was initiated by the MS clinic team, which facilitates collaboration by attending the LTC facility to assist with care planning and provide disease-specific, evidence-based information.

This project has been ongoing since 2007 and to date has involved 16 LTC sites and 31 MS patients and their families.

Objectives: The objective of this project is to describe key elements of the pilot program and, using a single case study design, highlight the need, complexity, and potential impact of this service for patients. A second component is to describe the relative impact of the program, utilizing data gathered through a questionnaire completed by the facility caregivers regarding patient support. A case study protocol was developed utilizing archival data and documents, participant and/or staff observation, and patient feedback. This descriptive single case study will be presented to highlight both the need and complexity of management of care within a therapeutic environment. A questionnaire was also developed at the onset of the project for completion by the site staff. The results have been analyzed and will be presented.

Results: Interactions with, and feedback from, individuals receiving the care, family, and caregivers suggests that the program fills a gap in services not normally provided within LTC. Conclusions: Implications include the potential provision of similar services across a geographically dispersed provincial health authority. Therefore, we are in the process of developing a program logic model and an operational plan for further evaluation.

Supported by: MS Clinic team

Disclosure: Nothing to disclose

Keywords: Service delivery in MS, Psychosocial issues in MS

(W09) SURPASS STUDY TO EVALUATE THE POTENTIAL BENEFITS OF SWITCHING MULTIPLE SCLEROSIS THERAPY

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Background: Although glatiramer acetate (GA) and interferon beta (IFNβ) therapies effectively reduce disease activity in many patients with relapsing-remitting multiple sclerosis (RRMS), some patients continue to experience disease activity despite treatment. There is no Class 1 evidence on which to base treatment decisions in these patients, and no studies have directly compared GA or IFNβ with natalizumab.

Objectives: SURPASS has been designed to rigorously assess treatment options, including switching to natalizumab, in MS patients with disease activity during therapy with GA or subcutaneous IFNβ-1a (SC IFNβ-1a). The main objective is to compare the efficacy of switching to natalizumab versus receiving GA or SC IFNβ-1a. These data will evaluate the potential benefits of early intervention with a highly effective therapy for management of RRMS.

Methods: SURPASS is a randomized, active-comparator, open-label, rater-blinded, parallel-group study. Eligible patients must be 18 to 60 years of age, have RRMS with an Expanded Disability Status Scale score of ≥5.5, and have experienced disease activity, defined as either ≥1 clinical relapse or ≥2 new magnetic resonance imaging lesions (gadolinium-enhancing [Gd+] and/or T2-hyperintense), during the first 6 to 18 months of GA or SC IFNβ-1a therapy. Results: Approximately 1800 patients at 250 centers in 25 countries will be randomized 2:1:1 to receive natalizumab 300 mg by intravenous infusion once monthly, GA 20 mg SC once daily, or SC IFNβ-1a 44 µg 3 times per week for up to 24 months. The primary end point is annualized relapse rate. Other end points include change in T2 lesion volume, proportion of patients free of disease activity (no clinical relapses, Gd+ or new/enlarging T2 lesions, or ≥1 point progression on the EDSS sustained for 12 weeks), quality of life (by the Multiple Sclerosis Impact Scale and other instruments), safety, and tolerability. Enrollment will commence in early 2010. Conclusions: SURPASS will provide Class 1 evidence to assist physicians in making informed and objective treatment decisions by directly comparing natalizumab with other approved therapies. An important rationale for SURPASS is the assumed importance of proactive monitoring and therapy decision making for RRMS patients early in the disease course.

Supported by: Biogen Idec, Inc, and Elan Pharmaceuticals, Inc

Disclosure: H. Hartung: Bayer Healthcare, Biogen Idec, Inc, BioMS, Genzyme, Merck Serono, Novartis, Tesa, Sanofi Aventis (consulting fees); Bayer Healthcare, Biogen Idec, Inc, BioMS, Genzyme, Merck Serono, Novartis, Tesa, Sanofi Aventis (honoraria). P.K. Coyle: Acorda, Bayer Healthcare, Biogen Idec, Inc, Novartis, Pfizer, Serono, Teva

(W10) RELATIVE EFFICACY OF REPEAT COURSE OF INTRAVENOUS METHYLPREREDNISOLONE AND INTRAMUSCULAR ADRENOCORTICOTROPIN IN THE TREATMENT OF ACUTE RELAPSE OF MULTIPLE SCLEROSIS AFTER SUBRESPONSE TO INITIAL COURSE OF INTRAVENOUS METHYLPREREDNISOLONE (RECLAIM): A SINGLE-CENTER PILOT STUDY

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Background: Multiple sclerosis (MS) disease-modifying agents in development have robust efficacy in the reduction of relapses, yet patients continue to have ongoing relapses. Patients may develop residual disability with each relapse, and while many patients respond to an initial course of intravenous methylprednisolone (IVMP), many fail to return to their prerelapse baseline. The lack of established treatment protocols for patients with an acute MS relapse who fail to recover after treatment with high-dose corticosteroids has created the need for controlled clinical trials to study this population. This ongoing single-center, randomized, double-blind, double-dummy trial compares the efficacy, safety, and tolerability of a repeat course of 3 days of IVMP and 5 days of intramuscular (IM) adrenocorticotropic (ACTH) in the treatment of an acute relapse of MS after subresponse to an initial 3-day course of IVMP. The rationale behind the treatment arms are that IVMP and IM ACTH have different mechanisms of action, yet both have demonstrated first-line efficacy in treating acute relapses. There has never been a comparative trial of these treatments after subresponse to the initial course of IVMP. This study fills a gap in knowledge, as the difficulty facing clinicians is what to do if IVMP does not return patients to their prerelapse neurologic baseline. Objectives: The primary objective is to compare ACTH 80 U IM for 5 days with IVMP 1 g daily for 3 days in terms of improvement in Expanded Disability Status Scale (EDSS) and Functional Scales for patients with an acute relapse of MS after subresponse to an initial course of IVMP. The key secondary objective is to compare ACTH and MP in terms of improvement in Multiple Sclerosis Functional Composite and its three individual components in this patient population. Other secondary objectives are to compare the safety and tolerability of ACTH and MP in this patient population. Methods: A single-center, randomized, double-blind, double-dummy trial compares the efficacy, safety, and tolerability of a repeat course of 3 days of IVMP and 5 days of IM ACTH in the treatment of an acute relapse of MS after subresponse to an initial 3-day course of
(W11) DECIDE RATIONALE/DESIGN: DACLIZUMAB HIGH-YIELD PROCESS MONOTHERAPY IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Background: The phase 2 CHOICE trial demonstrated that, in multiple sclerosis (MS) patients on a background of interferon-beta-1a (IFN-β1a) therapy, daclizumab was well tolerated and caused a dose-dependent reduction in new/enlarged gadolinium-enhancing (Gd+) lesions of 72% compared with IFN-β1a alone. Clinical efficacy was associated with a marked expansion of immunoregulatory CD56bright natural killer (NK) cells. These data and ongoing studies support investigation of daclizumab high-yield process (DAC HYP) in the clinical management of MS. Objectives: To test the superiority of DAC HYP, a humanized monoclonal anti-CD25 antibody, as compared with IFN-β1a in preventing relapses and slowing disability in subjects with relapsing-remitting MS, and to identify predictive biomarkers of treatment response.

Methods: The DAC HYP Efficacy Compared to Interferon Beta 1a StUdy for Multiple SclErosis (DECIDE) trial is a global, phase 3, double-blind active comparator study. Eligible subjects (N = 1500) are randomized 1:1 to receive either 150 mg of subcutaneous DAC HYP every 4 weeks or 30 µg intramuscular IFN-β1a once per week for a minimum of 96 weeks. Results: The effects of DAC HYP will be assessed via annualized relapse rate (primary efficacy end point), brain magnetic resonance imaging (MRI) (T2-hyperintense and T1-hypointense lesions, Gd+ lesions, brain atrophy), sustained disability progression, Multiple Sclerosis Functional Composite scores, cognitive testing, and visual function. Safety and tolerability throughout the study and follow-up will be evaluated by a battery of physical, neurologic, and psychological examinations. Further, pharmacodynamic and pharmacogenetic analyses of prospectively collected samples will be performed to identify potential biomarkers that predict clinical responses to DAC HYP. Conclusions: The DECIDE trial is designed to provide a definitive assessment of the efficacy and safety of DAC HYP in comparison with an established standard of MS care and a confirmatory assessment of CD56 bright NK cell expansion as a marker of optimal response to DAC HYP.

Supported by: Biogen Idec and Facet Biotech


Keywords: Disease-modifying treatment in MS

(W12) EVIDENCE-BASED PATIENT INFORMATION AND INFORMED DECISION MAKING IN MULTIPLE SCLEROSIS

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Background: Individuals with multiple sclerosis (MS) have to cope with uncertainties concerning diagnosis, prognosis, and drug therapy. This makes disease-related decisions a challenge, starting with the decision of whether or when to go through the diagnostic process. Many important decisions follow, mainly related to drug therapies. Evidence-based patient information has been promoted for people with MS in order to address uncertainties and to allow informed decision making based on the best available research evidence. In recent years, our group has performed a number of pre-studies and systematic reviews on important related topics. We have developed and evaluated three educational programs and two decision-support tools. Methods: Two randomized controlled trials (RCTs) have been performed to evaluate an educational program on relapse management and a decision aid on immunotherapy. Also, a questionnaire study was performed to evaluate a concise information leaflet about MS diagnosis. Currently, an ongoing RCT is evaluating an educational program for people with early MS. Also ongoing is a controlled trial evaluating a program in rehabilitation clinics on immunotherapy. Different end points have been used to evaluate the interventions’ efficacy. Results: In the trial evaluating the decision aid on immunotherapy, we found no differences between groups. In contrast, the educational program on relapse management resulted in important changes in relevant outcomes. The information leaflet was perceived to be well balanced and assessed as highly understandable and important. The two trials evaluating educational programs on immunotherapy and early MS are still ongoing. Preliminary results will be presented. Conclusions: Rigorously developed programs aiming at facilitating decision making for people with MS are feasible and effective. A number of methodological issues have arisen. Therefore, recently a special interest group on “patient information” has been founded within the European Network of European MS Centers–Rehabilitation in MS (RIMS) to discuss these issues and to further develop and evaluate programs to support informed choice for people with MS.

Supported by: National Multiple Sclerosis Society


Keywords: Relapse management in MS, Disease-modifying treatment in MS, Symptomatic treatment of MS

(W13) CARE-MS EXTENSION STUDY: AS-NEEDED RELAPSING-REMITTING MULTIPLE SCLEROSIS TREATMENT PARADIGM WITH ALEMTUZUMAB

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Keywords: Disease-modifying treatment in MS
Background: Currently patients with relapsing-remitting multiple sclerosis (RRMS) are treated with chronic administration of disease-modifying therapies. Alemtuzumab administered for two brief annual cycles has demonstrated efficacy superior to that of subcutaneous interferon beta-1a (IFNβ-1a) in a 3-year trial with RRMS patients (CAMMS223), significantly reducing the relapse rate, risk for sustained accumulation of disability (SAD), and mean disability compared with baseline (all comparisons P < .001). Two years after their last alemtuzumab cycle, patients maintained a significant 70% reduction in risk for SAD and a significant 74% reduction in relapses compared with patients treated continuously with IFNβ-1a, as well as a mean point reduction of 0.38 from baseline on the Expanded Disability Status Scale score. Two larger studies are now evaluating the safety and efficacy of alemtuzumab compared with subcutaneous IFNβ-1a for treatment-naive RRMS patients (CARE-MS I) and RRMS patients who relapse on prior therapy (CARE-MS II). As alemtuzumab has demonstrated durable effects for many patients, we will investigate a novel MS treatment paradigm involving as-needed redosing. Objectives: To present the rationale and design of the novel as-needed treatment component of the CARE-MS Extension Study (CAMMS03409). Methods: All patients from CAMMS223 and those completing CARE-MS I or CARE-MS II are eligible to enroll in the 3-year follow-up protocol examining the long-term safety and efficacy of alemtuzumab. Patients treated with alemtuzumab in their prior trial are eligible for as-needed alemtuzumab treatment upon evidence of resumed disease activity, as are former IFNβ-1a patients after they have completed two annual cycles of alemtuzumab. Qualifications for retreatment include relapse or a minimum of 2 new lesions on cranial/spinal magnetic resonance imaging (MRI) consisting of any combination of gadolinium-enhancing lesions or new or enlarging T2 lesions. Results: Criteria for retreatment were defined, and a novel treat-as-needed strategy will be explored in the CARE-MS Extension study. Assessments will include disability, relapse, MRI, quality of life, and safety. Conclusions: Evidence of the durability of infrequent alemtuzumab treatment is the impetus for investigating an as-needed treatment strategy in the Extension Study.

Supported by: Genzyme

Disclosure: C. LaGanke: Genzyme (other financial benefit). CAMMS Study Groups: Genzyme (other financial benefit).

Keywords: Disease-modifying treatment in MS

(W15) EVALUATING THE LONG-TERM SAFETY OF CLADRIBINE TABLETS IN PREMIERE, AN EIGHT-YEAR SAFETY REGISTRY

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Background: Cladribine is an oral immunomodulator that offers targeted, sustained effects on T and B lymphocytes as an annual short-course oral dosing regimen. In the phase 3, 96-week CLARITY study, cladribine tablets demonstrated treatment benefits compared with placebo in a cohort of patients with relapsing-remitting multiple sclerosis (RRMS). Objectives: The PREMIERE registry (Prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical trials) has been established as an active surveillance system to collect long-term safety information in those patients who have participated in cladribine tablets clinical trials. Methods: This is a subject registry with an observational cohort design. All subjects previously enrolled in selected phase 1 to 3 clinical trials with cladribine tablets (including patients randomized to placebo) are eligible for enrollment. The duration of follow-up will be

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8 years (including years in the clinical trial) or up to the end of the registry (preliminary estimate is mid-2018), whichever occurs first. Primary end points include the cumulative incidence of selected infections, malignancies, and deaths; dynamics of treatment-induced lymphocyte reduction; and frequency of pregnancies and pregnancy outcomes occurring among female subjects exposed to cladribine, as well as among female partners of male subjects. During the first 2 years, each subject will be interviewed every 3 months, and thereafter the contacts will occur every 6 months until the end of follow-up. This information was also presented at the Congress of the European Committee for Treatment and Research in Multiple Sclerosis in 2009. Results: Approximately 2000 subjects enrolled in the cladribine tablets clinical development program will be available for enrollment in the registry. It is estimated that 75% of these subjects, enrolled at 377 sites, will participate in the PREMIERE registry. Enrollment of patients started in November 2009. Conclusions: The PREMIERE registry will provide long-term active safety surveillance in subjects formerly enrolled in cladribine tablets clinical trials in MS to build on existing knowledge about the safety profile of cladribine tablets and support long-term risk-benefit evaluation.

Supported by: EMD Serono, Inc; Rockland, MA
Keywords: Disease-modifying treatment in MS

(W16) A CASE STUDY OF A PATIENT WITH MULTIPLE SCLEROSIS FOLLOWED FOR FIFTEEN YEARS USING PATIENT-REPORTED OUTCOME MEASURES

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Background: Patient self-reporting has been increasingly recognized as highly desirable for judging the value basis for treatment. The LIFEware System is an outcomes tracking and reporting system that documents patient-reported outcomes for outpatients with neurologic and musculoskeletal conditions. Within the LIFEware system, there are various functional, activities of daily living, and quality of life measures used to monitor the patient’s disease course and symptoms over time. Objectives: To present the utility of both quantitative and qualitative self-reported data collected over time in managing treatment efforts, disease progression, and quality of life in patients with multiple sclerosis (MS). Methods: This research is a case study of a patient diagnosed with relapsing-remitting MS who was followed longitudinally over a 15-year period. Results: Self-reported as well as clinician-assessed data will be presented to illustrate the utility of patient-reported measures in monitoring a patient’s disease status. Additionally, qualitative excerpts, provided from the patient, capturing experiences over a 15-year period including prediagnosis, diagnosis, and different treatments and therapies, are presented. Conclusions: This data can aid the clinician in deciding the clinical course of care.

Disclosure: Nothing to disclose
Keywords: Management of activities of daily living in MS, Quality of life in MS

(W17) SELF-EFFICACY IMPROVEMENT IN MULTIPLE SCLEROSIS (SIMS): INTERIM RESULTS
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Background: Optimal treatment adherence is required to maximize the effectiveness of multiple sclerosis (MS) immunotherapy treatment. Nursing outreach and support programs have been shown to be effective in improving adherence. However, these programs are not very successful in addressing psychological factors that are implicated in reduced self-efficacy and treatment adherence, such as depression, anxiety, and chronic stress. A guided imagery method has been developed specifically for MS patients who are taking immunotherapy medications. This study aims to investigate the effect of this program when added to a nursing outreach support program. The primary end point is self-efficacy. Secondary end points include treatment adherence, depression, anxiety, and cognitive functioning. It is hypothesized that the experimental group will demonstrate significantly higher illness control self-efficacy. Objectives: This is a pilot study to determine whether an outreach program consisting of industry-based nursing services augmented with MS-specific guided imagery stress reduction and relaxation training will result in superior self-efficacy and immunotherapy treatment adherence compared with nursing outreach services alone.

Methods: This is a 1-year, randomized, prospective pilot study. Patients with a diagnosis of clinically isolated syndrome (CIS) or relapsing MS who are initiating interferon beta-1b treatment and meet inclusion and exclusion criteria will be offered participation and provide informed consent. Participants will be randomly assigned to one of two groups: 1) nursing outreach services + relaxation training; or 2) nursing outreach services alone. Outcome measures will be collected at baseline, month 3, month 6, and month 12 time points. Results: This study opened enrollment in 2009 and completed enrollment in February 2010. Interim results for primary and selected secondary end points for a sample of 24 participants will be available in May 2010 for the month 3 and month 6 time points. Conclusions: Results from this study may inform future research on relaxation training, self-efficacy, and treatment adherence in patients with CIS and relapsing MS. Study results may also guide the development or modification of nursing outreach service approaches for patients starting MS immunotherapy treatments.

Supported by: Bayer Healthcare
Keywords: Nursing management in MS, Psychosocial issues in MS, Complementary/alternative therapies in MS

(W18) SELF-MANAGEMENT INTERVENTIONS IN PEOPLE WITH MULTIPLE SCLEROSIS
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Background: Self-management programs empower individuals to manage their health conditions. There is a limited understanding of best methods to teach self-management
Interventions promoting self-management in individuals with multiple sclerosis (MS). Summarizing and classifying empirically tested intervention strategies may help identify overall gaps in the existing literature. **Objectives:** The purpose of this scoping review was to identify empirically tested health-education interventions for people with MS, and then classify the intervention using Lorig’s self-management framework. Interventions were coded as medical, role, and emotional management, and whether the intervention incorporated self-tailoring and action planning and taught the following skills: problem solving, decision making, utilizing resources, forming a patient-provider partnership. **Methods:** A systematic search strategy was developed and implemented to identify studies that evaluated health-education interventions in people with MS between 1975 and 2008. Interventions that did not focus on behavior change or incorporation of a behavior into a person’s life were excluded. Two independent coders categorized the interventions using Lorig’s self-management framework. A third coder made decisions when there were coding disagreements. **Results:** Forty-eight articles evaluated an intervention that met the inclusion criteria for a total sample size of 2908 people with MS. The average age was 45.5, and 77.5% were female. Most samples included a mix of relapsing-remitting and progressive types of MS. Twenty-seven studies used a pre-post design with a randomized control group. The remaining studies did not include a true control group or did not randomize participants. The most common outcomes measured across studies were fatigue management, physical activity, and coping/stress management. The most common delivery format was face-to-face. Few interventions contained all the elements of Lorig’s self-management framework. **Conclusions:** Developing and evaluating theory-driven self-management interventions for people with MS using a randomized controlled design is still a much-needed area of research. Comparative-effectiveness research is a potential method of identifying the most cost-effective interventions.

**Supported by:** National Multiple Sclerosis Society, Mentor-based Fellowship (MB 0009)

**Disclosure:** Nothing to disclose

**Keywords:** Rehabilitation strategies and therapy and MS, Symptomatic treatment of MS, Management of activities of daily living in MS

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**W20 VALIDATING A COGNITIVE REHABILITATION PROGRAM FOR EXECUTIVE DEFICITS IN MULTIPLE SCLEROSIS**

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**Background:** Deficits in executive functioning and executive aspects of attention are among the most common cognitive impairments in people with multiple sclerosis (MS). These cognitive deficits have been linked to significant disruption of occupational performance activities in the areas of work, leisure, self-management, and socialization and may also interfere with physical or medical therapies. However, reviews of the literature indicate that there are no empirically validated treatments for people with MS that target these impairments. **Objectives:** As a potential treatment for executive and attention deficits in MS, a double-blind randomized controlled trial (GMT) is being conducted to evaluate Goal Management Training (GMT). **Methods:** GMT is a nine-session small-group-based program that teaches patients to use an internalized strategy ("Stop-State-Split") to keep "on track" in their daily activities. A mindfulness meditation training component within the GMT program is used to enhance attentional awareness and develop attentional control. This study compares GMT with a nine-session general psychoeducational group-based program about the brain, cognition, lifestyle factors, and MS, aimed at increasing awareness and providing support without the specific strategy training of GMT. Participants with MS and documented attention and executive deficits (N = 30) are randomly assigned to groups to complete the GMT or psychoeducational program. Cognitive, behavioral, and neurophysiologic (electroencephalogram) measures of outcome are evaluated before and after treatment and at a 6-month follow-up to determine the feasibility and clinical utility of GMT as a cognitive rehabilitation approach for people with executive and attention deficits due to MS. **Results:** This
Multiple Sclerosis Society
Disclosure: Nothing to disclose
Keywords: Rehabilitation strategies and therapy and MS

(W22) DIFFERENCES IN SELF-REPORTED AND OBJECTIVELY MEASURED PHYSICAL ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS VERSUS HEALTHY CONTROLS?
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Background: There is consistent evidence that participation in physical activity is greatly reduced in people with multiple sclerosis (MS) compared with healthy controls. The majority of the studies, however, have relied on measures of physical activity that do not have evidence supporting the validity of the scores and have not accounted for differences in mobility status. This undermines the veracity of the conclusion that individuals with MS are physically inactive and sedentary.

Objectives: This study included validated, self-report, and objective measures of physical activity and compared the levels of physical activity between adults with MS and controls without MS controlling for ambulatory status.

Methods: The sample included 12 individuals with a definitive diagnosis of MS and 7 controls who were similar in age, sex, height, weight, and mobility. Participants walked on a GAITRite mat for measuring ambulatory status and received instructions for wearing two accelerometers [Actigraph 7164 (uniaxial) and GT3X (triaxial) models] for the subsequent 6-day period. On the seventh day, all participants returned the accelerometers and completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ), International Physical Activity Questionnaire (IPAQ), and a 7-Day Physical Activity Recall (7dPAR). Data were analyzed using SPSS, version 17.

Results: Independent-samples t tests indicated that those with MS were substantially less physically active than controls based on total activity counts from the uniaxial (P = .019, d = 1.13) and triaxial (P = .015, d = 1.08) accelerometers, scores from the GLTEQ (P = .0015, d = 1.61), and IPAQ (P = .004, d = 1.38), and energy expenditure from the 7dPAR (P = .05, d = 0.83). Those differences were unchanged when controlling for mobility status measured by the GAITRite mat in subsequent analysis of covariance.

Conclusions: This study further confirms that individuals with MS are substantially less physically active than healthy controls when using validated measures and controlling for mobility status. Such results further support the importance of a targeted intervention for increasing physical activity in those with MS.

Supported by: Consortium of Multiple Sclerosis Centers
Disclosure: Nothing to disclose
Keywords: Quality of life in MS

(W23) TOOL FOR IDENTIFYING A PATIENT PROFILE OF DRUG COMPLIANCE
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Background: Treatment noncompliance resulting in the discontinuation of disease-modifying drugs for the treatment of multiple sclerosis (MS) can significantly impact the quality of life and functioning of patients. It is crucial to identify patients at high risk for noncompliance early to intervene and improve adherence.

Objectives: The objective of this study was to develop a tool for identifying patients at high risk for noncompliance with their disease-modifying drugs.

Methods: A comprehensive literature review was conducted to identify risk factors associated with noncompliance. A questionnaire was developed to assess these risk factors, and a scoring system was implemented to assign a risk score to each patient. The tool was validated using a cohort of patients with MS, and its effectiveness in predicting noncompliance was evaluated.

Results: The questionnaire included 15 items covering various domains such as demographics, health beliefs, social support, and medication characteristics. The scoring system assigned a risk score to each patient based on the number of positive items. The higher the score, the greater the risk of noncompliance.

Conclusions: The developed tool for identifying a patient profile of drug compliance can be a valuable resource for healthcare providers to screen for patients at high risk for noncompliance and promptly intervene to improve adherence.

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Disclosure: Nothing to disclose
Keywords: Rehabilitation strategies and therapy and MS

(W21) PRELIMINARY EVALUATION OF A MULTIPLE SCLEROSIS EDUCATIONAL TRACK FOR PHYSICAL THERAPY STUDENTS
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Background: The Education and Scholarship Track in Multiple Sclerosis (MS) is a unique collaboration between the University of North Carolina (UNC), Division of Physical Therapy (PT), and the Eastern North Carolina Chapter of the National Multiple Sclerosis Society. This track aims to provide services for individuals diagnosed with MS, to advance the competencies of entry-level physical therapists, and to serve as an educational model for other universities seeking to tailor class projects to focus on issues that affect patients with MS.

Objectives: The objectives of this track are to enhance the MS-related competencies of an annual cohort of Doctor of Physical Therapy (DPT) students. The desired outcome is to graduate DPT students who have a skill competency base specific to MS.

Methods: This 2-year educational track focuses on four key elements: didactic learning, clinical experiences, service, and advocacy. Students are provided with the opportunity to collaborate with neurologists and researchers who have expertise in the management of the neurologic and psychosocial needs of patients living with MS.

Results: Preliminary evaluation outcomes indicate increased student competencies in MS-specific knowledge and skills. Student competencies indicate a change from a pre-program Likert scale rating of “below average” to a mid-program rating of “above average” in several domains. Qualitative feedback from scholarship recipients, patients, and interdisciplinary preceptors further supports the importance of a targeted intervention for increasing physical activity in those with MS.

Disclosure: Nothing to disclose
Keywords: Rehabilitation strategies and therapy and MS

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of multiple sclerosis (MS) is an important issue in MS patient care; however, there has been no standard, universal system to score compliance in patients on therapies for MS. The availability of a tool that provides a numerical risk factor and suggested support algorithm might identify patients at risk of noncompliance and guide appropriate, risk-stratified intervention. Objectives: To identify the profile of a patient who may be at risk for discontinuation of subcutaneous (SC) interferon beta-1a (IFNβ-1a) by developing and testing a tool that uses a predictive scoring system that incorporates social and disease-related information. Methods: The Predictive Assessment Pilot Program (PAPP) is designed for field nurses to provide injection training for MS patients who are receiving SC IFNβ-1a and enrolled in the MS LifeLines patient-support program, and evaluate them through a risk-assessment algorithm. Discontinuation status is assessed monthly. Using the PAPP Score Sheet, patients are scored by field nurses on five domains that influence compliance (perception [P], cognition [C], lifestyle [L], activities of daily living [A], and support mechanisms [S]; PCLAS) using an objective and standardized scoring system (0–5 scale, where 5 represents the highest risk of noncompliance and a score ≥3 indicates elevated risk). From the individual scores, a total score (PCLAS) appropriate for the patient is determined and an intervention chart suggests to the nurse a corresponding intervention designed to aid planning and delivery of patient follow-up. Intervention levels include low risk (PCLAS 0–9; less frequent contact), intermediate risk (10–18; increased contact), and high risk (>18; detailed contact). Results: MS LifeLines field nurses began using the tool in November 2007 in the United States in Detroit, New Jersey, Cleveland, Denver, and Houston. A database has been developed to assess demographic information and component scores; results will be presented at a later date. Conclusions: Use of the PAPP risk-assessment algorithm and interventions has the potential to both identify patients at risk for discontinuation and target appropriate support.

Supported by: EMD Serono, Inc and Pfizer Inc


Keywords: Disease-modifying treatment in MS, Nursing management in MS

(W24) ELECTRONIC AUTOINJECTOR FOR SELF-INJECTED SUBCUTANEOUS INTERFERON BETA-1A

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Background: Patients receiving injectable therapies for multiple sclerosis (MS) may experience barriers to treatment adherence related to factors such as injection site reactions (ISRs), injection site pain, and negative perceptions of the tolerability or ease of use of the drug-administration device. Self-injection devices have demonstrated the potential to reduce the incidence of ISRs and improve treatment adherence. The RebiSmart autoinjector is an electronic self-injection device designed to enhance patient satisfaction by offering improved ease of use and convenience, needle shielding, and adjustable injection parameters (eg, needle depth, rate of injection). The device also monitors treatment adherence by recording injection times. Objectives: To present the design of a study to evaluate ease of use, patient acceptance and satisfaction, and functional reliability of the RebiSmart electronic autoinjector in patients using subcutaneous (SC) IFNβ-1a for the treatment of relapsing MS. Methods: The study is a 12-week, open-label, single-arm, multicenter phase 3b trial enrolling patients aged 18 to 65 years with relapsing MS (McDonald criteria) who have been undergoing treatment with IFNβ-1a 44 µg SC 3 times weekly (TIW) for ≥12 weeks. During the study, patients continue with IFNβ-1a 44 µg SC TIW injections using the RebiSmart electronic autoinjector. The primary end point of this study is the proportion of patients who rate the autoinjector as “easy to use” or “very easy to use” on a user trial questionnaire at the 12-week end point. Multiple secondary endpoints related to functional reliability, device characteristics, patient satisfaction, ease of use, and convenience are included based on answers to the questionnaire administered at weeks 6 and 12. A quality of life questionnaire is included at baseline and week 12. Monitoring of adverse events associated with treatment administration will be conducted throughout the study. Results: Enrollment for this trial will begin in February 2010 and will continue for 24 weeks or until 100 patients are enrolled. Conclusions: The data from this trial are expected to provide insights regarding the use of an electronic autoinjector for delivery of IFNβ-1a 44 µg SC TIW in patients with relapsing MS.

Supported by: EMD Serono, Inc, and Pfizer Inc


Keywords: Disease-modifying treatment in MS, Equipment in MS
(W25) A STEPWISE APPROACH FOR THE TREATMENT OF INTENTION TREMOR
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Background: To improve function in people with multiple sclerosis (MS) and tremor, therapists use a variety of techniques. Evidence to support them is limited, and there is no systematic protocol for administering these interventions. As such, there is an urgent need for a systematic, evidence-based approach for the treatment of upper limb intention tremor (ULIT) to address functional goals in people with MS. A preliminary study was completed to determine whether behavioral strategies and assistive devices administered using a systematic protocol were feasible with MS clients. The response to the protocol was positive. Using the results of that preliminary work, the current study made revisions to the protocol, and it is this modified protocol that is being tested in this study. Objectives: To test and provide initial evidence for the feasibility of an occupational therapy stepwise approach for the treatment of intention tremor (SWAT-IT) to improve function of eating and handwriting tasks in participants with MS and ULIT. Methods: Participants were recruited through the University of British Columbia’s MS clinic with a target sample of 30. Behavioral strategies and assistive devices are included in the SWAT-IT protocol to manage and improve function in handwriting and eating tasks for people with MS and ULIT. They were systematically introduced and removed to determine the most successful interventions. If more than one strategy was found useful, the techniques were coupled. Determination of the success of the interventions was completed by the participants and evaluated by the therapist. Participants used the most successful technique(s) daily for a week following the intervention session and completed daily evaluations to determine the ongoing use and impact. At 1 month post-intervention, a follow-up was completed to evaluate the retention of tested interventions. Results: Data collection is under way. It is expected that individuals with MS will develop their unique combination of strategies that will enable improved performance in eating and handwriting tasks. Conclusions: The SWAT-IT intervention for ULIT in MS is a unique, systematic, and clinically useful treatment. Future work includes conducting a randomized controlled trial to test the effectiveness and retention of SWAT-IT.


Keywords: Psychological issues and MS

(W26) THE USE OF BEHAVIORAL MEDICINE IN THE INTERDISCIPLINARY TREATMENT OF MULTIPLE SCLEROSIS PATIENTS
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Background: Behavioral medicine (BM) is an interdisciplinary field of medicine devoted to understanding and managing health and illness through disease prevention, health promotion, diagnosis, treatment, and rehabilitation. BM is important in the interdisciplinary treatment of multiple sclerosis (MS) because patients and family members might find a diagnosis of MS difficult to fathom. Hopes, dreams, and goals for the future may drastically change. Reactions may include grief, anxiety, anger, depression, fear, numbness, denial, and hopelessness. As individuals progress through treatment with disease-modifying agents (interferons, glatiramer acetate, mitoxantrone, natalizumab), noncompliance issues may arise due to frequent needle sticks or needle phobia. Pain management issues often arise, specifically neuropathies, trigeminal neuralgia, and neck and back pain. Fatigue is also a common complaint. Although several theories exist regarding the etiology, behaviorally it is more important to promote energy conservation and sleep hygiene. Cognitive and memory changes may occur, leading to confusion, anxiety, frustration, and hopelessness. Finally, in addition to depression as a common side effect of some MS drugs, as the disease progresses and continued damage to the myelin sheath occurs, neurotransmitter movement slows and signal transmission difficulties occur, potentially leading to mood disorders. Conclusions: BM can help in the following ways: 1) adjustment/coping with new diagnosis and associated fears: exploring fears, adjusting expectations, and setting appropriate life goals; 2) family/couples adjustment issues: exploring MS and the effects on the family system; 3) teaching wellness: achieving the benefits of maximum health by taking personal responsibility; 4) needle phobia: building a fear hierarchy and teaching CBT skills; 5) treatment compliance issues: exploring thoughts, reducing frequency of relapse, prolonging disability; 6) pain management: increase function, manage symptoms; 7) fatigue/energy conservation/sleep disorders; 8) mood disorders: premorbid conditions, treatment, medication recommendations; 9) relaxation skills training/biofeedback; 10) group psychotherapy: support and feedback from other similar individuals.

Disclosure: Nothing to disclose.

Keywords: Rehabilitation strategies and therapy and MS, Management of activities of daily living in MS, Symptomatic treatment of MS

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settings was convened to develop a curriculum for community yoga teachers interested in learning more about MS. A trainer-led, 6-hour, in-person program with accompanying materials was developed by this group, which focused on the needs of people with mild symptoms of MS (a training program focused on more advanced MS is also planned). Ten yoga poses common to most yoga traditions were selected to illustrate how a pose might be adapted to accommodate MS symptoms such as balance issues, weakness, spasticity, and so on, and help maximize participation. A manual was also developed that included photographs of the selected poses and adaptations. Results: The first pilot program, limited to 15 yoga teachers, was held in New York City in November 2009. Topics addressed in the program included an overview of MS, “trying-on” the symptoms of MS, adaptation of poses, hands-on workshop with people with mild symptoms of MS; and disability etiquette and accessibility concerns. Per the program evaluation, the program successfully met the needs of the target audience. Conclusions: Participant and trainer feedback and recommendations are being reviewed, and the program will be adjusted as needed. The program will be piloted at two other chapter locations in 2010.

Supported by: National Multiple Sclerosis Society and PVA Education Foundation, grant 623
Disclosure: Nothing to disclose

Keywords: Complementary/alternative therapies in MS, Rehabilitation strategies and therapy and MS

(W28) ACHIEVING CONCORDANCE IN MULTIPLE SCLEROSIS: A WORKSHOP PROGRAM FOR MULTIPLE SCLEROSIS SPECIALIST NURSES
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Background: Nonadherence to disease-modifying drug (DMD) therapy can adversely affect treatment outcomes. As the first point of contact with patients and their families, UK multiple sclerosis (MS) specialist nurses are in a unique position to help improve adherence by encouraging patients to take an active role in informed treatment decisions and managing expectations of treatment outcomes. Objectives: We developed a program of workshops to highlight the need for partnerships between MS nurses and patients in shared decision-making for initiating DMDs, which may help foster adherence to treatment in the long term. Methods: The Achieving Concordance in MS (ACMS) initiative consists of a program of 1-day workshops designed to be practical and interactive. Each workshop is run by two MS specialist nurses, covering topics such as factors influencing adherence, key concepts in achieving concordance (the process of negotiation between health-care professional and patient in order to reach shared decisions), and the effects of nonadherence on disease outcomes. The format is an informal mixture of presentations, group discussions, and practical sessions, intended to help nurses integrate shared decision-making into routine clinical practice. Materials (eg, slides, DVD) are also supplied to enable nurses to run further meetings at their own centers. Results: To date, eight regional workshops have been held across the UK, with approximately 5 to 14 attendees in each. Speakers were involved from the outset of the project, participated in the development of materials, and adapted the format to accommodate audience needs. Feedback was very positive, with attendees commenting that the workshops were engaging and relevant to practice, and encouraged useful debate around the definitions of compliance, adherence, and concordance and their relevance to the management of MS. Conclusions: The ACMS workshop program provides training and information to help MS nurses incorporate shared decision-making into routine clinical practice, which may help promote patient treatment adherence over the long term and lead to improved treatment outcomes. The workshops also provide a valuable forum for discussing all areas of MS nursing in a format that is easily transferable to other health-care professionals.

Supported by: Merck Serono SA–Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

Keywords: Disease-modifying treatment in MS, Nursing management in MS

(W29) DID YOU HEAR ABOUT THE GUY—GOES BY THE NAME OF FLASH—WITH MULTIPLE SCLEROSIS?
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Background: “Life is too important to be taken seriously,” wrote Oscar Wilde. A life with multiple sclerosis (MS) is certainly, most certainly, still a life—with a serious diagnosis. So, is this the time to hunker down and get serious? Absolutely not. Now is the time to pull out all the humor you can get your hands on. A group of men gather for an aquatic class. They know the value of humor. A common exchange between them goes something like this: Jim, via his walker, arrives at the pool. He yells to his friend, Vincent, “Come on, Lightning!” Vincent, walking with his AFO and cane, yells back to his friend Jim, “Hold on there, Flash, I’m comin’!” Not far behind Flash and Lightning comes Blaze, who transposes, hands-on workshop with people with mild symptoms of MS; and disability etiquette and accessibility concerns. Per the program evaluation, the program successfully met the needs of the target audience. Conclusions: Participant and trainer feedback and recommendations are being reviewed, and the program will be adjusted as needed. The program will be piloted at two other chapter locations in 2010.

Supported by: National Multiple Sclerosis Society and PVA Education Foundation, grant 623
Disclosure: Nothing to disclose

Keywords: Complementary/alternative therapies in MS, Rehabilitation strategies and therapy and MS

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1Hereford Primary Care Trust, Hereford, United Kingdom; 2Mardon Neuro-Rehabilitation Centre, Exeter, United Kingdom

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Supported by: Merck Serono SA–Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

Keywords: Disease-modifying treatment in MS, Nursing management in MS

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E.S. Vander Kamp
Aquatics, Lakeshore Foundation, Birmingham, AL

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Disclosure: Nothing to disclose

Keywords: Complementary/alternative therapies in MS, Rehabilitation strategies and therapy and MS
(W30) NEWLY DIAGNOSED MS DINNER SERIES AT VIRGINIA MASON MEDICAL CENTER

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Background: At the Neurosciences Institute at Virginia Mason Medical Center, approximately 173 new patients were diagnosed with multiple sclerosis in 2009. To help these individuals and their families better understand their disease, we designed the model for the Newly Diagnosed MS Dinner Series. Based on our experience with newly diagnosed multiple sclerosis (MS) patients, we have found that several key topics are important as patients begin to learn about their disease. These topics were planned carefully to be covered during five different sessions as follows: 1) Basic MS Pathophysiology; 2) Understanding Your MRI; 3) Symptom Management and DMT review; 4) Complementary Medicine; 5) Community Resources & What It’s Like to Live with MS. Our speakers include Dr. Mariko Kita, an MS neurologist; Piper Paul, RN, MSCN, a certified MS nurse; Laurie Mischley, ND, a naturopath; and Lisa A. Webb, LICSW, an MS social worker. The series is held on five consecutive Monday evenings for 2 hours, every other month. Dinner is provided from an unrestricted educational grant that covers the meal and parking. Patients are encouraged to bring family members or support partners to the program. During any given series we have between 4 and 24 participants. A new MS diagnosis can be overwhelming, and patients process their diagnosis emotionally and intellectually in different ways. In using this educational model, we provide a structured format over 5 weeks to help patients and their families learn about MS in a comfortable and therapeutic environment. We engage an evolving dialogue and provide a consistent presence during this critical time in their initial experience of their diagnosis. The series also offers the participants an important opportunity to meet other newly diagnosed patients in a setting that is validating to them. At the end of the series some participants have continued to stay in contact with one another. We have offered the program since summer 2007 and have presented over 60 dinners. A sequel for graduates of the series is also offered (“What’s Next”), and we continue to make changes to our program based on feedback. In 2010 we will offer participation in the series via live webcast and also a full-day session where all lectures are given on one day, for patients who live too far away.

Disclosure: Nothing to disclose

(W31) EVOLUTION OF THE MULTIPLE SCLEROSIS SOCIAL WORK COLLABORATIVE OF WASHINGTON (MSSWCW)

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Background: Social workers are key members of the inter-disciplinary multiple sclerosis (MS) specialty care team. They address the psychosocial and long-term-care needs specific to the MS community in ways that transcend what is typically available in a general clinical setting. The Seattle area has become a hub of MS specialists providing health care to individuals with MS living in Washington, Alaska, Oregon, Idaho, and Montana. In 2009, in an effort to improve the MS care network and clarify the role of the MS social worker, a group of social workers and other allied health professionals from Washington State collaborated and developed the first MS social work organization in our region, the Multiple Sclerosis Social Work Collaborative of Washington (MSSWCW). The MSSWCW is currently developing a formal network of MS social workers, developing best practices for MS social workers, and developing a forum for professional training and resources to serve the MS community. The group has recently elected its first officers and adopted the following mission and vision statements. Mission: To create a consortium where social workers in the MS community can consult, collaborate, educate, and support one another as a catalyst for greater service to, and advocacy for, the MS community. Vision: By studying research trends and participating in MS-related program development, the consortium will work toward the professionalization of MS social workers by: 1) improving clinical skills through ongoing professional training; 2) increasing social workers’ capacity to provide the highest standard of holistic care; 3) providing psychosocial education to people living with MS and their families, friends, and caregivers.

Supported by: National Multiple Sclerosis Society, Veteran Health Administration Multiple Sclerosis Center of Excellence—West, University of Washington Department of Rehabilitation Medicine, University of Washington MS & Aging Rehabilitation Research & Training Centers, Swedish Medical Center, Evergreen Hospital Medical Center, Virginia Mason Medical Center, and MultiCare Neurosciences Center of Washington

Disclosure: Nothing to disclose

(W32) A SINGLE-USE AUTOINJECTOR FOR SELF-INJECTED SUBCUTANEOUS INTERFERON BETA-1A

S. Wray, 1 R. Armstrong, 2 C. Herman, 3 E. Watsky, 4 F. Dangond, 5 A. Al-Sabbagh 3

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Background: Treatment adherence in patients receiving injectable therapies for multiple sclerosis (MS) can be negatively affected by the occurrence of injection site reactions (ISRs) and the patient’s subjective perception of tolerability and ease of use of the injection device. Studies have demonstrated that self-injection devices may reduce the incidence of ISRs. A ready-to-use, single-use autoinjector has been designed with the aim of simplifying subcutaneous (SC) injections of interferon beta-1a (IFNβ-1a) and improving patient satisfaction by eliminating the need for device preparation and featuring needle shielding both pre- and post-injection.

Objectives: To present the design of a study to evaluate an investigational, ready-to-use, single-use autoinjector for self-injection of IFNβ-1a SC with respect to the following domains: ease of use, patient satisfaction and acceptability, and functional reliability. Methods: Patients aged 18 to 65 years with relapsing MS (McDonald criteria) who have been undergoing treatment with IFNβ-1a SC 44 µg 3 times weekly (TIW) for at least 12 weeks were eligible for this prospective, multicenter, open-label, single-arm, 12-week, phase 3b study. During the study, patients continue therapy with IFNβ-1a SC.
44 µg TIW using the single-use autoinjector. The proportion of patients rating the autoinjector as “easy to use” or “very easy to use” on a user trial questionnaire at Week 12 is the primary end point. Functional reliability, ease of use, and simplicity of the device, patient satisfaction, impact on patient perception of quality of life, and convenience based on responses to the questionnaire at week 12 are secondary end points. Assessments will also include safety, tolerability, and compliance with the autoinjector. **Results:** This study has completed recruitment of 109 patients with relapsing MS. Baseline demographics, clinical characteristics, and 6-week interim data will be presented. **Conclusions:** Data from this study will provide information regarding the ease of use, reliability, and patient acceptability and satisfaction with drug administration via a single-use autoinjector for self-injection of IFNβ-1a SC to treat relapsing MS.

**Supported by:** EMD Serono, Inc, and Pfizer Inc

**Disclosure:** S. Wray: Bayer, Biogen Idec, EMD Serono, Genzyme, Novartis, Teva (consulting fees); Bayer, Biogen Idec, EMD Serono, Genzyme, Novartis, Teva (honoraria); Bayer, Biogen Idec, EMD Serono, Genzyme, Novartis (other financial benefits). R. Armstrong: Bayer, Biogen Idec, Teva (consulting fees); Biogen Idec, UCB (honoraria). C. Herrman: Biogen Idec (consulting fee). E. Watsky: Pfizer Inc (salary). F. Dangond: EMD Serono, Inc (salary). A. Al-Sabbagh: EMD Serono, Inc (salary).

**Keywords:** Disease-modifying treatment in MS, Equipment in MS
(P/T01) DISSECTING THE FUNCTIONS OF PD-L1 PATHWAYS USING MONOCLONAL ANTIBODIES

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Study Support: National Multiple Sclerosis Society and National Institute of Allergy and Infectious Diseases.

Background: PD-L1 is a B7 family member which is broadly expressed on hematopoietic and non-hematopoietic cells and has key inhibitory functions. PD-L1 regulates peripheral T cell tolerance and the progression of many autoimmune diseases. PD-L1 has two binding partners, PD-1 and B7-1, but the relative roles of PD-L1-PD-1 vs. PD-L1-B7-1 interactions in regulating self-reactive T cell responses are not yet known. Objectives: We aimed to dissect the functions of the PD-L1-PD-1 vs. PD-L1-B7-1 pathways in a murine model of autoimmunity.

Methods: We have employed two novel anti-PD-L1 antibodies that have differential blocking activities: anti-PD-L1 antibody 2H11 preferentially blocks the PD-L1-B7-1 interaction while anti-PD-L1 antibody 9G2 blocks both the PD-L1-B7-1 and PD-L1-PD-1 interactions. Results: Either the ‘single-blocker’ 2H11 antibody or the ‘dual-blocker’ 9G2 antibody can accelerate diabetes in non-obese diabetic mice. However, distinct effects of these antibodies point to important but different roles for these two PD-L1 pathways in controlling the responses of self-reactive T cells in vivo.

Conclusions: Our data indicate that PD-L1-B7-1, as well as PD-L1-PD-1 interactions, control tolerance checkpoints and the pathogenesis of autoimmune diseases.

(P/T02) PACAP RECEPTORS: PROMISING THERAPEUTIC TARGETS FOR MULTIPLE SCLEROSIS

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Study Support: National Multiple Sclerosis Society.

Background: Autoimmune demyelinating diseases such as multiple sclerosis (MS) are among the most common diseases of the central nervous system. The causes are unknown. Currently, treatments slow the progression of disability and reduce the severity and frequency of exacerbations, but no treatments have any impact on primary progressive disease. There is a great need for a better understanding of the disease, and new therapeutic strategies. Numerous works suggest that pituitary adenyl cyclase-activating peptide (PACAP), a widely-expressed neuropeptide initially discovered in the hypothalamus, is a potential new therapeutic target for the treatment of MS and other immune-based diseases. Indeed, PACAP administration attenuates dramatically the clinical and pathological features of murine models such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis.

Objectives: However, specific immunoprotective roles (if any) of endogenous PACAP in EAE model of MS have not been explored.

Results: PACAP-deficient mice were subjected to myelin oligodendrocyte glycoprotein (MOG35-55)-induced EAE and showed heightened pathological manifestations of EAE compared to wild type mice, with enhanced Th1/Th17 and reduced Th2/Treg responses. The increased sensitivity was accompanied by enhanced mRNA expression of proinflammatory cytokines (TNFα, IL-6, IFNγ, IL-12, IL-23 and IL-17), chemokines (MCP-1, MIP-1α, and RANTES) and chemotactic factor receptors (CCR1, CCR2 and CCR5), but down-regulation of the anti-inflammatory cytokines (IL-4, IL-10 and TGF-β) in the spinal cord. Moreover, the abundance of CD25+FoxP3+ Tregs in lymph nodes and levels of FoxP3 mRNA in the spinal cord were also diminished. The Treg reduction was associated with increased proliferation and decreased TGF-β secretion in MOG-stimulated lymph node cultures.

Conclusions: These data demonstrate that endogenous PACAP protects against EAE, and identify PACAP as an intrinsic regulator of Treg abundance after inflammation. To exploit PACAP receptors (PAC1, VPAC1 and VPAC2) as therapeutic targets for MS and other autoimmune diseases, it will be crucial to determine which specific effects and/or mechanisms are mediated by PACAP and its receptors on immune and other cell types.

(P/T03) THE MOLECULAR MECHANISMS UNDERLYING THE PROTECTIVE ROLE OF ALPHA-B CRYSSTALLIN IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Study Support: National Multiple Sclerosis Society.

Background: The wide range of clinical symptoms and diverse pathological features of the inflammatory, demyelinating disease multiple sclerosis (MS) underlies the difficulty in finding effective treatments for the disease. Therapeutic agents that are able to dampen the immune response and protect against neurodegeneration may provide a useful tool in treating this multifaceted disease. Earlier studies in our laboratory have found that αB-crystallin (cryab), a small heat shock protein (sHsp), occurs in very high levels in early active MS lesions as compared to control brains. Moreover, cryab was found to be one of the most abundant proteins in acute and chronic active MS lesions. These findings were of interest as cryab is a molecular chaperone that can be upregulated during pathological conditions. sHsps function by binding aberrantly folded proteins and can prevent deleterious aggregation which can lead to cellular toxicity and apoptosis. Thus, the increase in the levels of cryab may be a compensatory mechanism in order to prevent pathological changes that occur during MS.

Results: Previous studies in our laboratory found a potent anti-inflammatory property of cryab and protection from glial apoptosis. Cryab-/- mice induced with experimental autoimmune encephalomyelitis (EAE), an animal model of MS, displayed more severe symptoms and inflammation. There was an increase in T-cell proliferation, secretion of inflammatory cytokines and hyperactive macrophages. Additionally, an increase in apoptotic glial cells in cryab-/- EAE mice was observed. However, treatment with cryab substantially reduced the neurological deficits of the disease, decreased the immune response and diminished cell loss.

Conclusions: These findings indicate a protective role for cryab possibly by augmenting the apoptotic process. Our objective is to elucidate the pathways responsible for the ability of cryab to reduce apoptosis.
(P/T04) TARGETING UBC13 FOR TREATMENT OF MULTIPLE SCLEROSIS
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Study Support: National Multiple Sclerosis Society. Background: Ubiquitination of proteins is a well-known mechanism for targeting proteins for degradation by the proteasome. UBC13 is the only ubiquitin conjugating enzyme (UBC) recognized to mediate K63-linked ubiquitination. Multiple cytokines, cytokine receptors, and receptors involved in innate immunity have been implicated in multiple sclerosis (MS). TRAFs are adapter proteins that function as critical intermediaries in cytokine signaling mechanisms in autoimmune diseases. Therapeutic strategies currently used against MS provide symptomatic relief but cures are rare. Recent studies, by our group and others, of mice in which the ubc13 gene has been ablated have validated UBC13 as an attractive target for suppressing inflammation. Objectives: 1) To develop a novel high-throughput screening (HTS) assay for UBC13-UEV1A based on time resolved-fluorescence energy transfer (TR-FRET) useful in executing a HTS campaign 2) To devise NMR-based methods for performing fragment-based screens and to confirm hits from primary HTS screen 3) To configure secondary cell-based and counter-screen assays for evaluating hits from primary HTS screen. Methods: 1. TR-FRET based methodology relied on two complementarily labeled ubiquitins incorporated into polyubiquitin chains formed by UBC13-UEV1A. 2. 1D 1H NOESY NMR spectral data were acquired using a 600 MHz Bruker spectrometer to identify chemical hits interacting with unlabeled UbC13. 3. Secondary cell-based assays were developed to evaluate chemical hits in the presence and absence of inflammatory signal inducers. Results: The hit rate from TR-FRET based UBC13-mediated methodology, demonstrated for its utility in HTS campaign of a large chemical library (400,000), was high. Hits are being evaluated by NMR-based methodology to identify chemical inhibitors interacting with UBC13-UEV1A. Several downstream cell-based assays that address selectivity, mechanism of action, and cellular activity are ongoing. Conclusions: Chemical hits were identified from TR-FRET based UBC13-mediated primary HTS campaign. Together with structure-activity-relationship (SAR) analysis, 3D-computational modeling, NMR and cell biology methods, hits will be evolved into suitable lead candidates for testing in EAE animal models simulating MS.

(P/T05) MAST CELL DERIVED TRANSFORMING GROWTH-FACTOR-β1 CONTRIBUTES TO EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS
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Study Support: National Multiple Sclerosis Society and National Institutes of Health. Background: Mast cells have been associated with the development of experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis, in mast cell deficient W/Wv mice and IL-9R deficient mice. However, the extent to which specific mast cell products can contribute towards EAE has been largely unexplored. The generation of mast cell specific Mcpt5 cre mice has now allowed conditional deletion of mast cell products. We are utilizing these mice to address this for transforming growth factor-β (TGF-β), a pleiotropic cytokine that in some contexts can promote Th17 differentiation. Objectives: To study the effects of mast cell derived TGF-β during EAE. Methods: We have crossed Mcpt5 cre mice with floxed TGF-β mice to generate mice in which mast cells no longer express this cytokine. The resulting mice were then challenged with disease. Results: We found that mice with conditional deletion of mast cell derived TGF-β have significantly attenuated disease in comparison to littermate controls. Studies to understand the basis for the reduction of disease are underway. Conclusions: These results suggest that mast cells contribute to disease through their expression of TGF-β.

(P/T06) ROLE OF IL-23 IN THE DEVELOPMENT OF PROINFLAMMATORY TH17 CELLS IN INDUCTION OF EAE
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Study Support: National Multiple Sclerosis Society. Background: CD4+ T cells, upon activation, differentiate into Th1, Th2 and Th17 cells. We and others identified TGF-β and IL-6 as the differentiation factors for the generation of IL-17 producing Th17 cells but loss of IL-23 results in a defect in the generation of Th17 cells. However, the role of IL-23 and IL-23 responsive cells in generation of pathogenic Th17 cells in EAE is not clear. Th17 subset of T cells is critical in the pathogenesis of many organ-specific autoimmune diseases including multiple sclerosis. Objectives: To understand the role of IL-23 in generation of Th17 cells during EAE. Methods: Generation of the IL-23R-KI mice. A BAC clone (RP23-204M15) containing the IL-23R gene was used as a template for PCR amplification to generate 5.1- and 1.8-kb arms that were subcloned into enhanced GFP containing a TKPbs-LoxP-Neo cassette. The targeting construct was electroporated into Bruce4 embryonic stem (ES) cells. Targeted ES cells were injected into BALB/c blastocysts and male chimeras were bred with female C57BL/6 mice. Recall response. WT and IL-23R-KI mice were immunized with 100 µg MOG35-55 peptide emulsified in CFA. On day 8 after immunization, spleen and lymph node (LN) cells were prepared and cultured with 20 µg/ml MOG35-55 and 25 ng/ml rIL-23. After 4 days of stimulation, cells were analyzed for IL-23R(GFP) expression. Results: To understand the function of IL-23 in generation and maintenance of Th17 cells in EAE, we have generated a novel “knock-in” mouse in which we have replaced the intracellular domain of the IL-23R with the GFP. We show that in addition to Th17 cells, a subset of myeloid cells express IL-23R and respond to IL-23 by producing IL-17 and IL-22. Our studies further demonstrate that IL-23R expression is crucial for generation of encephalitogenic Th17 cells, but its expression on the innate immune system is dispensable in the development of experimental autoimmune encephalomyelitides. Conclusions: Our data demonstrate an important role of IL-23 in the development of Th17 cells and EAE. Our data further shows that IL-23R expression is more important for T cells rather than innate immune cells in the development of EAE.
very severe form of spontaneous EAE. Furthermore, we have used adoptive transfer of Th1 and Th17 cells to determine whether these populations cooperate with B cells during EAE. **Results:** We have determined that an active cooperation between T and B cells induces the production of MOG specific IgG1 antibodies by MOG-specific B cells in 2D2/TH mice. In turn, T cells activated and differentiated by antigen specific B cells produce more IFN-γ and IL-17. In addition, the transfer of MOG specific Th17 cells induces disease with a different pathological phenotype compared to Th1 cells and the recruitment of more B cells. **Conclusions:** Together, these data highlight the complex interplay between MOG specific T and B cell populations in a new model of spontaneous EAE and offer perspectives for the understanding of current therapies and the development of new therapies for the treatment of MS.

(P/T09) IDENTIFICATION OF TRANSCRIPTIONAL REGULATION OF SUPPRESSOR FUNCTION OF REGULATORY T CELLS INDUCED BY TOLERGENIC DENDRITIC CELLS IN VIVO

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**Study Support:** National Multiple Sclerosis Society, Howard Hughes Medical Institute, and American Diabetes Association.

**Background:** Multiple Sclerosis (MS) and its animal model, Experimental Autoimmune Encephalomyelitis (EAE), are caused by the breakdown of immune tolerance that leads to continuous disease progression. An important component of tolerance is a function of induced T reg cells that in contrast to thymic-derived natural regulatory T cells arise outside the thymus. Such extra-thymic T reg cells can be induced by tolerogenic dendritic cells (DCs) that mediate immune tolerance, which is characterized by T cell unresponsiveness to rechallenge with antigen. In patients with multiple sclerosis and in the animal disease models, regulatory T cells have been found to have a compromised function. The function of regulatory T cells may be particularly important during the initial insult on the CNS by the immune system and early intervention to enhance the function of regulatory T cells could be a valuable therapeutic tool for prevention of serious nervous damage characterizing progressive MS. One of the obstacles to such a progress is an incomplete understanding of the mechanisms of function of such T reg cells. Particularly, the specific molecular factors required for the function of T reg cells induced in vivo by tolerogenic DCs remain unknown.

**Objectives:** Identification of specific molecular factors and understanding their mechanism of function that controls suppressor function of DC-induced regulatory T cells. **Methods:** Gene-expression and functional analysis based on all in vivo experiments using an experimental system of tolerance induced by dendritic cells in vivo. **Results:** Here we identified a critical and novel role for the member of the homeobox gene family of transcription factors for the suppressive function of DC-induced T reg cells that mediate DC-dependent T cell tolerance in vivo. **Conclusions:** Our findings could lead...
to better methods of immunomodulation and silencing the autoimmune response in MS.

(P/T10) STRUCTURAL CHARACTERIZATION OF THE UNUSUAL BINDING TOPOLOGY OF MYELIN SPECIFIC TCRS

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Study Support: National Multiple Sclerosis Society. Background: We have previously reported the first crystal structure of a TCR (Ob.1A12) from a patient with relapsing remitting MS. Unlike virus-specific TCRs, this structure showed a highly unusual binding topology as the TCR was not centered over the peptide/MHC surface. Rather, Ob.1A12 TCR only contacted the N-terminal half of the MHC-bound myelin basic protein (MBP) peptide. Objectives: In the present study we sought to examine whether altered binding modes would also be observed for other human MBP specific T cells. Methods: We expressed the human Hy.1B11 TCR which had been isolated from a relapsing-remitting MS patient. This TCR is specific for the same peptide (MBP85-99) as Ob.1A12 TCR, but bound to HLA-DQ1. Crystals of the Hy1b11-MBP85-99/HLA-DQ1 complex were obtained by hanging drop vapor diffusion and X-ray diffraction data were collected at the Brookhaven National Laboratories. Structure was determined by molecular replacement and refined. Results: We determined the structure of TCR Hy.1B11 bound to MBP85-99/HLA-DQ1 to 2.55 Å resolution, this is the first structure in which the TCR is restricted by HLA-DQ rather than HLA-DR. The TCR was centered over the MHC in a diagonal manner; the crossing angle was determined to be 40°. There was, however, a tilt of the TCR of 15° towards DQ1 α-helix relative to the HA1.7-HA-DR1 complex which has a typical binding mode. As a result of the tilt the germline encoded TCR loops CDRα1 and α2 were prevented from engaging the β helix of the DQ1. This is highly unusual as the germline encoded CDRs α1, α2, β1 and β2 are known to be involved in MHC restriction and in the majority of the TCR-peptide/MHC complex structures all four engage the MHC molecule. Additionally the CDRβ3 which is involved in peptide recognition does not engage the peptide, due to a shorter CDRβ3 loop in Hy.1B11 as compared to other TCRs sharing the same Vβ. Conclusions: This structure shows another unusual binding mode by a TCR from a MS patient. The unusual interaction with the peptide-MHC complex may have allowed this TCR from escaping negative selection in the thymus.

(P/T11) A CRITICAL ROLE FOR IFN-\(\gamma\)-GAMMA PRODUCING TH1 CD4 T CELLS DURING EAE

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Study Support: National Multiple Sclerosis Society. Background: CD4 T cells regulate adaptive immune responses through their ability to produce cytokines and chemokines, and thus have a critical role in the induction and maintenance of chronic inflammatory diseases such as multiple sclerosis (MS). Typically, effector CD4 T cells are segregated in subsets by virtue of the cytokines they produce, and various effector cell types are associated with the development of autoimmune chronic inflammation. Objectives: It is well established that IFN-\(\gamma\)-producing Th1 effector CD4 T cells are present in the plaques of patients with MS and these cells are elicited during mouse models of MS. Nevertheless, the significance of this effector CD4 T cell population during disease remains elusive. The objective of this study is to understand the contribution of these cells during disease. Methods: To investigate the importance of the Th1 lineage during experimental MS, we have generated a transgenic mouse model, the IFN-\(\gamma\)-knock-in mouse, in which IFN-\(\gamma\)-producing CD4 T cells can be identified by virtue of the cell surface Thy1.1 reporter molecule. The combination of this unique transgenic mouse system and the murine model of experimental MS, experimental autoimmune encephalomyelitis (EAE), has enabled us to dissect this question. Results: Induction of EAE in the IFN-\(\gamma\)-knock-in mice is associated with an upregulation of the Thy1.1 reporter molecule on CD4 T cells in the CNS, not those resident in the secondary lymphoid tissues. Moreover, we find the key Th1-associated transcription factor Tbet is also expressed by effector CD4 T cells within the inflamed tissue and it is critical for the development of disease. To further probe the significance of the IFN-\(\gamma\)-producing CD4 T cells during EAE, we physically depleted these cells during the course of the disease. Interestingly, we did not detect an impact on the induction of EAE and the disease severity when IFN-\(\gamma\)-producing cells were removed. Strikingly, however, these mice did not maintain chronic EAE and appeared to recover. Conclusions: Together these results indicate an essential role for Th1 effector CD4 T cells in maintaining chronic EAE.

(P/T12) CELL TYPE-SPECIFIC RESPONSES TO IFN-\(\gamma\) IMPLICATIONS FOR UNDERSTANDING THE MECHANISM OF IFN-\(\gamma\) THERAPY IN MS

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Study Support: National Multiple Sclerosis Society. Background: Interferon (IFN)–\(\gamma\) is a major treatment for MS, but is unfortunately not effective in a significant portion of patients, and the molecular mechanism of successful treatment is still unknown. Studies using cell lines showed that IFN-\(\gamma\) activates formation of the trimer ISGF3 (STAT1, STAT2, IRF9), which induces the expression of many genes. It is however unclear how primary human leukocytes signal in response to IFN-\(\gamma\). Objectives: To study the signaling response in primary leukocytes of healthy subjects after stimulation with IFN-\(\gamma\) in vitro, and to determine the response in leukocytes of MS patients after injection with IFN-\(\gamma\) (Avonex) ex vivo. Methods: We used flow cytometry to measure the amount of IFN-\(\gamma\)-induced phosphorylated STAT1, 3 and 5 in single CD4+ and CD8+ T cells, B cells, and monocytes present in whole blood. Results: In contrast to monocytes and CD8+ T cells, few B cells or CD4+ T cells activated STAT1 in response to IFN-\(\gamma\), a finding that did not depend on the dose of IFN-\(\gamma\) or the time of stimulation. These data show that, in contrast to many cell lines, ISGF3 is not the main activator of gene expression in primary human B cells and CD4+ T cells in response to IFN-\(\gamma\). Notably, B cells and in particular CD4+
T cells activate STAT5, which has effects on cell survival opposite from those of activated STAT1. Leukocyte subsets of MS patients showed different STAT and P38MAPK activation patterns after Avonex injection, which might explain cell type-specific induction of TRAIL and other genes by type 1 IFNs.

Conclusions: Our results show cell type-specific signaling responses after stimulation in vitro and to IFN-β injection in MS patients ex vivo, which may relate to mechanisms of action of IFN-β therapy in MS. We also found some differences between MS patients within given leukocyte subsets, and are in the process of determining whether differential STAT and kinase activation in blood cells by IFN-β injection correlates with response to therapy, defined as MRI stability after start of treatment.

(P/T14) BINDING OF RECOMBINANT T CELL RECEPTOR LIGANDS (RTL) TO APC PREVENTS UPREGULATION OF CD11B AND LY6C AND INHIBITS T CELL ACTIVATION AND TRANSFER OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Study Support: National Multiple Sclerosis Society and the Biomedical Laboratory R&D Service, Department of Veterans Affairs. Background: Recombinant T cell receptor ligands (RTLs) induce antigen-specific T cell tolerance and reverse clinical and histological signs of experimental autoimmune encephalomyelitis (EAE) when administered after onset of disease. However, little is known about the RTL tolerance-inducing mechanism(s). To address this issue, we evaluated in-vitro effects of RTLs on spleen cell populations from mice with EAE and the effects of RTL-treated antigen presenting cells on T cell activation and transfer of EAE. Objectives: To study RTL-immune cell interaction Methods: Fluorescent-labeled RTL401-containing the I-As moiety linked to PLP-139-151 was used to demonstrate that RTL molecule binds with high avidity to antigen presenting cells. CFSE labeled T cells were co-cultured with APCs in the presence of respective anti-gens to study RTL effect on T cell proliferation and cytokine secretion. Using an adoptive transfer approach, we show that encephalitogenic T cells activated with RTL401-armed APC have reduced capacity to transfer EAE. Results: RTLs bound to surface receptors on B, macrophages and dendritic cells, but not T cells, through the MHC class II αβ1 moiety of the RTL in an antigenic peptide-independent manner. RTL binding reduced expression of CD11b and Ly6c on splenic macrophages and RTL-conditioned macrophages, but not B cells, inhibited T cell activation in vitro. Splenocytes incubated with RTLs had reduced ability to transfer EAE, even in the presence of added PLP-139-151 peptide. Inhibition of encephalitogenic activity was likely mediated through RTL-conditioned macrophages as well, since B cells were found to be unnecessary for RTL transfer effects on EAE. These results demonstrate for the first time a novel pathway of T cell regulation that involves binding of RTLs to the surface of myeloid APC and down-regulation of the CD11b and Ly6c macrophage markers. RTL binding and conditioning thus accounts for the enhanced ability of macrophages but not B cells to inhibit T cell activation and induction of EAE. Conclusions: RTL-armed myeloid APC deliver tolerogenic signals to cognate T cells to reverse the EAE disease process.

(P/T13) ORGANIZATIONAL AND ACTIVATIONAL EFFECTS OF SEX HORMONES IN EAE

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Study Support: National Multiple Sclerosis Society. Background: Most autoimmune diseases are more common in women than men, suggesting a role for sex hormones and/or chromosomes. Sex hormones can have permanent organizational effects, during development, as well as reversible activational effects. Adult sex hormones have been extensively studied for their activational effects in autoimmune diseases, while organizational effects remain unclear. A novel transgenic system permits examination of organizational and activational sex hormone effects independent of sex chromosomes. The gene that encodes for testicular development (Sry) is deleted from the Y chromosome (termed Y–), then added back at an autosomal location. This permits independent study of sex chromosome and sex hormone effects. Gonadectomy can then be used to focus on the role of developmental, as opposed to adult, hormones. Objectives: To determine the influence of developmental sex hormones on EAE. Methods: Transgenic mice were backcrossed onto the SJL background, a strain known to have increased susceptibility in females. Mice were gonadectomized at age 4 weeks, then active EAE was induced using PLP peptide 139-151 at age 8 weeks. EAE disease scores were attained and spleens assessed for T cell immune markers by flow cytometry. Comparisons were made between XX (female) and XX Sry (male) mice that differed in gonadal type, while sharing a common x chromosomal complement (XX). Analogously, comparisons were also made between YY (female) and XY-Sry (male) mice that again differed in gonadal type, while sharing a common sex chromosome complement (XY). Results: We found that mice exposed to developmental male hormones, as compared to female hormones, had relatively more severe EAE. T lymphocytes from mice which had been exposed to male developmental hormones demonstrated relatively increased expression of CD69, ICAM-1 and VLA-4. Additionally, exposure to male development hormones, as compared to female, resulted in less naive and more effector memory T cells as revealed by CD62L/CD44 staining. Conclusions: Exposure to male, as compared to female, hormones during development confers relatively greater susceptibility to EAE. This is the first evidence for opposing roles of developmental versus adult hormones in autoimmune disease susceptibility.

(P/T15) CD98 IS REQUIRED FOR AUTOIMMUNE DISEASE IN MOUSE MODELS

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Study Support: National Multiple Sclerosis Society. Background: CD98 (4F2 antigen) is a T cell activation marker with an uncertain role in T-dependent immune responses. Early in vitro experiments utilizing blocking or cross-linking antibodies suggested that CD98 may provide a co-stimula-
were tested in vitro for reactivity to myelin-derived sulfatide. Results: Whereas these mice exhibited normal T cell populations, they were protected from development of Experimental Autoimmune Encephalomyelitis (EAE) induced by MOG peptide immunization. We also utilized a mouse model for autoimmune diabetes (T1D) in which OVA-specific T cells (OT-1) are transferred to mice expressing OVA in beta cells of the pancreas (RIPmOVA). Transfer of CD98-null T cells did not result in diabetes, as occurred after transfer of CD98+ control T cells. We found that CD98-null T cells exhibit impaired proliferation to a variety of mitogens in vitro, and slower homeostatic proliferation in vivo. In addition, loss of CD98 profoundly inhibited antigen-driven T cell proliferation in vivo and resulting clonal expansion. This was confirmed in the disease model when CD98 null OT1 T cells exhibited normal homing, but defective proliferation and expansion in pancreatic draining lymph nodes of RIPmOVA recipients. Loss of CD98-driven clonal expansion also led to profoundly impaired T-dependent antibody responses. Conclusions: Thus, CD98 is required for rapid clonal expansion and T dependent immune responses, thus accounting for protection from T cell-driven pathologies in mice lacking CD98 on their T cells.

(P/T16) T CELL REACTIVITY TO SULFATIDE AND INVOLVEMENT OF APOLIPOPROTEIN E IN MULTIPLE SCLEROSIS

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Study Support: National Multiple Sclerosis Society and Multiple Sclerosis Society of Canada. Background: MS involves an autoimmune attack on the myelin sheath, which is primarily composed of lipids. While a great deal of investigation has focused on myelin proteins as targets of autoimmunity, relatively little has been done on lipids as immune targets. Our lab has been studying T cells which recognize lipid antigens with the rationale that these lipid-reactive T cells may recognize myelin lipids and contribute to the pathogenesis of MS. Lipids are presented to T cells by the MHC-like molecule CD1. One of the most abundant lipids in myelin is sulfatide, which has been shown to bind human CD1 molecules and thus may be recognized by CD1 restricted T cells. We have also shown that the lipid transporter apolipoprotein E (apoE) can promote the capture and subsequent presentation of lipid antigens by CD1. Since apoE is abundant in the central nervous system (CNS), we hypothesize that it may mediate the presentation of myelin lipids such as sulfatide. Objectives: To determine whether myelin-derived sulfatide is recognized by CD1-restricted T cells in the context of MS, and whether this recognition is promoted by CNS apoE. Methods: MS and healthy control peripheral blood T cells were analyzed ex vivo and human CD1-restricted T cell lines were tested in vitro for reactivity to myelin-derived sulfatide. The presentation of sulfatide to T cells was investigated in the presence or absence of apoE. Results: Myelin-derived sulfatide was found to be strongly antigenic for T cells in both MS patients and controls in a CD1-dependent manner. The presentation of sulfatide could be mediated by both serum and CSF-derived apoE. Conclusions: Sulfatide, one of the most abundant lipids found in myelin, is presented to human CD1-restricted T cells, and may thus be an important autoantigen in MS. ApoE, a CNS lipid-transporter which has been previously implicated in MS, can mediate the presentation of sulfatide by antigen presenting cells to T cells, and thus serves as a pathway for enhanced immunoreactivity to the myelin sheath. These findings have important implications for the pathogenesis of MS and may lead the way to new therapeutic strategies.
(P/T19) THE ANTIPROLIFERATIVE GENE TOB1 IS INVOLVED IN MS AND EAE PATHOGENESIS

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Study Support: National Multiple Sclerosis Society and National Institutes of Health. Background: Fractalkine, a chemokine anchored to CNS neurons of peripheral (but not CNS) endothelial cells, serves as an adhesion molecule or as a soluble chemotactant after proteolytic cleavage by ADAM-family proteases. In the CNS, fractalkine binds CX3CR1 on microglia, promoting microglial survival and tonically inhibiting microglial neurotoxicity. CX3CR1 is not required for microglial development, but coincides with early microglial precursors in the developing CNS. CX3CR1 is also expressed by circulating monocytes, NK cells and T cells.

(P/T20) FRACTALKINE RECEPTOR REGULATES TRAFFICKING OF DEFINED MONOCYTE SUBSETS DURING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Study Support: National Multiple Sclerosis Society and National Institutes of Health. Background: Fractalkine, a chemokine anchored to CNS neurons of peripheral (but not CNS) endothelial cells, serves as an adhesion molecule or as a soluble chemotactant after proteolytic cleavage by ADAM-family proteases. In the CNS, fractalkine binds CX3CR1 on microglia, promoting microglial survival and tonically inhibiting microglial neurotoxicity. CX3CR1 is not required for microglial development, but coincides with early microglial precursors in the developing CNS. CX3CR1 is also expressed by circulating monocytes, NK cells and T cells.

Among these, the antiproliferative gene TOB1 was 7-fold downregulated. We then showed that TOB1 was downregulated in T cells shortly after in-vitro stimulation, during in-vivo immunization, and in the CNS of animals with EAE. These data suggest that TOB1 is required to maintain T cell quiescence and its deficiency may lead to increased cell cycle activity thus facilitating the development of autoimmunity in susceptible individuals. Objectives: We hypothesized that Tob1 deficient mice will show an earlier disease onset, a more severe phenotype, or both. We then set out to characterize the immunological and neurodevelopmental properties of Tob1-/- animals. Methods: We used Tob1-/- mice to assess the effects of this gene in EAE pathogenesis. We also conducted immunological studies to characterize the properties of Tob1-/- T cells. In addition, we tested the effect of the histone deacetylase inhibitor (HDAC) TSA to suppress EAE.

Results: Tob1-/- mice experienced both an earlier onset and a more severe EAE. Analysis of motoneuron function and apoptosis suggest the earlier onset is associated to neural toxicity in the Tob1-/- animals. Tob1-/- T cells proliferate more, and express more IL-17 and IL-23 than their WT counterparts. Tob1-/- mice showed a significant delay in spinal cord myelination at P5 when compared with WT mice. Finally, we found that the HDAC inhibitor TSA (which increases Tob1 expression by >10-fold in vitro) ameliorated EAE. Strikingly, Tob1-/- animals showed no improvement, suggesting that Tob1 expression is required for the beneficial effects of TSA. We confirmed these results in in-vitro experiments. Conclusions: Our results suggest a dual role of Tob1 in the CNS and the periphery. We found that while Tob1 is required for keeping quiescence in T cells in the periphery, it may also be critical for oligodendrocytes to (re)myelinate axons in a timely manner. Tob1 is required for TSA to exert its beneficial effect in EAE and to suppress T cell proliferation in vitro.

INFLAMMATION: CELL ACTIVATION & RECRUITMENT

(P/T18) EPIDERMAL FATTY ACID-BINDING PROTEIN REGULATES TH17 DIFFERENTIATION VIA NUCLEAR RECEPTOR PEROXISOME PROLIFERATOR-ACTIVATING RECEPTOR

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Study Support: National Multiple Sclerosis Society. Background: Fatty acid binding proteins, FABPs, are cytoplasmic lipid chaperones that function as regulators of both metabolic and inflammatory pathways. Epidermal fatty acid-binding protein (E-FABP) has been shown to contribute to the development of experimental autoimmune encephalomyelitis (EAE) by promoting the inflammatory function of macrophages and dendritic cells. Objectives: Th17 cells have been associated with many autoimmune diseases like multiple sclerosis (MS), but the mechanisms that lead to the differentiation of Th17 cells remain elusive. We hypothesized that expression of E-FABP in CD4+ T cells promotes their differentiation to the Th17 phenotype. Methods: E-FABP-deficient and wild-type mice were immunized with MOG(35-55) peptide. Expression of E-FABP in T cells, Th17-cell percentage, cytokine expression and nucleolar receptor expression/activity were investigated using confocal microscopy, flow cytometry, real-time PCR, western blot, gene super array and DNA binding assays. Results: We found that E-FABP-deficient mice generated reduced levels of Th17 cells as compared with wild-type mice. The impaired Th17 differentiation by E-FABP-deficient CD4+ T cells was associated with lower levels of IL-21 expression in response to IL-6, and reduced expression of RORγt and RORc. Further results showed that E-FABP-deficient CD4+ T cells expressed higher levels of the nuclear receptor peroxisome proliferator-activating receptor γ (PPARγ) than did wild-type CD4+ T cells. Treatment with the PPARγ antagonist GW9662 restored expression of IL-21, RORγt, RORc, and IL-17 by E-FABP-deficient T cells to wild-type levels. The negative influence of E-FABP deficiency on IL-17 expression was attributed to PPARγ-mediated suppression of IL-6-induced STAT3 activity. In addition, analysis of the impact of E-FABP on nuclear receptors revealed elevated Nr0b2 expression in E-FABP-deficient CD4+ T cells, which in turn may serve to positively regulate PPARγ. Conclusions: In summary, we report a novel mechanism regulating Th17 cell differentiation through an E-FABP-PPARγ pathway. These data implicate E-FABP as a potential target for anti-inflammatory therapies targeting MS.

(P/T19) THE ANTIPROLIFERATIVE GENE TOB1 IS INVOLVED IN MS AND EAE PATHOGENESIS

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Study Support: National Multiple Sclerosis Society. Background: Epidermal fatty acid-binding protein (E-FABP) has been shown to contribute to the development of experimental autoimmune encephalomyelitis (EAE). In this study, we investigated the role of E-FABP in relationship to Th17 cell differentiation. Methods: E-FABP-deficient and wild-type mice were immunized with MOG(35-55) peptide. Expression of E-FABP in T cells, Th17-cell percentage, cytokine expression and nucleolar receptor expression/activity were investigated using confocal microscopy, flow cytometry, real-time PCR, western blot, gene super array and DNA binding assays. Results: We found that E-FABP-deficient mice generated reduced levels of Th17 cells as compared with wild-type mice. The impaired Th17 differentiation by E-FABP-deficient CD4+ T cells was associated with lower levels of IL-21 expression in response to IL-6, and reduced expression of RORγt and RORc. Further results showed that E-FABP-deficient CD4+ T cells expressed higher levels of the nuclear receptor peroxisome proliferator-activating receptor γ (PPARγ) than did wild-type CD4+ T cells. Treatment with the PPARγ antagonist GW9662 restored expression of IL-21, RORγt, RORc, and IL-17 by E-FABP-deficient T cells to wild-type levels. The negative influence of E-FABP deficiency on IL-17 expression was attributed to PPARγ-mediated suppression of IL-6-induced STAT3 activity. In addition, analysis of the impact of E-FABP on nuclear receptors revealed elevated Nr0b2 expression in E-FABP-deficient CD4+ T cells, which in turn may serve to positively regulate PPARγ. Conclusions: In summary, we report a novel mechanism regulating Th17 cell differentiation through an E-FABP-PPARγ pathway. These data implicate E-FABP as a potential target for anti-inflammatory therapies targeting MS.
Objectives: To determine the role of CCR2 and CX3CR1 in monocyte recruitment to the brain of EAE affected mice. 

Methods: CX3CR1-GFP mice were crossed with CCR2-red fluorescent protein (RFP) knock-in mice to generate double heterozygous Cx3cr1+/GFP/Ccr2r+/RFP and CX3CR1-deficient Cx3cr1GFP/GFP/Ccr2r+/RFP mice. EAE was induced with MOG(35-55) peptide and brain leukocytes isolated at peak of disease. Samples were stained with antibodies against CD115, CD11c and Ly6C to categorize the cells as monocytes/macrophages, dendritic cells and inflammatory myeloid cells respectively. Results: Lack of CX3CR1 correlated with severe EAE, and CCR2-deficiency associated with delayed disease onset. Contrasting the effects of CCR2-deficiency that induced a defective recruitment of inflammatory Ly6Chi monocytes to the CNS, CX3CR1 deficiency was associated with an increased accumulation of CD115+/Ly6C– CD11c+ monocytes. Comparison of the CX3CR1 and CCR2 expression showed that Ly6C– cells expressed higher levels of CX3CR1-GFP (P=0.008) than Ly6C+ cells and lower levels of CCR2-RFP (P=0.016). Conclusions: Ly6C+CCCR2+ and Ly6C–/CX3CR1+ subsets retain functional specialization in the inflamed CNS. The results indicate that fractalkine acting on resident microglia and peripheral monocytes appear to play important function during the inflammatory response that develops during EAE.

(P/T21) INVESTIGATING THE MECHANISMS OF IGG TRANSPORT AT THE BLOOD BRAIN BARRIER 
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Study Support: National Multiple Sclerosis Society. Background: There is increasing evidence that IgGs play an important role in MS. The brain and the spinal cord are generally inaccessible to blood-borne components due to the presence of cellular barriers such as the blood-brain barrier (BBB), which tightly regulate the selective transport of macromolecules to and from the central nervous system. The cells that constitute these barriers express the neonatal Fc receptor (FcRn), which is known to mediate the bidirectional transport and recycling of IgGs across and within cells of diverse origin. The dual roles played by FcRn in recycling as well as transcytosing IgGs have several implications at the BBB. For example, these transport pathways could regulate the movement of (therapeutic) IgGs in and out of the brain and also regulate the persistence of (pathogenic) IgGs in the brain. However, the role of the BBB in regulating the transport of IgGs and immune complexes (ICs) are poorly understood. The current project aims at studying both the quantitative and mechanistic aspects of IgG or IC transport across the BBB. By using well characterized in vitro models of the BBB, we are investigating the extent of IgG or IC recycling and transport at the BBB in normal and inflammatory conditions. Specific emphasis is placed on identifying the intracellular trafficking pathways that are involved in IgG transport at the BBB. Recently, we developed a three-dimensional, cellular imaging technique called multifocal plane microscopy (MUM), which enables the study of intracellular trafficking pathways at very high spatial and temporal resolution. Using MUM, we have imaged complex intracellular trafficking pathways of IgGs at the single molecule level (1), which is otherwise not possible with classical imaging techniques. Using MUM in conjunction with cellular and molecular techniques, we propose to study the transport of IgGs and other macromolecules in various in vitro BBB models. Conclusions: The results of this study should provide much needed knowledge concerning IgG transport at the BBB. The proposed analyses could also have value for improving the delivery of therapeutic IgGs or IgG-tagged drugs to the brain.


(P/T22) MICROGLIAL ACTIVATION BY FIBRONECTIN AND VITRONECTIN IN DEMYELINATING DISEASE 
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Study Support: National Multiple Sclerosis Society. Background: Early in the pathogenesis of multiple sclerosis (MS) the blood-brain barrier (BBB) is compromised, which leads to deposition of the plasma proteins fibronectin and vitronectin in brain tissue. Within the brain, resting microglia are activated into aggressive migratory cells that destroy oligodendrocytes. Based on our finding that microglial activation in vitro is strongly promoted by fibronectin and vitronectin, we are testing the hypothesis that modulation of microglial activation by fibronectin or vitronectin is an important contributory mechanism in the pathogenesis of MS. In this project, we have already demonstrated deposition of fibronectin and vitronectin in the brains of EAE mice, and described a close association between ECM deposits and microglial activation. In addition, in vitro studies have shown that the influence of fibronectin and vitronectin on microglial activation and MMP-9 production is mediated via the αvβ3 integrins respectively. Objectives: As vitronectin is the most potent stimulator of microglial activation, the current objective is to identify the precise αvβ3 integrin receptors that mediate this effect. Microglial activation is being examined, both in vitro, and in vivo, in mice deficient for the two microglial αvβ3 integrins, αvβ3 and αvβ5. Methods: Using primary cell cultures of microglia, we examine microglial adhesion, activation (defined by cell surface marker expression), MMP-9 expression and phagocytosis. In parallel, we examine microglial activation and clinical progression in the EAE mouse model of MS. Results: Microglia derived from single knockouts (β3 or β5 integrin) failed to show any defect in adhesion, activation or MMP-9 production, in response to vitronectin. Conclusions: This suggests that redundancy exists within the microglial vitronectin receptors. We are currently examining the phenotype of double knockout (β3 and β5 integrin) mice.

(P/T23) IN VIVO IMAGING STUDY OF THE EARLY EVENTS THAT LINK MICROGLIAL ACTIVATION TO BLOOD-BRAIN BARRIER DISRUPTION 
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**Study Support:** National Multiple Sclerosis Society, National Institutes of Health, American Heart Association, Howard Hughes Medical Student Research Fellowship, and Dana Program in Brain and Immuno-imaging.

**Background:** Microglial activation appears early in multiple sclerosis (MS) pathology, correlates temporally and spatially with blood-brain barrier (BBB) disruption, and regulates disease onset and severity. Microglia continuously survey their cellular environment and are rapid responders at sites of central nervous system (CNS) injury. However, the initial signals that induce microglial activation in MS remain elusive.

**Objectives:** Our aim is to examine the immediate effects of BBB disruption to microglial activation in vivo. In this study we examined the real-time responses of microglia to blood factors that could leak in the CNS after BBB disruption.

**Methods:** We performed in vivo imaging using two-photon microscopy to study the dynamic interactions between microglia and the vasculature through a thinned area of the skull in anesthetized mice. We used transgenic mice (CX3CR1GFP/+ ) in which microglia express the green fluorescent protein (GFP) and we labeled the vasculature by intravenous injection of dye. Finally, we performed in vivo imaging while locally injecting blood proteins and plasma in the mouse cortex through a small craniotomy.

**Results:**

- 3D reconstruction and time lapse analysis of in vivo imaging data detailed the dynamic interaction between microglia and the vasculature in the unperturbed mouse cortex. Our prior studies have shown that the blood protein fibrinogen is not merely a marker of BBB disruption, but a potent inducer of microglial activation and a regulator of MS pathology.

- Following microglial responses while injecting different blood proteins in the cortex showed that fibrinogen can induce a rapid chemotactic response from microglial processes within minutes after injection, a response that persists over several hours. By recording microglial responses during cortical injections of plasma derived from wt and fib/- mice we confirmed that fibrinogen is specific among blood factors in inducing acute microglial responses.

**Conclusions:**

- Our results suggest that fibrinogen is a specific inducer of microglial activation in the CNS that initiates rapid microglial responses within minutes upon BBB disruption. Our ultimate goal is to identify novel therapeutic targets for MS by studying the sequence of events that link vascular abnormalities to early cellular responses and MS pathogenesis.

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**Study Support:** National Multiple Sclerosis Society and National Institutes of Health. **Background:** Hypoxic tissue alterations are associated with early stages of multiple sclerosis (MS) pathology. However, the regulation of the hypoxic response in MS and its contribution to inflammatory demyelination is unknown. The transcription factor Hypoxia Inducible Factor 1 alpha (HIF1-α) is upregulated in MS lesions. HIF1-α links hypoxic responses to inflammation, since it regulates gene expression of inflammatory mediators such as IL1-β and TGF-β. In turn, inflammation regulates HIF1-α, as the transcription factor NF-κB is a critical activator of HIF1-α.

**Objectives:** The goal of this study is to determine the regulation of HIF1-α in inflammatory demyelination and explore if HIF1-α plays a role in the development of MS-type lesions using cell-specific HIF1-α conditional knock-out mice.

**Methods:** We induced EAE in HIF1-α/luc mice, which express the luciferase gene fused to the oxygen-sensing domain of HIF1-α. Moreover, we performed immunohistochemistry for HIF1-α and gene expression analysis of HIF1-α target genes at different stages of experimental autoimmune encephalomyelitis (EAE) in mice.

**Results:**

- We show that HIF1-α is upregulated early after the induction of EAE. In vivo bioluminescence imaging showed that HIF1-α is detected early at day 7 post immunization, precedes the onset and correlates with EAE severity.

- HIF1-α is induced mainly in astrocytes and to a lesser degree in microglia/macrophages in myelinated areas and is also upregulated in motor neurons. In accordance, EPO and iNOS, which are regulated by HIF1-α are also induced in EAE, suggesting that HIF1-α is transcriptionally active.

- To examine the functional significance of HIF1-α in inflammatory demyelination, we are currently analyzing the effects of astrocyte-, microglia/macrophage- and astrocyte/microglia/macrophage-specific deletion of HIF1-α on the onset and progression of EAE in GFAP-cre/HIF1α/f, Lysozyme-cre/HIF1α/f and GFAP-cre/Lysozyme-cre/HIF1α/f mice, respectively.

**Conclusions:** Overall, our study showed that HIF1-α is induced before the onset of EAE, suggesting that HIF1-α might be involved in the early events that trigger inflammatory demyelination. Studies of the early molecular changes in the cascade of events that lead to inflammatory demyelination might reveal novel strategies for therapeutic intervention in MS.

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**Study Support:** National Multiple Sclerosis Society. **Background:** Myelination by brain oligodendrocytes is affected by kinases activated by the Ras family of small G-proteins, yet effects of Ras signaling on the oligodendrocyte lineage are poorly understood. Significant brain defects and MRI abnormalities occur in patients with mutations in Ras pathway genes including Neurofibromatosis Type 1 and Costello syndrome. Similar MRI abnormalities are found in patients with Multiple Sclerosis (MS), which are thought to be due to

**P/T25**

**THE NF1-RAS SIGNALING PATHWAY REGULATES OLIGODENDROCYTE MYELINATION**

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**Study Support:** National Multiple Sclerosis Society. **Background:** Myelination by brain oligodendrocytes is affected by kinases activated by the Ras family of small G-proteins, yet effects of Ras signaling on the oligodendrocyte lineage are poorly understood. Significant brain defects and MRI abnormalities occur in patients with mutations in Ras pathway genes including Neurofibromatosis Type 1 and Costello syndrome. Similar MRI abnormalities are found in patients with Multiple Sclerosis (MS), which are thought to be due to

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**P/T24**

**REGULATION OF THE HYPOXIA INDUCIBLE FACTOR HIF1-A IN AUTOIMMUNE ENCEPHALOMYELITIS**

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**Study Support:** National Multiple Sclerosis Society and National Institutes of Health. **Background:** Hypoxic tissue
changes in myelination within the brain. **Objectives:** Define the role of the NF1-Ras pathway in oligodendrocyte myelination. **Methods:** NF1+/− mutant, PLP-CreERT; NF1 fl/fl, and CNP-HaRasV12 mice were generated to examine the role of NF1 and Ras in oligodendrocyte myelination and remyelination. Electron microscopy (EM) and immunohistochemistry were performed upon the brain of control, NF1 mutant, and CNP-HRAS12V mice after cuprizone-induced demyelination in order to examine the Ras-GAP function of NF1 in myelination and remyelination. EM and MRI abnormalities were confirmed in PLP-CreERT; NF1 fl/fl mice - indicating that these defects in myelination are cell autonomous to oligodendrocytes. **Results:** We show that activation of Ras-GTP through loss of the NF1 results in failure to myelinate large diameter axons in adult mouse corpus callosum, which is mimicked by cell autonomous transgenic expression of constitutively active CNP-HaRAS12V or loss of NF1 specifically in oligodendrocytes. This myelination defect is specific to large, not small or medium caliber axons. EM analysis of all three mouse models showed frequent splitting of lamellae within the myelin. The PLP-Cre; NF1 fl/fl model mimics MRI abnormalities found in patients with MS and Neurofibromatosis Type 1. After cuprizone injury, remyelination is accelerated in NF1 mutants but demyelination and remyelination are delayed in HRAS12V mutants. **Conclusions:** Results from this study implicate an important role for the NF1-Ras signaling pathways in control of oligodendrocyte myelination and may be relevant to aspects of brain dysfunction in patients with MS, Neurofibromatosis and Costello syndrome.

**P/T26** ACTIVATION OF PANCREATIC ENDOPLASMIC RETICULUM KINASE SPECIFICALLY IN OLIGODENDROCYTES ATTENUATES EAE-INDUCED DEMYELINATION

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**Study Support:** National Multiple Sclerosis Society. **Background:** Endoplasmic reticulum (ER) stress is involved in the disease pathogenesis of MS and EAE. ER stress activates the pancreatic ER kinase (PERK), which coordinates an adaptive program that balances protein biosynthesis with ER-folding capacity and contributes to the activation of most adaptive program that balances protein biosynthesis with ER-folding capacity and contributes to the activation of most.

**Objectives:** We generated transgenic mice that allow for controllable activation of the PERK-eIF2α pathway, in the absence of ER stress, specifically in oligodendrocytes. We examined the effects of PERK activation specifically in oligodendrocytes on immune-mediated demyelination using MOG peptide 35-55-induced EAE. **Results:** We demonstrated that moderate activation of the PERK-eIF2α pathway specifically in oligodendrocytes is not deleterious to the animals. Moreover, we found that activation of the PERK-eIF2α pathway specifically in oligodendrocyte before EAE onset significantly attenuated EAE disease severity, and ameliorated EAE-induced demyelination, oligodendrocyte loss and axonal degeneration in the CNS. **Conclusions:** PERK activation specifically in oligodendrocytes attenuates EAE-induced tissue damage. Our data suggest that therapeutic approaches to activate the PERK-eIF2α pathway could prove beneficial in MS.

**P/T27** THE TETRASPANIN KAI1/CD82 REGULATES OLIGODENDROCYTE PROGENITOR MIGRATION AND DIFFERENTIATION

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**Study Support:** National Multiple Sclerosis Society. **Background:** Cell autonomous transgenic expression of constitutively active CNP-HaRAS12V or loss of NF1 specifically in oligodendrocytes. This myelination defect is specific to large, not small or medium caliber axons. EM analysis of all three mouse models showed frequent splitting of lamellae within the myelin. The PLP-Cre; NF1 fl/fl model mimics MRI abnormalities found in patients with MS and Neurofibromatosis Type 1. After cuprizone injury, remyelination is accelerated in NF1 mutants but demyelination and remyelination are delayed in HRAS12V mutants. **Conclusions:** We hypothesized that CD82 could be a factor that restricts migration and promotes differentiation of maturing oligodendrocytes. Our objective is to elucidate the role of CD82 through its interactions with the HGF receptor, c-Met, in regulating migration and differentiation of oligodendrocyte progenitors in the adult brain. **Methods:** We use several in vitro and in vivo techniques including establishment and maintenance of cell cultures, immunopanning, Western analysis, immunofluorescence, tissue processing, retroviral production and stereotactic injections into the rat brain. **Results:** Western analysis confirms the elevated levels of CD82 in isolated adult O4+ cells, which continues to be expressed as these become O1+ in vitro. In the adult rat white matter CD82 is co-expressed with CC1 and olig2 but not with NG2 or GFAP. Immature cells of the neonatal SVZ that constitutively expresses CD82 differentiate either into CC1+ and MBP+ myelinating oligodendrocytes in the white matter or zebrin+ astrocytes in the cortex. Their migration is severely restricted. Downregulation of CD82 in SVZ cells in vivo, using retroviral-expressed shRNAs, prevents differentiation into myelinating oligodendrocytes. shRNA-expressing cells remained PDGFRe+, olig2+ or NG2+, or became CC1+ non-myelinating oligodendrocytes, or GFAP+ astrocytes. cMet is also expressed in adult and neonatal O4+ cells as shown by Western analysis and immunofluorescence. **Conclusions:** CD82 appears to be a critical molecule in the regulation of oligodendrocyte progenitor migration and myelination. Further analysis is required to define how c-Met and CD82 interactions affect progenitor migration and differentiation.

**P/T28** MAXIMIZING THE MYELINOGENIC POTENTIAL OF OLIGODENDROCYTES FOR REPAIR

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Study Support: National Multiple Sclerosis Society. Background: Current efforts have focused on identifying global determinants (transcription and growth factors) that promote differentiation of OPCs into myelinating oligodendrocytes during development. Based on this view, myelination is an all or none event that is controlled in part by the transcriptional program responsible for differentiation. However, it is clearly evident that the CNS is composed of heterogeneous microenvironments that shape the unique architecture and relationship between neurons and glia. As an alternative approach, myelination can also be viewed as a graded process and maximizing the capacity of an oligodendrocyte to form numerous myelin segments with varying internode lengths (myelinogenic potential) may offer an effective strategy for future therapies. Objectives: The objective of our work is to ascertain the nature of this myelinogenic potential, and identify the molecular cues that promote the formation of myelin internodes. Methods: Generation of a transgenic mouse-line with sparsely labeled oligodendrocytes (0.1-0.5%), and biochemically and genetically manipulating the microenvironment of the oligodendrocyte in both in vivo and in vitro paradigms. Results: We establish that individual oligodendrocytes within the same local brain region and along the same axon tracts can form from 10-60 myelin internodes with lengths that vary from 100-400 µm. Here we show that inhibitory cues expressed by oligodendroglia modulate the myelinogenic potential of individual oligodendrocytes within a dynamic and complex environment. We identify the amino-terminal region of Nogo-A expressed by oligodendroglia, as necessary and sufficient to inhibit the number and length of myelin internodes. Conclusions: Together, these findings suggest that myelination is a graded process, subject to competition within the microenvironment and identify a novel physiological role for Nogo-A in the precise myelination of the developing CNS. Maximizing the myelinogenic potential of oligodendrocytes may offer an effective strategy for repair in future therapies for demyelination.

(P/T30) TIMP-1 REGULATES ASTROCYTE MEDIATED CNS MYELINATION

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Study Support: National Multiple Sclerosis Society. Background: Tissue inhibitor of metalloproteinase-1 (TIMP-1) is an endogenously expressed extracellular protein and metalloproteinase inhibitor that is secreted by astrocytes in response to CNS myelin injury. Mice deficient in TIMP-1 (TIMP-1 KO) have been previously shown to exhibit poor myelin repair following inflammatory injury. Objectives: The objective of this study was to determine whether TIMP-1 exerts a regulatory function in the process of CNS myelination. Methods: CNS tissue samples from wildtype (wt) and TIMP-1 KO mice were collected for electron microscopy and immunohistochemistry to analyze and compare postnatal myelination in vivo. Cultured murine neurospheres were analyzed for differentiation differences and primary glial cultures were prepared from wt and TIMP-1 KO mice to culture immuno-panned A2B5 oligodendrocyte progenitors to test cell non-autonomous differentiation. Results: We determined that compact myelin formation is significantly delayed in TIMP-1 KO mice, which coincides with a dramatic reduction in the numbers of astrocytes in the developing CNS. Differentiation of cultured myelination or demyelination affect transport of axonal mitochondria. Objectives: In this study, we examined how myelination and demyelination alter trafficking and localization of axonal mitochondria, using confocal time-lapse imaging of rat organotypic slice culture. Methods: The organotypic slice culture was prepared from cerebellum of P10 Sprague-Dawley rats, and lentiviral vectors expressing mitochondria-targeted DsRed2 were introduced into Purkinje neurons. After 14 days, mitochondrial distribution and movement were observed by time-lapse imaging and confocal microscopy. To investigate the effect of demyelination, the slices were treated with 0.05% lyssolecithin. Then the time-lapse images were superimposed on the immunostaining for nodal and paranodal markers. Results: In myelinated axons, stationary mitochondria are relatively long and large in juxtaparanodal regions, whereas they are short and small around the nodes. Motile mitochondria frequently slowed or stopped around the nodes, and mean velocity was significantly lower at the nodes. When axons are demyelinated, the velocity of motile mitochondria was significantly increased, and the size of stationary mitochondria was also increased along the entire axons. Conclusions: Since energy demand and axonal Ca2+ are hypothesized to be increased around the nodes of myelinated axons and in demyelinated axons, our results suggest that mitochondrial motility is dynamically modulated by myelination and demyelination to maintain homeostasis of axons.

(P/T29) AXONAL TRANSPORT OF MITOCHONDRIA IS ALTERED BY MYELINATION AND DEMYELINATION

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Study Support: National Multiple Sclerosis Society. Background: Mitochondria are essential organelles locally playing multiple roles such as energy production and Ca2+ buffering. Adaptation of mitochondrial transport is thus necessary for axonal metabolism. Although abnormal distribution as well as function of mitochondria have been implicated in multiple neurodegenerative diseases, including inherited and acquired myelin disorders, it is poorly understood how
neural progenitor cells from TIMP-1 KO mice identified a specific deficit of NG2+ oligodendrocyte progenitor cells, while A2B5 oligodendrocyte progenitors grown in conditioned media derived from TIMP-1 KO primary glial cultures exhibit a lack of differentiation into mature O1+ oligodendrocytes. Administration of recombinant murine TIMP-1 (rmTIMP-1) to cultured TIMP-1 KO neural progenitors increased the production of NG2+ cells while treatment with an MMP inhibitor did not. In addition, administration of rmTIMP-1 to cultured astrocytes resulted in a dose-dependent proliferative response. **Conclusions:** Together these findings describe a previously uncharacterized role for TIMP-1 in CNS myelination through the regulation of astrocytes and provide a novel perspective on the function of TIMP-1 in demyelinating diseases of the CNS.

**(P/T31) OPCS REVERSIBLY EXIT THE CELL CYCLE AND GIVE RISE TO REACTIVE ASTROCYTES IN RESPONSE TO IFN-γ**

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**Study Support:** National Multiple Sclerosis Society.

**Background:** Oligodendrocyte progenitor cells (OPCs) populate the CNS with oligodendrocytes. OPCs are exquisitely sensitive to their environment and are targets of many developmental and adult diseases. Understanding how OPCs respond to their environment is crucial to understanding 1) how these cells function in the nervous system and 2) how to best design strategies to promote their appropriate and therapeutic proliferation and differentiation. **Results:** We show here that the neuroinflammatory cytokine interferon-gamma (IFN-γ) decreases proliferation of highly purified populations of perinatal corpus callosum OPCs. IFN-γ treatment decreases markers of OPC proliferation and increases levels of cell cycle inhibitors. IFN-γ also significantly increases the proportion of cells in G0/G1 phase of the cell cycle consistent with cell cycle exit. This attenuated self-renewal is reversible. The withdrawal of IFN-γ after 3 days exposure into proliferative conditions allows for both renewed proliferation and differentiation of OPCs. IFN-γ also significantly decreased OPC differentiation into oligodendrocytes induced by either thyroid hormone or CNTF. IFN-γ led to the generation of a number of GFAP positive astrocytes alone or in combination with either BMP-4 or fetal bovine serum. Further examination revealed that these GFAP positive OPC-derived cells co-express markers of reactive or scar astrocytes. **Conclusions:** Taken together, these results suggest a reversible inhibitory effect of IFN-γ on OPC proliferation with a concomitant generation of reactive/scar astrocytes.

**(P/T32) ORGANOPTHIC CEREBELLAR SLICE CULTURES: A RELEVANT SYSTEM TO TEST REMYELINATION THERAPEUTICS**

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**Study Support:** National Multiple Sclerosis Society and Multiple Sclerosis Society of Canada.

**Background:** Oligodendrocyte progenitor cells (OPCs) are essential for CNS remyelination during development and injury but failed to promote remyelination in adult MS. **Objectives:** The purpose of this study is to elucidate the roles of retinoids and thyroid hormone (TH) during oligodendrocyte (OG) development. **Methods:** Zebrafish embryos were therefore treated with RA, TH, as well as RA receptor (RAR) and retinoid X receptor (RXR) agonists and antagonists at three time points [(36, 50 and 74 hours postfertilization (hpf)], which correspond to different stages of OG development. **Results:** RA (1uM) treatment at 36hpf causes a dramatic reduction in myelin gene expression. RARα selective agonist treatment mimics RA’s negative effect on myelin gene expression. In contrast, treatment with a pan-RXR antagonist increases myelin gene expression. Co-administration of RA with the pan-RXR antagonist at 36hpf restores myelin gene expression to control, suggesting that the antagonist interferes with RA signaling. However, unlike RA, the pan-RXR antagonist’s increase in myelin gene expression is seen at all stages, suggesting that its effect at later stages is independent of RA signaling. As RXRs are also the obligate heterodimer partners of TH receptors, the pan-antagonist could impact TH signaling, which has been shown to enhance OG differentiation. Consistent with studies in other species, treatment of zebrafish embryos with TH dramatically increases myelin gene expression regardless of the stage of development. Furthermore, co-
administration of TH with the pan-RXR antagonist results in an additive positive effect on myelin gene expression. **Conclusions:** Thus, RA appears to act negatively on myelin gene expression through RARs, and RXRs likely act negatively in concert with RA. In addition, RXRs appear to negatively regulate the TH induction of myelin gene expression. This is the first report of a role for RXRs in oligodendrocyte development.

**SEARCHING FOR MS GENES**

**(P/T34) GENETIC ANALYSIS OF MULTIPLE SCLEROSIS SUSCEPTIBILITY IN AFRICAN AMERICANS**

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**Study Support:** National Multiple Sclerosis Society and National Institutes of Health. **Background:** Although MS affects African Americans, albeit to a lesser extent than in individuals of European descent, genetic studies of MS in African Americans have been limited. Recently completed studies of the genomes in people of European descent have shown the utility of performing such studies for elucidating genetic causes and pathways involved in MS susceptibility. Expanding the analysis to non-European samples can enhance the power of these studies. Furthermore, the extent of linkage disequilibrium in the MHC region of European cohorts hinders the ability to distinguish independently MS associated genes within this region. Studies in cohorts of non-European descent, especially populations with less extensive linkage disequilibrium such as African Americans, can help clarify the roles of genes in MS susceptibility across ethnicities, as well as to identify ethnic specific genetic factors associated with MS susceptibility. **Objectives:** Our objectives are to identify genetic variation associated with MS susceptibility across the genome and to clarify the role of the MHC in African American MS. **Methods:** Genotyping and association analyses of approximately 900k single nucleotide polymorphisms (SNPs) and 1.8 million copy number variation probes assayed on 503 and 826 African American MS patients and controls, respectively, and 6,040 MHC region SNPs on 499 and 750 African American MS patients and controls, respectively, were performed. **Results:** Based on their strength of association, 17 non-MHC SNPs were selected for genotyping in an independent population of 540 and 826 African American MS patients and controls, respectively. In addition, 10 CNV regions significantly different between patients and controls are being tested for replication. From the HLA region analyses, ten SNPs were selected for genotyping in an independent population of 451 and 718 African American MS patients and controls, respectively. **Conclusions:** Analyses of these replication datasets are currently underway and will be discussed.

**(P/T35) GENETIC ANALYSIS OF NEUROMYELITIS OPTICA: TWO DIFFERENT ARG19 MUTATIONS IN AQUAPORIN-4 SUGGEST A MOLECULAR MECHANISM FOR SUSCEPTIBILITY TO NMO**

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**Study Support:** National Multiple Sclerosis Society and The Guthy-Jackson Charitable Foundation. **Background:** Familial aggregation and non-Caucasian predilection suggest genetic susceptibility for NMO. Autoantibodies to aquaporin-4 (AQP4) are highly specific and pathogenic. We hypothesized that AQP4 SNPs are associated with NMO risk and/or that some patients may harbor mutations leading to structural changes in AQP4 enhancing susceptibility to NMO. **Objectives:** To perform a SNP association study of AQP4 SNPs and to screen for novel AQP4 coding mutations in NMO patients. **Methods:** We genotyped seven AQP4 SNPs chosen based on their MAF, location and novelty in NMO cases and 1363 matched controls by TaqMan based assay. We performed bidirectional sequencing of the promoter(1kb), exons 0-4, and flanking splice consensus sequences, and the 5' and 3' untranslated regions of 162 sporadic and 10 familial NMO cases and used Mutation Surveyor v3.12 to survey for mutations. **Results:** One of seven SNPs (MAF=0.01) was associated with NMO (NC 18.8; chrom. pos. 22695167: T>A; OR (95%CI) = 13.1(1.4-126.7); p = 0.026. Twenty-one of previously reported SNPs (NCBI) were polymorphic in NMO patients. We detected 27 novel mutations, 6 in the promoter, 7 in coding regions and 14 in the 3' UTR. In three NMO patients (two related), we detected two different missense allelic mutations at Arg19 (R19I and R19T). No control subject had Arg19 mutations (p=0.001). **Conclusions:** Arg19 missense mutations are within the 22 residues of genomic DNA unique to the AQP4 M1 isoform may confer M23-like properties on the mutant product perhaps by interfering with palmitoylation. Large orthogonal arrays might facilitate complement activation by NMO-IgG or lead to breakdown of immune tolerance and predispose to NMO.

NMO Genetics collaborators include: W. Kristoferitsch MD and W. Lang MD (Austria); F. Paul MD and S. Jarius MD (Germany); A. Jacob MD and M. Boggild MD (UK); A. Barreira MD and D. Brum MD (Brazil); A. Cross MD and L. Piccio MD (St. Louis, MO); Accelerated Cure Project (Waltham, MA); G. Parry MD (Minneapolis, MN); T. Scott MD (Pittsburgh, PA); G. Pardo, MD (Oklahoma City, OK).

**(P/T36) THE HLA B*44 ALLELE IS PROTECTIVE FOR SUSCEPTIBILITY AND DISEASE COURSE**

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**Study Support:** National Multiple Sclerosis Society and National Institutes of Health. **Background:** In addition to the very strong effect of HLA DRB1*1501, several different groups of investigators have reported the existence of protective alleles: HLA A*02, HLA B*44, and HLA C*05. However, these reports have yet to be validated, and it is not clear whether these three alleles are markers for one or multiple protective alleles. **Objectives:** To resolve whether the MHC Class I alleles HLA A*02, HLA B*44, and HLA C*05 have independent protective effects on MS susceptibility.
Secondarily, to assess whether there is also a protective effect on disease course as measured by brain atrophy and lesion volume. **Methods:** We explore the role of three MH class I alleles in a clinic-based sample of patients with a diagnosis of either MS or a clinically isolated syndrome (n=532), compared to subjects in a bone marrow donor registry (n=776). All subjects have 2 digit HLA data. Stepwise logistic regression was used to determine the independence of each allele’s effect. We used linear regression and an additive model to test for evidence of correlation between an allele and MRI parameters of disease course (Brain Volume; and T2 hyperintense lesion volume, T2LV). **Results:** Two independent protective alleles exist after accounting for HLA DRB1*1501:HLA A*02 (P=0.00003) and HLA B*44 (P=0.0002). While HLA A*02 and B*44 both reduce susceptibility to MS, only HLA B*44 is associated with a better disease course. MS subjects with HLA B*44 have larger brains (P=0.03) and a lower lesion burden (P=0.03) on MRI. MS subjects with HLA B*44 may also have a slower rate of brain atrophy of T2LV accumulation than those without this allele, in univariate analysis and in the presence of the other alleles (p<0.05 for each). **Conclusions:** The possible role of B*44 in disease course as well as susceptibility suggest that we may be able to modify disease course by exploring further the role of specific class I and KIR molecules in CD8+ and NK cells.

**MS DIAGNOSIS, THERAPY, AND DISEASE COURSE**

**P/T37 PROGRESSIVE CORTICAL GRAY MATTER ATROPHY IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS**

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**Study Support:** National Multiple Sclerosis Society. **Background:** Multiple sclerosis (MS) is a putative autoimmune disease of the central nervous system, however, understanding of the neurodegenerative aspect of MS has grown in recent years. Gray matter atrophy measured by magnetic resonance imaging (MRI) is an important correlate to clinical disability and disease duration in multiple sclerosis. **Objectives:** The objective of this study was to evaluate the extent of gray matter atrophy measured in vivo using MRI in the most commonly used animal model of MS, experimental autoimmune encephalomyelitis (EAE). **Methods:** Living C57BL/6 mice with EAE (n = 5) underwent MRI longitudinally at 20, 40 and 80 days after active EAE induction with MOG 35-55 peptide. The cerebellum and cerebral cortex were manually delineated on the 3-dimensional MR images and anatomical volumes calculated. **Results:** Cerebellar volumes were observed to decrease over time with a mean volume of 58.6 mm³ (SEM = 1.3) at day 20, 53.2 mm³ (1.5) at day 40, and 49.1 mm³ (1.4) at day 80; demonstrating a 16% decrease in volume between day 20 and 80. Additionally, cerebral cortex volumes were observed to decrease over time with a mean volume of 135 mm³ (2.1) at day 20, 127 mm³ (2.2) at day 40, and 118 mm³ (2.6) at day 80; demonstrating a 12% decrease in volume from day 20 to day 80. **Conclusions:** Both cerebellar and cerebral cortex atrophy in EAE are consistent with cerebellar and cerebral cortex atrophy visualized by MRI in MS. This preclinical model can now be used to screen neuroprotective agents aimed at preventing atrophy in MS. This is the first report detecting progressive cortical gray matter atrophy development in vivo using MRI in a mouse model.

**P/T38 LOWER VITAMIN D LEVELS ARE ASSOCIATED WITH A HIGHER RATE OF SUBSEQUENT RELAPSE IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS**

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**Study Support:** National Multiple Sclerosis Society. **Background:** Vitamin D insufficiency is a risk factor for developing multiple sclerosis (MS), but whether it also influences the disease course is unknown. **Objectives:** To determine if vitamin D status influences the risk of subsequent clinical relapses in pediatric-onset MS. **Methods:** We performed a retrospective study in patients with pediatric-onset MS or clinically isolated syndrome who were consecutively recruited at their clinical visits at the UCSF or SUNY Stony Brook Pediatric MS Center. Serum 25-hydroxyvitamin D3 levels were measured by batched chemiluminescent assay. The levels were adjusted based on date of blood draw, stratified by race/ethnicity, to reflect a deseasonalized value. The deseasonalized serum 25-hydroxyvitamin D3 level was the primary predictor in multivariate negative binomial regression models in which the number of subsequent relapses was the outcome. **Results:** Among 110 subjects (mean age 15 ± 3 years; median [interquartile range] disease duration 1.0 year [0.1-8.3], median [interquartile range] Expanded Disability Status Scale score 1.75 [0.7-5]), the mean unadjusted 25-hydroxyvitamin D3 level was 22 ± 9 ng/mL. Only 16 patients (15%) had normal (≥30 ng/mL) unadjusted serum 25-hydroxyvitamin D3 levels. After controlling for age, gender, race, ethnicity, disease duration, length of follow-up and use of disease-modifying therapy, every 10 ng/mL greater deseasonalized 25-hydroxyvitamin D3 level was associated with a 34% lower subsequent relapse rate (incidence rate ratio 0.66, 95% CI [0.46, 0.95], p=0.024). **Conclusions:** Lower serum 25-hydroxyvitamin D3 levels are associated with a substantially increased subsequent relapse rate in patients with pediatric-onset MS or clinically isolated syndrome. The short disease duration and limited disability of the cohort makes it unlikely that disease-associated disability caused lower vitamin D levels. Interventions that increase serum vitamin D stores may strongly benefit patients with MS. A randomized control trial is needed to determine if vitamin D supplementation improves the disease course.

**P/T39 THE COEXISTENCE OF MULTIPLE SCLEROSIS AND AMYOTROPHIC LATERAL SCLEROSIS**

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** objective:**

- To determine if vitamin D status influences the risk of subsequent clinical relapses in pediatric-onset MS.
- The study was a retrospective analysis of 110 subjects with pediatric-onset MS or clinically isolated syndrome, who were consecutively recruited at their clinical visits at the UCSF or SUNY Stony Brook Pediatric MS Center.
- Serum 25-hydroxyvitamin D3 levels were measured by batched chemiluminescent assay and adjusted based on date of blood draw, stratified by race/ethnicity, to reflect a deseasonalized value.
- The deseasonalized serum 25-hydroxyvitamin D3 level was the primary predictor in multivariate negative binomial regression models.
- Among 110 subjects, the mean unadjusted 25-hydroxyvitamin D3 level was 22 ± 9 ng/mL. Only 16 patients (15%) had normal (≥30 ng/mL) unadjusted serum levels.
- After controlling for age, gender, race, ethnicity, disease duration, length of follow-up, and use of disease-modifying therapy, every 10 ng/mL greater deseasonalized 25-hydroxyvitamin D3 level was associated with a 34% lower subsequent relapse rate (incidence rate ratio 0.66, 95% CI [0.46, 0.95], p=0.024).
- **Conclusions:** Lower serum 25-hydroxyvitamin D3 levels are associated with a substantially increased subsequent relapse rate in patients with pediatric-onset MS or clinically isolated syndrome. Interventions that increase serum vitamin D stores may strongly benefit patients with MS. A randomized control trial is needed to determine if vitamin D supplementation improves the disease course.
supplementation in relapsing-remitting MS. **Methods:** This study is a prospective double-blind, dual arm cohort trial with RRMS patients divided in a 1:1 fashion to low dose (800 IU daily) vs. high dose (10,000 IU daily) cholecalciferol supplementation for six months. Clinical and laboratory assessments for safety will be done at baseline, 3 months, and 6 months, as well as EDSS scores and serologic cytokine testing (IFNγ, IL-4, IL-5, IL-6, IL-10, IL-17, TNFα, TGFβ). Effects on T-cell subsets and FOXp3 activity will also be evaluated.

**Conclusions:** The safety and immunologic effects of vitamin D in MS are increasingly important as large clinical trials are being planned, and prolonged high-dose supplementation is often needed to correct serum 25(OH)D levels adequately. Demonstrable immunologic changes in the setting of vitamin D supplementation would add further support to the role of vitamin D in the immune system and MS.

**(P/T41)** NMO-SPECTRUM RECURRENT MYELITIS AND MYASTHENIA GRAVIS IN A PATIENT WITH AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 3

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**Study Support:** National Multiple Sclerosis Society.

**Background:** Autoimmune disorders tend to occur in clusters among susceptible patients. Autoimmune polyglan- dular syndromes represent such a cluster. Presentation of multiorgan autoimmune dysfunction. **Objectives:** We present a case of a woman who developed myasthenia gravis and recurrent longitudinally-extensive transverse myelitis (LETM), an NMO-spectrum disorder, in the setting of multiple autoimmune disorders, including autoimmune polyglan- dular syndrome type 3. **Methods:** Case presentation

**Results:** Patient had been previously diagnosed with vitiligo (1971), Graves disease (1974), primary ovarian failure (1974), myasthenia gravis (1985), sarcoidosis (1985) and vitamin B-12 deficiency (1998). The patient underwent thymectomy for myasthenia gravis in 1987. In 1991 she presented with the first of several episodes of transverse myelitis. In 2008 she tested positive for NMO-IgG in serum. Her clinical presentation, treatment and course of disease are reviewed. We also present her family history of autoimmune disorders, along with known HLA typing information. We discuss the potential effects of her genetic background and thymectomy on the emergence of recurrent LETM, and the ramifications for her ongoing treat- ment.

**Conclusions:** NMO-spectrum disorders and myasthe- nia gravis may occur with increased frequency among the patients with autoimmune polyglandular syndromes. In addition to her genetic predisposition to autoimmunity, thymectomy for myasthenia may have contributed to the development of recurrent NMO-spectrum myelitis.

**(P/T42)** PREVALENCE OF ANTI-NUCLEAR ANTIBODIES AND THEIR IMPACT ON RESPONSE TO IMMUNOMODULATORY THERAPY IN RELAPSING REMITTING MULTIPLE SCLEROSIS

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**Study Support:** National Multiple Sclerosis Society Clinical Care Fellowships.

**Background:** Multiple sclerosis is an...
autoimmune, demyelinating disease of the CNS white matter. Previous studies have estimated the prevalence of anti-nuclear antibodies (ANA) to be between 20% and 80% in MS; higher than in the general population. It has been noted that in untreated MS patients, the presence of ANA is associated with clinical exacerbations as well as increased MRI disease activity. There have also been reports of nuclear autoantigens in MS lesions, hinting that ANA may bear some pathogenetic relevance. Objectives: We proposed to evaluate the prevalence and effect a positive ANA has on the response to immunomodulatory therapy in relapsing remitting patients.

Methods: A list of patients seen between 2000 and 2008 at UT SW with an ICD-9 code of RRMS and a CPT code of ANA was assembled. All patients that had a positive ANA, a diagnosis of RRMS, and at least 2 years of follow up were selected as our cases. We then identified 40 ANA negative patients which were age and sex matched to act as controls. All patients charts were analyzed for number of relapses occurring during a follow up period of 2-5 years. Results: We identified a total of 107 RRMS patients receiving follow up in our clinic. Of these, 20 patients (18.7%) were found to have a positive ANA titer. The average annualized relapse (ARR) rate of the ANA positive patients was 0.25. The average ARR for the control patients was 0.16. Additionally, we looked at subgroups of ANA positive patients based on titer; <1:160; 1:160; and >1:160. The average ARR for these subgroups were 0.09; 0.28; 0.33 respectively. We performed a one-way Analysis of Variance to test the hypothesis that the average mean value across categories of subgroups were equal. Statistics were performed using WINKS SDA Software. There was no statistically significant difference in average ARR between the ANA positive and control patients or the subgroup analysis (p value equal to 0.52).

Conclusions: The presence of ANA antibodies in relapsing remitting multiple sclerosis patients was similar to previous prevalence studies. However, the presence of ANA positive did not statistically alter or correlate with disease activity.

(P/T43) MULTIPLE SCLEROSIS RELAPSE RISK IN THE POST-OPERATIVE PERIOD

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Study Support: Michigan Institute for Clinical and Health Research and National Multiple Sclerosis Society. Background: The risk of multiple sclerosis (MS) relapse in the postoperative period is a common concern among anesthesiologists and surgeons. The perception that patients with MS are at an increased risk of relapse after surgery, particularly following general anesthesia, can have a deleterious impact on clinical decision making and health resource utilization, resulting in surgical delays or unnecessary preoperative testing. To our knowledge, there are no published large-scale studies that definitively address the effects of surgery or anesthesia administration on relapse rate. Objectives: 1) To determine whether the MS relapse rate increases during the 90 day postoperative period. 2) To compare pre- and postoperative relapse rates between subjects who have undergone procedures using general vs. local anesthesia. 3) To investigate the effects of clinical features of MS (disease severity, duration, immunomodulatory therapy) and postoperative complications on postoperative relapse rates. Methods: DATA ACQUISITION: We will perform a retrospective chart review within the Veteran’s Administration Health System Compensations and Pension Record Interchange database (CAPRI) to identify subjects with RRMS or SPMS who have undergone one of several specified surgical procedures (identified by CPT codes) between 1/1/06 and 12/31/07. Pre- and postoperative relapses will be identified by one or more of the following: acute changes on brain or spinal cord MRI, administration of corticosteroids, neurological consultation, inpatient admission or re-admission. Perioperative complications, such as fever, infection or DVT/PE, will be identified by ICD-9 codes. DATA ANALYSIS: Relapses will be defined as any acute neurologic change lasting longer than 24 hours. Annualized exacerbation rates in the 90 day postoperative period will be compared to exacerbation rates in the 2 year preoperative period using the paired t-test. Perioperative relapse rates between anesthesia subgroups will be compared with an independent samples t-test. General linear modeling will be used to estimate the effects of anesthesia type, perioperative complications, and clinical features of MS on postoperative relapse rate. Results: In progress Conclusions: In progress.
the lesion sites. Objectives: To identify a biomarker of NPC using 1H-MRS in vivo and to evaluate its clinical correlations in patients with MS. Methods: 1H-MRS was performed on 30 HC and 50 RRMS patients. NAWM, EL (if present), and NEL were imaged in MS patients, and for all subjects the hippocampus was imaged as a positive control. All subjects were evaluated with cognitive and clinical measures for future clinical correlations with 1H-MRS findings. Results: In HC, NPC peaks were increased in the left hippocampus versus WM (p=0.022). The HC vs. MS hippocampi contained significantly more NPC/Cr (p=0.05) but no difference was seen between the NAWM of MS vs. HCWM (p=0.6). In MS, EL contained significantly more NPC/Cr compared to both NEL (p=0.041) and NAWM (p=0.007). Conclusions: This is the first demonstration of a biomarker of NPC in the brain regions of individuals with MS. The NPC biomarker is increased in the EL vs. NEL MS lesions, possibly representing migration of NPC at the time of acute injury. Further research to address the causes of NPC recruitment and their potential role in recovery is needed.

(P/T45) SMOKING NEGATES PLATFORM THERAPY IN MULTIPLE SCLEROSIS
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Study Support: National Multiple Sclerosis Society Clinical Care Fellowship. Background: Brain atrophy is a marker of current neurologic impairment and correlates with future disability. Cigarette smoking is associated with poorer disease prognosis, including greater lesion volume and volume loss (cerebral atrophy). Disease modifying agents (DMA) slow the rate of brain volume (BV) loss. To date, the relative effects, and associations between, BV changes in patients with RRMS who smoke and who use DMA has not been reported. Objectives: To evaluate changes in smokers with relapsing remitting multiple sclerosis (RRMS) versus those on DMA. Methods: A literature review was performed using keywords: brain atrophy, brain parenchymal fraction (BPF), brain volume, and smoking from 1999 to 2010. BPF and BV change were analyzed in untreated patients and during therapy with IFN-β or glatiramer acetate (GA). Change in BPF or BV was also studied in patients with a history of smoking. Results: BPF loss occurs at a faster rate in smokers than in non-smokers with RRMS. Healy et al showed BPF declines 0.3% per year in non-smokers versus 0.4% per year in smokers (who were evenly matched between treated and untreated). Khan et al found the rate of brain atrophy in untreated MS patients was 0.95% versus 0.46-0.64% in patients on DMA (0.31-0.49% reduction). Rudick et al reported patients taking weekly IFN-1b had a 0.69% BV loss in the first year which then stabilized to 0.38% BPF loss in the 2nd and 3rd years (0.18% reduction vs. placebo). Similar trends were found by Frank et al in a 3-year trial with IFN-1b. Patients lost 1.68% BV (mean 0.56% per year) (0.04-1.44% reduction vs. placebo). A small 2 year trial of GA showed BV loss of 0.6% per year (1.2% reduction). Conclusions: Smoking, with a 0.1% less loss of BV per year, appears to lessen or negate the protective effects of DMA, with 0.04-1.44% less loss of BPF per year. The mechanisms by which cigarette smoke affects multiple sclerosis is not entirely understood but is likely multifactorial. In animal models, cigarettes increase levels of metalloproteinase 9, free oxygen radicals, and may cause axonal degradation via nitric oxide. Products of smoking may also bind to the aryl hydrocarbon receptor on immune cells activating Th17 cells, worsening autoimmunity.

(P/T46) FOIX-ALAJOUANINE SYNDROME MIMICKING DEMYELINATING DISEASE
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2. Department of Neurology, University of Washington, Seattle, WA, United States.
Study Support: National Multiple Sclerosis Society Clinical Care Fellowship. Background: Foix-Alajouanine Syndrome is an acquired spinal dural arteriovenous fistula (SDAVF) presenting as a progressive myelopathy that can be mistaken for many disorders, thus delaying diagnosis and treatment. Objectives: To describe Foix-Alajouanine Syndrome in the differential diagnosis of demyelinating disease. Methods: Case presentation and literature review. A 65-year-old man with family history of multiple sclerosis presented with 4 years of progressive lower extremity paresthesias worsening over 4 months; 3 years of urinary retention and erectile dysfunction; and one year of fatigue, progressive leg weakness and gait imbalance. Results: Magnetic resonance imaging (MRI) showed 2 non-specific white-matter brain lesions, mild thoracic cord expansion, abnormal T2 signal from T7-T12, and contrast enhancement. Transverse myelitis was suspected by outside provider but spinal angiogram demonstrated a right-sided SDAVF arising from T6/T7 segmental arteries, and was successfully treated with onyx embolization. Conclusions: SDAVF is the most common vascular malformation of the spinal cord, yet diagnosis is frequently delayed months to years due to non-specific presentation mimicking more common disorders such as inflammatory demyelinating disease, spinal cord tumor, or degenerative disc disease. Course is slowly progressive but may remit in a stepwise fashion. This case patient had a 4-year delay in diagnosis with symptoms attributed to presumed peripheral neuropathy and transverse myelitis. Unlike patients with demyelinating disease, SDAVF patients are typically male (80%) in the 6th to 7th decade (mean age 60). Diagnosis is difficult, as SDAVF symptoms overlap with those of other spinal cord disorders: leg weakness (48%), leg paresthesias (35%), back pain (22%), and bladder dysfunction (7%). MRI findings are useful to distinguish SDAVF from demyelinating disease: homogenous, centrally increased T2 signal, enhancement over 6-7 lower thoracic or upper lumbar vertebral levels, and dilation of congested corona!plexus veins should raise concern for SDAVF. This case highlights the need to consider SDAVF early in the differential diagnosis of progressive myelopathy, as failure results in delayed diagnosis and treatment and accrual of neurologic disability.

(P/T47) SPECTRUM OF ADVERSE NEUROLOGICAL EVENTS WITH BIOLOGIC THERAPIES IN AUTOIMMUNE DISEASE
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Study Support: National Multiple Sclerosis Society Clinical Care Fellowship. Background: Biologic therapies (such as infliximab, natalizumab and alemtuzumab) have revolutionized the management of relapsing-remitting MS. However, biologic therapies can cause several adverse events, including gastrointestinal perforation, respiratory infections, demyelinating disease, and aseptic meningitis. Objectives: To describe a spectrum of adverse neurological events in patients receiving biologic therapies for MS. Methods: Case reports of patients presenting with neurological symptoms during biologic therapy were identified from January 2008 to December 2018. Results: 12 cases were identified, including 10 with relapsing-remitting MS and 2 with primary progressive MS. The most common adverse events included transverse myelitis (n=5), acute disseminated encephalomyelitis (n=3), and progressive multifocal leukoencephalopathy (n=2). Conclusions: Biologic therapies can cause a wide spectrum of neurological adverse events, including demyelinating disease, which can be life-threatening. Early recognition and intervention are crucial to ensure optimal care and outcomes.
as tumor necrosis factor inhibitors) for autoimmune disorders offer a promising therapeutic option for patients with breakthrough disease or intolerance to standard platform therapies. However, neurological side effects including demyelination are a rare and serious risk. Adverse events related to biologic therapies for autoimmune disease are not well understood.

**Objectives:** To define the spectrum of adverse neurological effects in patients with autoimmune disorders on biologic therapies. **Methods:** Analysis of a series of patients who presented for neurological consultation after side effects from biologic therapies. Demographic data, disease, medication, neurological symptoms, lab, imaging findings and subsequent disease course were collected. **Results:** Six patients (1 male) were included, with follow-up from 2 to 2.5 months. Autoimmune diagnoses included rheumatoid arthritis (3), psoriasis (2) and autoimmune collitis (1). Biologic treatments included tumor necrosis factor inhibitors (adalimumab, etanercept and infliximab) and efalizumab, a monoclonal antibody to the leukocyte surface antigen CD11. Presenting symptoms included sensory disturbance (4), optic neuritis (1) and transverse myelitis (1). Oligoclonal bands were noted in the cerebrospinal fluid of 60% of patients tested (3/5). Imaging revealed non-specific white matter abnormalities (3), demyelinating brain lesions (2), and longitudinally extensive transverse myelitis (1). A family history of multiple sclerosis was present in 2, and a personal history of migraines was noted in 2. All patients with available follow-up (5) stabilized off biologic therapy. **Conclusions:** Presenting neurological symptoms related to biologic therapies range from sensory disturbances to optic neuritis and severe transverse myelitis. MRI imaging correlated with symptoms in 2 patients, but was nonspecific in the remainder. Symptoms may improve with removal of the inciting biologic therapy. No patients in our series developed a relapsing-remitting course suggestive of multiple sclerosis. Long-term follow-up of patients treated with biologic therapies is recommended to improve understanding of risk of future neurological events.

**P/T48** HPV VACCINATION ASSOCIATED WITH THREE EPISODES OF DEMYELINATION

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**Study Support:** National Multiple Sclerosis Society.

**Background:** The HPV vaccine Gardasil© is a quadrivalent vaccine that targets HPV types 6,11,16 and 18. It is indicated for use in females ages 9-26 for the prevention of vulvar and vaginal cancer, cervical cancer, precancerous vaginal and cervical lesions, and genital warts. There is no known link between Gardasil© vaccination and demyelinating episodes. However, there has now been a small number of cases published that report demyelinating events shortly after vaccination for HPV. **Objectives:** The objective of this study is to review three cases identified in two different clinic populations where a demyelinating episode occurred in close temporal proximity to Gardasil© vaccination. **Methods:** A retrospective review of the clinical, laboratory and radiologic data of these three cases was performed. **Results:** Patient 1, a 22-year-old female, developed left sided sensory symptoms 9 days after her second Gardasil© vaccination. She was found to have an enhancing lesion at C2. Patient 2, a 26-year-old female, developed episodes of paroxysmal, transient left-sided weakness most likely representing tonic spasms within 28 days of her third Gardasil© vaccination. Brain MRI showed multiple white matter lesions. C spine MRI showed a lesion at C3-C4. Lumbar Puncture revealed the presence of oligoclonal bands as well as increased IgG index and synthetic rate. Patient 3, a 15-year-old female, received her second dose of Gardasil© and then four days later had an episode of decreased level of consciousness followed by a three day period of confusion. MRI revealed an enhancing right thalamic lesion which subsequently resolved on repeat imaging. **Conclusions:** We present 2 cases of CIS involving the spinal cord and 1 case of presumed post-vaccination encephalitis which occurred in close time proximity to Gardasil© vaccination. Although causality cannot be established from this small case series, the association of these cases with recent vaccination cannot be overlooked. Interestingly, in all 3 cases the neurologic episodes occurred after either the second or third inoculation, which may suggest a priming effect.

**P/T49** QUANTIFYING HUMAN CERVICAL SPINAL CORD INJURY BY TRACT-SPECIFIC DIFFUSION MRI

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**Study Support:** National Multiple Sclerosis Society and National Institutes of Health.

**Background:** We hypothesize that, in multiple sclerosis (MS) and neuromyelitis optica (NMO) patients, decreased white matter (WM) tract axial diffusivity reflects axonal injury in acute or sub-acute stage. Chronically, increased WM tract radial diffusivity reflects the axonal loss and myelin injury. **Objectives:** The objective is to develop in vivo MRI biomarkers of CNS WM injury in MS and NMO patients with cervical spinal cord lesions and to assess the potential use of these biomarkers as the surrogate endpoint for developing disease modifying therapies. **Methods:** Transaxial cervical spinal cord diffusion tensor imaging (DTI) were performed at 3 T with in-plane resolution of 0.9 x 0.9 mm. Robust DTI calculation based on motion correction and outlier rejection was performed. Tract-specific region-of-interests were determined based on the cord geometry to avoid bias. Axial and radial diffusivities in the posterior columns and lateral corticospinal tracts were correlated with the degree of neurologic deficits in the upper and lower extremities. **Results:** In the cross-sectional study, stable MS (n = 3) and NMO (n = 7) patients with poor recovery showed significantly increased radial diffusivity, consistent with axonal loss and myelin injury. Both axial and radial diffusivities measured from stable MS (n = 7) patients with good recovery were within one standard deviation of values from healthy controls (n = 17). Longitudinally, acute MS (n = 4) and NMO (n = 5) patients were scanned at disease onset and followed up to one year. Preliminary results showed significantly decreased axial diffusivity in the cord lesion within a month of the clinical onset. **Conclusions:** The good correlations between the axial and radial diffusivity and functional outcomes presented herein suggest that directional diffusivities are promising biomarkers for developing disease modifying therapies in MS and NMO patients.
(P/T50) QUANTITATIVE SENSORIMOTOR MEASURES IDENTIFY ABNORMALITIES THAT ARE NOT DETECTED WITH RATING SCALES IN MULTIPLE SCLEROSIS

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**Study Support:** The National Multiple Sclerosis Society and National Institutes of Health. **Background:** Rating scales are the clinical gold standard for evaluating disability in multiple sclerosis (MS). These scales rely heavily on tester’s experience and clinical judgment making it difficult to reliably and accurately capture subtle changes in disability. Quantitative devices may offer a reasonable means to more objectively evaluate specific and subtle impairments compared to rating scales. **Objectives:** To determine the relationships among lower extremity quantitative sensorimotor measures and their respective Functional System Score (FSS) of the Expanded Disability Status Scale (EDSS) in individuals with MS. **Methods:** We evaluated 145 MS subjects. Great toe vibration threshold was quantified using a Vibratron device. Lower extremity strength was quantified by a hand-held dynamometer. ICC’s were calculated for inter-rater and test-retest reliability for vibration and strength. We compared FSS with quantitative measures. **Results:** Our cohort’s mean disease duration was 10.4 years, median EDSS 3.5, FSS=0-4, and 66% were females. Test-retest ICC’s, 0.77-0.95. Quantitative sensorimotor measures detected impairments in up to 32% of MS subjects with normal sensory and pyramidal FSS. Poorer vibration sensation correlated with a worse sensory FSS and EDSS (both: R=0.64;p<0.0001). Hierarchical regression showed that vibration sensation and diagnosis were the most significant predictors of sensory FSS (R=0.41;p<0.0001). Weaker ankle and hip strength correlated with a worse pyramidal FSS and EDSS (ankle: R=-0.49,-0.48; hip: R=-0.65,-0.62; all p<0.0001). Hierarchical regression showed that hip strength and diagnosis were the most significant predictors of pyramidal FSS (R=0.54;p<0.0001). **Conclusions:** Our data show that quantitative devices can reliably measure specific sensory and motor impairments in MS that relate to global disability. Our data suggest that these quantitative tools may be more sensitive in detecting subtle abnormalities than rating scales. We propose that these tools may be an important addition to clinical outcome measures in practice and for future MS clinical trials.

PATIENT MANAGEMENT, CARE, AND REHABILITATION

(P/T51) PHYSICIAN VERSUS PATIENT GAIT ASSESSMENT IN MULTIPLE SCLEROSIS: DESIGN AND RATIONALE FOR A STUDY UTILIZING NOVEL DATA COLLECTION TECHNIQUES

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**Study Support:** National Multiple Sclerosis Society. **Background:** The Knowledge Project (KP) is a Cleveland Clinic initiative to electronically collect longitudinal patient data. Data on 5,000 multiple sclerosis (MS) patients have been collected thus far. The KP questionnaire assesses the EuroQol-5D, the Patient Health Questionnaire-9, and an MS performance scale (assessing mobility, hand function, vision, fatigue, spasticity, and cognitive and bladder symptoms). There are additional questions pertaining to pain, tremor, and coordination. After each appointment, clinicians enter information into the database as well. This information includes the patient’s date of diagnosis, clinical course, nine-hole peg test time, and results of the timed 25-foot walk (T25FW). Few data exist comparing objective disability measures to self-reported patient assessments. The KP is a novel tool that can be used to assess the correlation between physician and patient perceptions of disability. It may also help determine if current MS disability measures are reflective of everyday functioning in MS patients and help to identify factors predictive of poor patient gait perception. **Objectives:** 1. Assess the validity of KP data. 2. Assess the relationship between physician and patient gait assessments. 3. Determine factors predictive of a discrepancy between patient and physician gait perception. **Methods:** The study will be a retrospective database analysis. For validation, 100 KP records (2%) will be selected and compared to the corresponding medical record for accuracy. The variables of greatest interest will be physician assessment of ambulation (T25FW) and the patient’s response to the MS performance scale mobility question. The mobility question includes 7 options from normal to bedridden. The mean value of the T25FW will be calculated among subjects within each of the mobility response groups. Those patients whose T25FW value is more than one standard deviation from the mean for their group will be flagged as having a significant discrepancy. Regression modeling will be performed to identify factors predictive of discrepancies. Reversal of these factors may improve patient quality of life. **Results:** Not yet available **Conclusions:** Not yet available

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(P/T52) PATIENT EDUCATION PROGRAM ON DIAGNOSIS, PROGNOSIS AND EARLY MS THERAPY FOR PERSONS WITH EARLY MS: RESULTS OF PRE-STUDIES, OUTLINE AND FIRST RESULTS OF A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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**Study Support:** National Multiple Sclerosis Society. The randomized controlled trial is supported by Merck-Serono. **Background:** A number of immunomodulatory drugs have been licensed for treatment in early or suspected MS. In parallel, new diagnostic criteria were developed to allow for earlier diagnoses and treatment. Uncertainty remains about long-term efficacy of early MS treatment. There is ongoing discussion about possible benign courses of MS. Therefore, evidence-based patient information on diagnosis, prognosis and early therapy is a prerequisite to allow for informed treatment choices and shared decision making. **Objectives:** To perform pre-studies in order to develop and evaluate a patient education program and decision support system on prognosis, diagnosis and early therapy. **Methods:** Two systematic reviews on prognostic and diagnostic studies were performed. Also, an evidence-based leaflet for persons with
suspected MS was developed and presented to 136 persons with MS. We assumed that the leaflet would be considered as new, understandable, and relevant. Also we hypothesized that the leaflet would increase the difficulty to make a decision on diagnostic testing, but would not increase anxiety.

**Results:** The review on diagnostic studies included 26 studies on MRI, 7 studies on CSF and 8 studies combining MRI and CSF, with variable results for diagnostic accuracy. The review on prognostic studies included 51 prognostic studies and revealed only few important prognostic factors, most importantly disease course and age at onset of MS. After reading the leaflet, 70% of participants claimed that they wanted to be informed about a possible MS diagnosis before testing, only 10% did not. The leaflet was considered new, understandable, and relevant by most participants and did not elicit anxieties. However the information had no effect on participants’ attitude to undergo diagnostic testing. **Conclusions:** Results highlight uncertainties about diagnosis, prognosis and early MS therapy. Based on these results, we developed a 4-hour interactive educational program that has been pre-tested and is currently evaluated in a randomized controlled trial (ISRCTN12440282) within 6 academic MS centers in Germany. Preliminary results will be presented.

**(P/T53) POSITIVE AFFECT MEDIATES THE EFFECT OF A TELEPHONE-BASED EXERCISE INTERVENTION ON DEPRESSION IN A SAMPLE OF INDIVIDUALS WITH MULTIPLE SCLEROSIS**

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**Background:** Evidence from survey and intervention studies has shown that exercise is associated with reduced depressive symptoms and rates of depressive disorders in the general population and among those with multiple sclerosis (MS). We have previously found that a telephone-based exercise intervention resulted in significant reductions in depressive symptoms in an MS sample. However, we have yet to identify mechanisms by which the intervention is related to positive changes in mood. **Objectives:** The aim of this study was to test negative affect (NA) and positive affect (PA) as mediators of the treatment effect on depressive symptoms. **Methods:** Participants were 99 adults (14 male; Mean age = 48.8 years) with MS and major depressive disorder who were randomized to treatment (48) or wait-list control group (51). Measures of exercise in the past week, NA and PA (PANAS, Watson, Clark, and Tellegen, 1988), and depressive symptoms (HAM-D, Hamilton, 1960) were administered at baseline and 12 weeks post-baseline. The intervention, based on the principles of Motivational Interviewing (Miller & Rollnick, 2002), included an initial 60-minute session followed by 11 weeks of 1X/week 15-30 minute phone sessions. Mediation was tested with a path-analysis model (using MPlus 5.21 statistical program), predicting change in depressive symptoms from treatment/control, with changes in physical activity, PA and NA as mediational variables. **Results:** Results indicated that the treatment was associated with increased physical activity ($\beta$=.26, $P<.01$) and PA ($\beta$=.25, $P=.01$), and decreased NA ($\beta$=-.35, $P<.01$) and depressive symptoms ($\beta$=-.20, $P=.01$). Furthermore, the effect of treatment on PA was mediated by increased physical activity; PA, in turn, mediated the association between increased physical activity and decreased depressive symptoms. Physical activity was not related to NA and NA did not mediate the treatment effect on depression. **Conclusions:** Findings from path analyses suggest that the effects of the exercise treatment on depressive symptoms are partially mediated by changes in positive affect, which are related to increases in physical activity.

**(P/T54) VALIDATION OF AN INSTRUMENTED GAIT MEASURE, THE ITUG, IN MULTIPLE SCLEROSIS**

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**Study Support:** Medical Research Foundation of Oregon. **Background:** Clinical outcome measures in multiple sclerosis (MS) such as relapse rate and disability are notoriously subjective and insensitive. Instrumented measures may reduce these errors. Gait dysfunction is frequent in MS and thus a promising outcome measure. Gait evaluation typically requires time-consuming analysis in a sophisticated laboratory setting. A new automated system using sensors attached to the arms, legs and trunk transmits gait information from simple walking tests performed in the clinic wirelessly to a computer for analysis. The instrumented Timed Up and Go test, iTUG, distinguishes early Parkinson’s disease from healthy controls in patients with clinically normal gait. We hypothesize that the iTUG will be more sensitive than traditional measures in detecting differences between MS patients with clinically normal gait and healthy controls. **Objectives:** To develop a practical and sensitive clinical outcome measure in MS. **Methods:** Adult early MS subjects (goal 20) with clinically normal gait and healthy age- and sex-matched control subjects were recruited from the Oregon Health & Science University MS Center. The instrumented and timed TUG, 25-Foot Timed Walk (25FTW), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Walking Score-12 (MSWS12), and Activities-Specific Balance Confidence (ABC) questionnaires were collected. A one-way ANOVA compared results between MS and controls in a cross-sectional manner. **Results:** 14 RMS subjects (38 + 12.8 years, 86% female, EDSS 3.3 + 1.5) and 16 healthy controls (39.2 + 11.6 years, 63% female) were tested. The iTUG detected significant differences between MS and controls in gait parameters including cadence ($p < 0.001$), stride length ($p < 0.05$), stride velocity ($p < 0.001$), and turning duration ($p < 0.01$). Some standard clinical tests were also able to distinguish between MS and controls including 25FTW ($p < 0.05$), timed TUG ($p < 0.05$), and MSWS12 ($p < 0.01$), but not ABC. **Conclusions:** The iTUG captures clinically undetectable gait abnormalities in MS and may be useful to aid clinical decision-making and increase efficiency of therapeutic trials. Further analysis is necessary to determine the sensitivity of the iTUG compared to standard measures and to change over time.