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Updates in MS

Faculty

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CME/CE Information

TARGET AUDIENCE

This activity is intended for neurologists, neurology nurses and nurse practitioners, neurology physician assistants, case workers and any other healthcare providers involved in the care of patients with MS.

STATEMENT OF NEED

Multiple sclerosis (MS) affects more than 350 000 people in the United States and 2.5 million worldwide. In the United States, prevalence estimates are approximately 90 per 100 000 population and MS-related health care costs are estimated to be more than $10 billion annually in the United States. Advances continue in the diagnosis and management of the disease.

Constant developments in treatment options available for MS patients are occurring. Interferon beta (IFN-β), the first therapy in randomized trials to reduce the number of relapses that people with MS experience, has revolutionized the management of MS, and introduced the concept of disease-modifying treatment (DMT). The year 2010 marked the beginning of the era of oral medications for the treatment of MS, with the approval of dalfampridine to improve walking and fingolimod as the first oral disease- modifying agent. Therapeutics in late-stage development for MS include non-selective immunosupressants, targeted immune- modulators, and monoclonal antibodies. Oral agents including cladribine and laquinimod, as well as monoclonal antibodies alemtuzumab, daclizumab, ofatumumab, ocrelizumab and rituximab are also being studied.

The emergence of oral disease-modifying therapies, such as the recently approved oral agents teriflunomide and dimethyl fumarate, will have a significant impact on the evolving scenario of immunomodulatory treatments in MS where current therapies are all injectable (with the exception of fingolimod).

EDUCATIONAL ACTIVITY LEARNING OBJECTIVES

Upon completion of this course, the participants should be able to:

- Review latest research and clinical information available on the accurate diagnosis of MS
- Review latest research and clinical information available on the appropriate treatment of MS

ACCREDITATION STATEMENT

The France Foundation is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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1. There are no fees for participating in and receiving credit for this activity.
2. Review the activity objectives and CME/CE information.
3. Complete the CME/CE activity.
4. Go to **www.cmeaims.org/Updates-in-MS** and complete the posttest. A score of at least 75% is required to successfully complete this activity. The participant may take the test until successfully passed.
5. Complete the CME/CE evaluation/attestation form at **www.cmeaims.org/Updates-in-MS**, which provides each participant with the opportunity to comment on how participating in the activity will affect their professional practice; the quality of the instructional process; the perception of enhanced professional effectiveness; the perception of commercial bias; and his/her views on future educational needs.
6. Your CME/CE certificate will be available for download.

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ESTIMATED TIME TO COMPLETE ACTIVITY:
60 minutes

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- **Amy Perrin Ross, APN, MSN, CNRN, MSCN**, has served as a consultant for Acorda, Bayer Healthcare, EMD Sorono, Genzyme, Novartis, Questcor, and Teva. She has received honoraria from Acorda, Bayer Healthcare, Biogen Idec, EMD Serono, Genzyme, Novartis, Pfizer, Questcor, and Teva.
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Introduction

The American Academy of Neurology (AAN) 66th annual meeting was held April 26–May 3, 2014 in Philadelphia, Pennsylvania. Clinical topics at the AAN meeting included a wide variety of subjects; this monograph provides a summary of selected presentations focusing on multiple sclerosis. Care was taken to highlight new findings with practical clinical relevance. This summary is not sanctioned by, nor part of the American Academy of Neurology. Readers are reminded that new material presented at AAN should be considered preliminary until publication in peer-reviewed journals.

Diagnosis

NEWLY DIAGNOSED PATIENTS

Brain volume loss (BVL) is a natural process of aging that is accelerated in patients with multiple sclerosis (MS).[1] BVL begins early in the disease and is one of the best magnetic resonance imaging (MRI) predictors of subsequent disability. At the neurology conference in May, Bourre et al reported on BVL in early MS.[2] These authors presented an exploratory study with 78 patients at 3 French centers. Patients were examined at diagnosis and at 2 years for clinical parameters associated with MRI-detected brain atrophy. At baseline the Go-No-Go portion of the Brief Repeatable Battery (BRB), the Temporal Right Eye test by Optical Coherence Tomography, and the 9-Hole Peg Test (9-HPT) of the MS Functional Composite Score were each significantly associated with brain volume, grey volume, and white volume. The only identified baseline parameter that was significantly associated with brain volume change assessed at 2 years was the Timed 25-Foot Walk test (T25-FW, $P = 0.025$). The study design includes a 5-year assessment.

A presentation by Azevedo and colleagues compared brain volumes of 21 subjects with radiologically isolated syndrome (RIS) with 42 healthy controls.[3] There were no differences in total parenchymal volume, total white matter, total grey matter, or cortical grey matter. The RIS individuals had slightly less subcortical grey matter than controls (0.126 vs 0.131, $P = 0.04$). Normalized thalamic volumes were reduced in RIS subjects compared with controls (0.0045 vs 0.0049, $P = 0.004$). The authors speculate that demyelination and reduced neuronal density contribute to thalamic atrophy. The contribution of thalamic volume loss to conversion to clinically isolated syndrome (CIS) or clinical MS is not known.

NEUROMYELITIS OPTICA (NMO)

As NMO may be part of the differential diagnosis of MS, it is useful to review the distinguishing features of these inflammatory demyelinating diseases (Table 1).

Unlike MS, a highly specific serum biomarker exists for NMO, namely aquaporin-4 antibody (AQP4-IgG). In May, Pittock et al reviewed the performance of 6 NMO-IgG assays.[4] While the specificities were extremely high (98%–100%), the sensitivities varied. Cell-based assays (visual observation-based and flow cytometry-based) were the most sensitive (73%–77%), followed by ELISA-R (60%), fluorescence immunoprecipitation assays (53%), and indirect immunofluorescence assay (48%).[6] Accurate diagnosis should translate to initiation of appropriate therapies for patients with NMO, as standard MS therapies are ineffective and may even exacerbate NMO. Rituximab, azathioprine, or mycophenolate mofetil are commonly used for relapse prevention in patients with NMO, and emerging strategies include complement inhibition with the anti-C5 monoclonal antibody eculizumab, interleukin-6 receptor blockade via tocilizumab, maintenance plasma exchange, and inhibition of AQP4 antibody binding.[7]

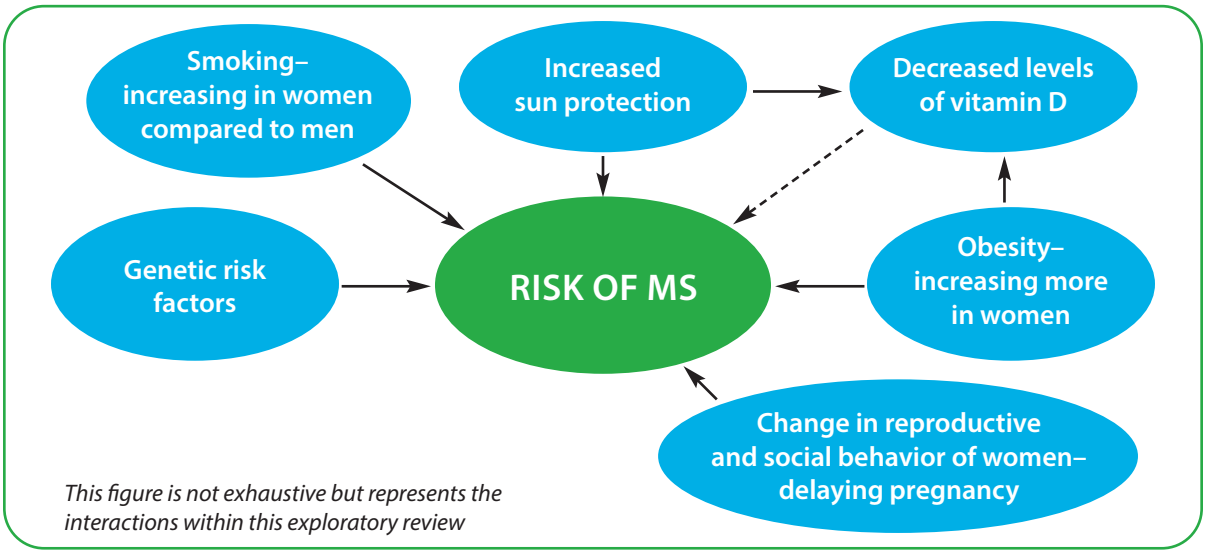
Table 1: Comparing MS and NMO (adapted[4,5])

Feature	Multiple Sclerosis	Neuromyelitis Optica
Median age of onset (years)	29	39
Sex (F:M)	2:1	9:1
Course	85% relapsing-remitting 15% primary-progressive Not monophasic	80%-90% relapsing course 10%-20% monophasic course
Attack severity	Usually mild	Usually severe
Secondary progressive course	Common	Uncommon
Autoimmune diseases	Uncommon	15%-30%
CSF cells	Mild pleocytosis Mononuclear cells	Occasional prominent pleocytosis PMNs and mononuclear cells
CSF oligoclonal bands	85%	15%-30%
MRI: spinal cord	Short-segment peripheral lesions	Longitudinally extensive (≥ 3 vertebral segments)
MRI: brain	Periventricular white matter lesions	Usually normal or nonspecific white-matter lesions; 10% unique lesions

Risk Factors for MS Disease and Course

The prevalence of MS is rising, and the ratio of relapsing-remitting MS (RRMS) in women compared to men has increased from 2:1 to 3:1. Klein and Burton found 32 articles in the PUBMED database appearing between 2005 and 2013 on possible factors contributing to the increasing disparity in MS prevalence.[8] Obesity, smoking, reduced serum levels of vitamin D metabolites, and changes in the reproductive behavior of women in the West are candidates for environmental factors that may be modifying MS risk. Several observational studies support approximately a 50% increase in the risk of MS associated with smoking.[9,10] Palacios et al found a very strong correlation between the increase in MS sex ratios and the increase in smoking sex ratios in several national registries.[10] The increased ratio of female to male smokers, however, is due to decreased smoking among males, suggesting that smoking is not the only environmental factor contributing to the increase in MS. Both sun avoidance and obesity can result in low levels of vitamin D, a known risk factor for MS. Increases in both of these factors may contribute to increased risk of MS in women. Finally, the authors identify changes in reproductive behavior such as delaying pregnancy, in vitro fertilization, and number of offspring as possible risk factors for MS or MS relapse. The contribution of these various factors to risk for MS is summarized in the schematic in Figure 1.

Figure 1: Schematic of the Interaction of Various Factors and MS (adapted)[8]



DIETARY FACTORS

Recent studies have shown that excess salt (NaCl) uptake can impact the immune system. Kleinewietfeld et al reported in *Nature* that exposure of naïve human T cells to high-salt conditions (similar to levels found in the interstitium of animals fed a high-salt diet) results in induction of an enhanced Th17 phenotype, expression of proinflammatory cytokines, and activation of the p38/MAP kinase pathway.[11] These investigators have also shown that mice fed a high-salt diet develop accelerated onset and increased severity of experimental autoimmune encephalomyelitis (EAE) compared with controls on a normal diet.[11] Farez et al reported results of an observational study of sodium intake and MS disease activity in a cohort of patients with RRMS.[12] Sodium intake was calculated from urine samples collected over the 2-year study; clinical and radiological assessments were conducted every 3 to 6 months, or in the case of a relapse. Regression analysis was used to estimate the effect of sodium intake on MS disease activity. The mean age of the 70 patients was 37.5 years, median disease duration was 5 years (range 1-16 years), the median Expanded Disability Status Scale (EDSS) was 1 (range 0-3.5), and 77% of patients were female. Regression analysis showed that increased sodium intake was associated with increased relapse rate and increased radiological activity **(Table 2)**.

In a similar evaluation of a second cohort of 52 RRMS patients, these authors reported that increased sodium intake was associated with increased T2 lesion load. Interestingly, Doty et al presented a poster on gustatory dysfunction in patients with MS.[13] This study in 73 patients with MS and 73 matched controls tested the ability of subjects to correctly identify a given stimulus (tasting sweet, sour, bitter, or salty) and to rate the intensity of such stimuli. Overall, approximately one-fifth of patients with MS exhibited lower test identification scores compared with controls, with the largest deficits noted for sodium chloride. While sodium intake is clearly a modifiable factor, it is noteworthy to consider that patients with MS may have an altered sense of taste, particularly for salt.

Table 2: Sodium Intake and Disease Activity in 70 Patients with RRMS[12]

	Incidence Rate Ratio	95% Confidence Interval	*P*-value
Relapse Rate			
Sodium Intake < 2 grams/day	1	---	---
2–4.8 grams/day	2.75	1.3–5.8	0.008
> 4.8 grams/day	3.95	1.4–11.2	0.01
MRI Activity			
Sodium Intake < 2 grams/day	1	---	---
2–4.8 grams/day	2.86	1.52–5.4	0.001
> 4.8 grams/day	3.42	1.37–8.55	0.008

Linker et al studied the effect of another dietary factor, saturated fatty acids, in the murine EAE model.[14] These investigators showed that mice fed a high-fat diet had severe clinical symptoms of EAE compared with milder symptoms in animals fed a normal diet. At 14 days following EAE induction, animals on a high-fat diet had increased frequencies of splenic effector T cells and increased Th17 cells in the spinal cord compared with normal diet controls. In addition, in vitro experiments showed that exposure of naïve murine T cells to lauric acid promoted p38/MAPK-dependent Th17 development. Yadav et al conducted a study to examine the potential benefits of a low-fat, plant-based diet in patients with RRMS. In this 1-year prospective randomized controlled trial, 61 MS patients were assigned to either a low-fat diet or a wait-listed control group.[15] The plant-based diet is very low in saturated fat, with an estimated caloric breakdown of 10% fat, 14% protein, and 76% carbohydrate. Study outcomes included changes over 1 year in new brain T2 lesion count and other MRI disease activity parameters, safety, relapse rate, EDSS, Timed 25-Foot Walk (T25-FW), Fatigue Severity Score (FSS), blood lipids, body weight, and diet compliance. Of the 61 patients randomized, 27 patients in the control group and 26 patients in the diet group completed the study. Four of the 26 patients in the diet group were non-compliant. After adjusting for baseline parameters, there were no significant differences between groups in MRI endpoints, relapse rate, EDSS, or T25-FW. FSS changed significantly in the diet group relative to baseline measures. Average weight, low density lipoprotein, and total cholesterol improved in the diet compliant group relative to the control group (-16.3 vs + 1.6 lbs, -12.4 vs -5.6 mg/dL, and -16.2 vs -4.7 mg/dL, respectively). The authors indicated that the small sample size, and one year of follow-up may have contributed to reduced power to detect changes on MRI and clinical outcomes.

GUT MICROBIOME

The gut wall is populated by immune cells that are capable of antigen processing and presentation, raising the possibility that it is an active player in immune recognition. Exposure to gut microbiota can trigger EAE in genetically susceptible transgenic mice.[16] There are findings connecting gut flora to new onset rheumatoid arthritis (RA),[17] inflammatory bowel disease (IBD),[18] and type 1 diabetes.[19] Jhangi et al investigated gut microbiome differences between patients with MS and healthy controls.[20] They analyzed the diversity of bacteria in stool samples of 168 patients with RRMS and 44 healthy controls by sequencing hypervariable regions of bacterial 16s ribosomal RNA. Some RRMS patients were untreated (n = 44), others were treated with Interferon (IFN) (n = 49), glatiramer acetate (GA) (n = 46), or other drugs, but patients with recent antibiotic or probiotic use and those with a history of autoimmune disease, bowel surgery, or other drug use (prednisone, rituximab, methotrexate, etc) were excluded. They found similar levels of overall diversity in both groups. The methanobrevibacter *M smithii* was present in about half of the MS patients (regardless of treatment) at level 10–50 times higher than in healthy controls. Methanobrevibacter is also associated with obesity and IBD. The level of stimulation of peripheral blood mononuclear cells (PBMCs) and the prevalence of high titer antibodies to this organism were not different in the subject groups. Butyrate can promote colonic T_{reg} expansion.[21] Butyrate-producing bacteria were less prevalent in MS patients (37%) than in healthy controls (57%) and in untreated MS patients compared to treated patients.

WHIPWORM EGGS

The "hygiene hypothesis" proposes that the increased frequency of autoimmune diseases like MS in industrialized countries is due to a reduction in exposures to infectious bacteria, viruses, and parasites resulting from a high level of sanitation in the modern environment. Fleming and colleagues reported a small study of the safety and effectiveness of the helminth *Trichuris suis* ova (TSO) (porcine whipworm) in subjects with early RRMS.[22] This approach has been tried for IBD[23] and allergic rhinitis.[24] The study reported at AAN was a small trial with 15 treatment-naïve, recently diagnosed RRMS subjects. Each participant underwent 5 months of pre-treatment observation and 10 months of treatment with TSO (2500 live ova orally every 2 weeks). The primary outcome measures were as follows: (1) safety and tolerability and (2) changes in the number of gadolinium enhancing lesions (Gd+) detected by monthly brain MRI scans. No significant safety or tolerability issues were observed. With 90% of time points analyzed to date, the mean number of Gd+ lesions per month was 3.2 during 5 months of observation and 2.1 during the last 5 months of treatment, a 34% relative reduction. TSO was associated with increases in T regulatory cells and a modified Th2 immune response. Transcriptional analyses of peripheral blood mononuclear cells suggested that treatment led to diminished expression of the pellino E3 ubiquitin protein ligase 1 (pelli 1) gene, recently demonstrated to be a central activator of microglia in EAE and possibly in MS itself.

VACCINES AND RISK OF MS

There have been anecdotal reports of a temporal association between receipt of vaccines and the onset of CNS demyelinating diseases including MS; however, such a link is not supported by robust studies.[25] Langer-Gould et al presented results of a case-control study from the membership of Kaiser Permanente Southern California that was performed to determine whether there is increased risk for MS with vaccine exposure (hepatitis B vaccine [HBV] and human papillomavirus vaccine [HPV] in particular).[26] Cases were newly diagnosed with MS and other CNS acquired demyelinating syndromes (CNS ADS) between January 2008 and December 2011; up to 5 controls were matched on date of birth, sex, and ZIP code. Vaccination records within 3 years of the index date were obtained, and any vaccination was considered exposure. There were 780 cases of CNS ADS and 3885 matched controls identified, including 92 cases and 459 controls who were women 9–26 years (target population for HPV). Analysis of the data indicated no association between HBV (OR 1.12, 95% CI 0.72-1.73), HPV (OR 1.05, 95% CI 0.62-1.78), or any vaccination (OR 1.03, 95% CI 0.86-1.22) and risk for CNS demyelinating diseases up to 3 years later. According to the authors, an apparent short-term risk for CNS ADS onset within the first 30 days after any vaccination in younger persons (< 50 years) may reflect transition from subclinical disease to symptom onset accelerated by receipt of a vaccine. No long-term association of vaccines with MS or other CNS ADS was found.

SMOKING

Cigarette smoking is a known susceptibility factor for MS.[27] Kavak et al presented results of a study conducted to determine if there was an association between smoking and indicators of psychosocial wellbeing in patients with MS.[28] Subjects were obtained from the New York State Multiple Sclerosis Consortium database. At enrollment,

patients were asked about smoking status and were then categorized as smokers or non-smokers. Patients were asked to rank their level of loneliness, pessimism, tension, panic, irritation, morbid thoughts, and feelings of guilt on a 1 to 5 scale ("none" to "extremely"). A cumulative mood state measure was determined from the sum of the 7 Rasch scored items, ranging from 14 to 700 (lowest to highest mood state, respectively). The cumulative measure was normalized by log-transformation. Of 2249 subjects enrolled, 761 (33.8%) were current smokers. Using a cutoff of 3 to 5 as most affected by each of the mood states; smokers were significantly more likely to report loneliness, pessimism, panic, irritation, and morbid thoughts than non-smokers with MS. The groups did not differ in levels of tension or feelings of guilt. Cumulative mood state was significantly lower for smokers (548.0 vs 574.7 for non-smokers; $P < 0.001$). The authors indicated that it is not possible to ascribe directionality to this association, as psychosocial factors may be associated with increased tendency for smoking. Constantinescu et al conducted a study to investigate whether smoking cessation in patients with MS can affect the risk for disability progression.[29] Smoking and clinical data from 681 patients with MS were obtained, and Cox proportional hazard regression models were used to estimate the effects of smoking cessation on time to reaching EDSS scores of 4.0 and 6.0. In this cohort of MS patients, 39% of males and 31% of females were smokers at disease onset (21 and 17% were ex-smokers, respectively). Patients smoked for an average of 22.8 years, and smoking intensity was 18.7 cigarettes per day. Current smoking status by gender was 14.7% of males and 16.5% of females, representing a 62% and 46% reduction in smokers, respectively. Each year that elapsed from smoking cessation was associated with a 3% decreased risk of reaching EDSS 4.0 (HR: 0.97, 95% CI: 0.95-0.98, $P < 0.001$), and a 5% decreased risk of reaching EDSS 6.0 (HR: 0.95, 95% CI: 0.93-0.97, $P < 0.001$). Collectively, these studies may help to inform discussions with MS patients about the importance of smoking cessation.

OBESITY

Obesity is associated with a chronic inflammatory state and abnormal cytokine release. Correale et al presented a study of 210 patients with RRMS and 210 healthy controls.[30] Patients reported their height and weight or used a visual scale to estimate their BMI. There is an inverse correlation between vitamin D and BMI ($r = -0.87$, $P < 0.001$) and a positive correlation between serum leptin and BMI ($r = 0.77$, $P < 0.001$).

The authors showed that obesity at 20 years of age was associated with a higher risk of MS (OR = 2.1) after adjustment for smoking and vitamin D levels. Obesity at 20 years of age was also associated with vitamin D deficiency and increased serum leptin. In vitro exposure of myelin basic protein (MBP)-peptide specific CD4+ T cells to leptin inhibits steroid-induced apoptosis. Cytokines IL-1α, IL-2, IL-6, IL-15, IL-17, IFN-γ, and TNF-α were increased with elevated BMI, but leptin exerts opposite effects on T_{reg} (anergy and hyporesponsiveness) and CD4+ effector T cells (induction of proliferation, secretion of pro-inflammatory cytokines, and inhibition of apoptosis). The authors speculated that leptin may be a link between obesity and autoimmunity.

MENOPAUSE

CLIMB (Comprehensive Longitudinal Investigation of Multiple sclerosis at the Brigham and Women's

Hospital, Partners MS Center) is a 20-year longitudinal study of patients with MS. One of the primary goals is to refine prognosis based on early disease. Patients with MS were enrolled within 3 years of diagnosis and characterized with neurological examinations, MRI imaging, immunologic, genetic, neuropsychological, and quality of life studies.[31] Bove and colleagues sent a survey on MS during menopause to 1202 women with CIS or MS and received 391 responses.[32] The responses show that progression of MS (measured with the standard EDSS scale) changed at or around menopause toward a more rapid accumulation of disability. The team is following up on this finding; if hormonal shifts are responsible, it may present an opportunity to find a solution for women with MS going through menopause.

COMORBIDITIES: METABOLIC SYNDROME

Berriosmorales et al presented results of a retrospective study that investigated the association between metabolic syndrome and disease severity in patients with MS.[33] Consecutive MS patients were identified from the UMass MS center database. Metabolic syndrome was defined by the presence of obesity (BMI ≥ 25 kg/m^2), and 2 of the following: fasting blood glucose > 100 mg/dL; blood pressure > 130/85; serum triglyceride ≥ 150 mg/dL; or HDL cholesterol < 40 mg/dL in men, < 50 mg/dL in women. New T2 and/or gadolinium-enhancing lesions were used as indices of MRI activity; EDSS, T25-FW, and modified 9-Hole Peg Test (m9-HPT) were used as disability measures. The study population was comprised of 399 patients with MS (75% relapsing and 25% progressive); the mean age was 48.1 years, 74% were female, and the median EDSS was 2.5. Ten percent of the patients (38) had metabolic syndrome. Mean T25-FW and m9-HPT were significantly different in patients with metabolic syndrome compared with those without: 8.5 vs 6.5 seconds, $P = 0.037$; and 20.9 vs 14.9 seconds, $P = 0.027$, respectively). There were no differences between groups in EDSS or in brain MRI activity. In multivariate logistic regression analysis, the presence of metabolic syndrome was a significant independent predictor of T25-FW ($P = 0.025$), and m9-HPT ($P = 0.005$).

COMORBIDITIES: HEADACHE

Wilcox et al presented results of a prospective survey-based study of headache in patients with MS.[34] The single center study included patients with MS and a self-identified history of headaches. Over a 6-month period, patients were invited to complete a survey that included questions about headache history, frequency and pain description, triggers, and impact on daily functioning. Of the 72 patients who completed the survey, 65% had headaches prior to MS onset. Over half of the patients experienced headaches ≥ 4 days per month. Eighty-five percent of patients rated their pain as severe at least some of the time and 63% of patients indicated that headaches worsened during MS exacerbations. In patients without headache history prior to onset of MS, 64% had migraine headaches with aura with disease progression. Stress and fatigue were the most common headache triggers identified by 78.1% and 64.1% of patients, respectively. Patients indicated that headaches very often or always limited daily activities (35.5%), necessitated rest

(59.7%), affected mood (42.0%), and impaired concentration (40.3%). While the prevalence of headache in patients with MS may be variable, these results indicate that including headache inquiry during routine examinations of patients with MS may be warranted in order to minimize the negative impact on quality of life.

COMORBIDITIES: THYROID DISEASE

Barone et al presented a poster reporting the prevalence of thyroid disease in a cohort of patients from their MS clinic.[35] This retrospective review of 380 patients with MS from 2010–2011 identified 46 (12.1%) with thyroid disease (45 were hypothyroid and 1 had thyroiditis alone). Of the hypothyroid patients, 2 patients had thyroid surgery, 1 patient had benign thyroid nodules, and 4 patients had thyroiditis. Eighty-nine percent of the patients with thyroid disease were female, compared with 77% females in the overall MS cohort. All but 1 of the patients with thyroid disease had been treated with disease-modifying therapies; 37% with IFNβ, 20% with GA, 17% with GA and IFNβ, and 24% with multiple medications. Awareness of the prevalence of thyroid disease in patients with MS is important, particularly with the potential for autoimmune side effects associated with therapeutic agents.

COMORBIDITIES: DEPRESSION

Depression is a frequent comorbidity in women with MS. Winder et al explored associations between MRI changes and clinical parameters of depression.[36] They assessed scores of the 20-item Beck Depression Inventory-V (BDI-V)[37] and physical disability using EDSS in 50 women with MS (37.0±9.9 years). They performed Spearman Rank correlations of BDI-V scores with patient age, disease duration, EDSS, and MS-lesion-load in frontal, parietal, temporal, occipital, opercular, cingulate, thalamic, midbrain, cerebellar, pontine, medulla oblongata, and spinal cord areas ($P < 0.05$).

BDI-V scores did not correlate with patient age, disease duration and EDSS scores. BDI-V scores correlated indirectly with MS-lesion volume in the right temporal middle/inferior/fusiform gyral area (Spearman Rho, -0.32; $P = 0.032$), BDI-V scores correlated directly with the MS lesion load in the right opercular region (Spearman Rho, 0.29; $P = 0.043$) and total area of enhancing MS-lesions in the supratentorial brain (Spearman Rho, 0.31; $P = 0.029$). The authors conclude from these reduced depression scores in women with right temporal lobe lesions suggest that the right temporal lobe contributes to disinhibiting depressive mood changes. The increasing BDI-V scores with lesions in the right operculum and cumulative active supratentorial MS lesion load suggest that these areas contribute to inhibiting depressive mood changes. These findings are consistent with Mohr et al, who found that BDI results at 6-month follow-up, residualized for end-of-treatment BDI, were predicted by total lesion volume ($R^2 = 0.22$, $P = 0.005$), lesion volume in many discrete areas, and neuropsychological functioning ($R^2 = 0.29$, $P = 0.0009$).[38] They also found weak but significant relationships between BDI and right temporal periventricular lesion volume ($R^2 = 0.32$, $P = 0.002$) and left temporal grey-white junction lesion volume ($R^2 = 0.19$, $P = 0.02$).

Disease Modifying Therapies

MRI LESIONS PREDICT RELAPSES

Markers for predicting MS relapses would be useful for clinical management. In 2009 Sormani et al conducted a meta-analysis of the relation between new or enlarging T2 MRI lesions and clinical relapses.[39] They discovered a strong correlation between a treatment's average effect on MRI lesions and its effect on relapse rates (coefficient of determination, $R^2 = 0.81$). The authors encouraged using MRI as a phase 2 endpoint for clinical trials of drugs related to existing therapies but warned against using MRI lesions as a primary endpoint in pivotal trials, especially of drugs of novel mechanism.

Using a large dataset of subjects with relapsing MS who received placebo in the AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis), DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing Remitting Multiple Sclerosis), and CONFIRM (Comparator and an Oral Fumarate in Relapsing Remitting Multiple Sclerosis) clinical trials, Richert and colleagues evaluated the relationship of brain lesions with later disease course.[40] They found that subjects who had one or more new or enlarging T2 MRI lesions during the first year were twice as likely to experience a relapse during the second year compared to those who did not have these lesions. The odds ratio (OR) for a relapse in year 2 for placebo-treated patients generally increased with lesion activity in year 1.

The authors also examined the active treatment arms of phase 3 clinical trials of IM IFNβ-1a, natalizumab, dimethyl fumarate (DMF), and glatiramer acetate. A significant association between T2 lesion activity in year 1 and relapse in year 2 was observed for patients treated with IM IFNβ-1a in the SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) study. The ORs ranged from 1.4 to 2.7 for different levels of lesion activity and all were statistically significant. Interestingly, the ORs observed for patients in AFFIRM, DEFINE, and CONFIRIM receiving natalizumab, DMF, or glatiramer acetate were not statistically significant. This study shows the relation of T2 activity with subsequent relapses in the natural history of MS but also shows that this relationship may be useful for patients receiving some DMTs but not others.

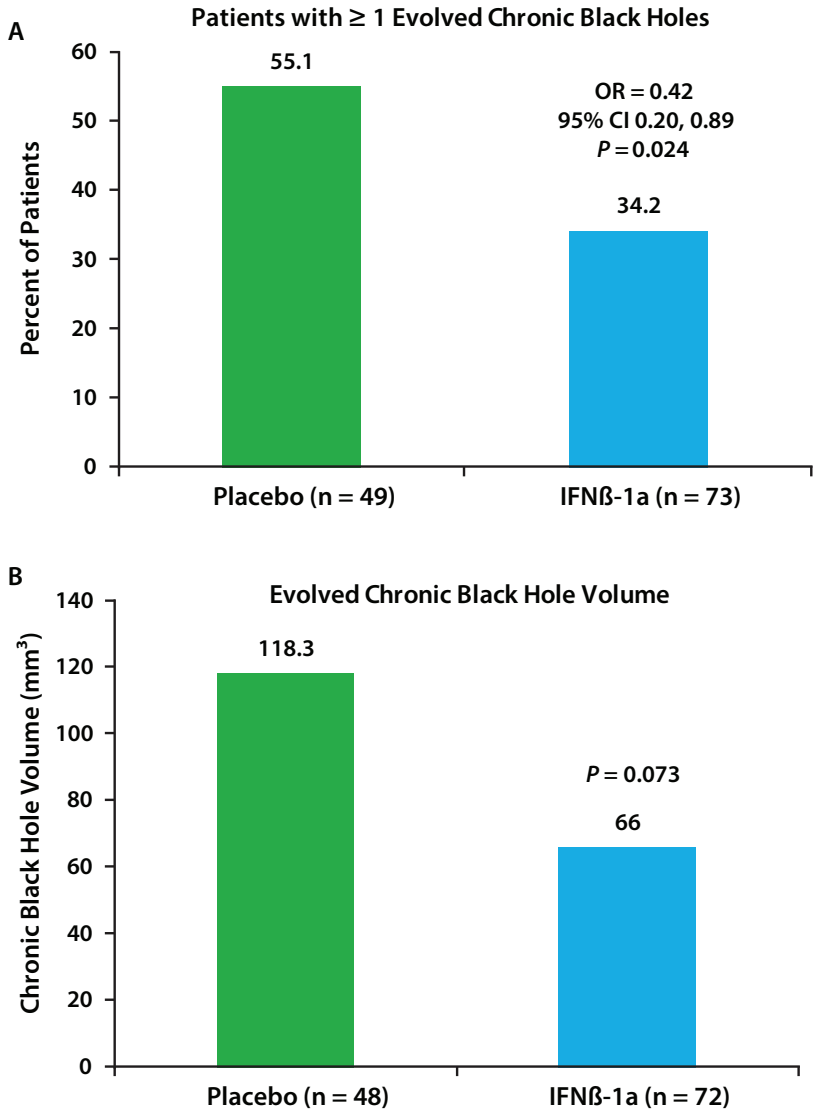
INJECTABLE DISEASE MODIFYING THERAPIES

Interferon

Traboulsee et al presented a poster on an exploratory post hoc analysis of data from the PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) study.[41] All patients in the PRISMS study had MRI twice yearly, and a subgroup of patients had monthly MRI scans in the first 9 treatment months.[42] The current analysis was conducted to specifically look at the effect of IFNβ-1a on the evolution of chronic black holes in patients with RRMS. Patients included in the analysis were those who had monthly MRI scans from study months -1 to 9 and had ≥ 1 newly enhancing T1 gadolinium (Gd+) lesions from study months -1

to 3. MRI scans were reanalyzed to assess for the evolution of chronic black holes. A chronic black hole was defined as a T1 Gd+ lesion that evolved into a T1 hypointense lesion that was visible for ≥ 6 months. [For patients without a month 9 scan, data were analyzed from MRI scans at months -1 to 2 and month 8] The analysis endpoints were the percentage of newly enhancing T1 Gd+ lesions on scans from Months -1 to 2/3 that evolved into chronic black holes at Month 8/9; and the presence of ≥ 1 evolved chronic black holes and total volume of evolved chronic black holes at Month 8/9. One hundred twenty-two patients with newly enhancing Gd+ lesions were included, 73 of whom were treated with IFNβ-1a (44 or 22 µg SC three times per week) and 49 of whom were from the placebo group. For patients treated with IFNβ-1a, 12.6% of T1 Gd+ lesions from Months -1 to 2/3 evolved into chronic black holes at Month 8/9 compared with 19.8% for patients in the placebo group (36% reduction, $P = 0.033$). In the subgroup of patients with baseline EDSS scores ≤ 3.5, IFNβ-1a was associated with a 51% reduction in the percentage of Gd+ lesions evolving into chronic black holes (10.4% vs 21.2% for placebo, $P = 0.010$). The percentage of patients with ≥ 1 evolved chronic black holes at Months 8/9 and chronic black hole volumes per patient are shown in Figure 2.

Figure 2: IFNβ-1a and Evolved Chronic Black Holes[41]



In the subgroup of patients with baseline EDSS scores ≤ 3.5, the evolved chronic

black hole volume was 129.0 mm^3 in the placebo group and 46.9 mm^3 in the IFNβ-1a group ($P = 0.035$). Overall, these results suggest that treatment with IFNβ-1a is associated with a reduction in chronic black holes evolving from new Gd+ lesions, with the effect most apparent in patients with lower disability scores at baseline.

Pegylated IFNβ-1a (PEG IFN) is in clinical development as a lower frequency dosing formulation for patients with RRMS. The safety and efficacy of PEG IFN (125 µg) administered subcutaneously once every 2 weeks (Q2W) or every 4 weeks (Q4W) was evaluated in the 2-year, phase 3, ADVANCE trial. Recently published results from the first 48 weeks showed that treatment with PEG IFN significantly reduced the ARR by 36% and 28% compared to placebo, for the Q2W and Q4W groups, respectively.[43] Both treatment schedules significantly reduced the risk of disability progression by 38% compared to placebo. Calabresi et al presented 2-year safety and efficacy data from ADVANCE.[44] Of 1516 patients randomized at the start of the study, 1332 completed year 1 (the placebo-controlled phase of the study). After the first year, patients in the placebo arm were re-randomized to either PEG IFN Q2W or Q4W groups. Patients originally in the PEG IFN treatment groups continued through study completion on the same treatment and schedule. The ARR over 2 years favored the PEG IFN treatment groups; 0.29 and 0.22 for the PEG IFN Q4W and PEG IFN Q2W groups compared with 0.35 for the placebo arm (17% reduction, $P = 0.091$; and 37% reduction, $P < 0.0001$, respectively). Continuous treatment with PEG IFN was associated with a reduced risk for time to disability progression compared with the placebo to PEG IFN patients (Q2W HR = 0.67, 95% CI 0.49-0.95, $P = 0.0257$; Q4W HR = 0.75, 95% CI 0.53-1.05,

Figure 3: ADVANCE: Brain MRI over 2 Years[43]

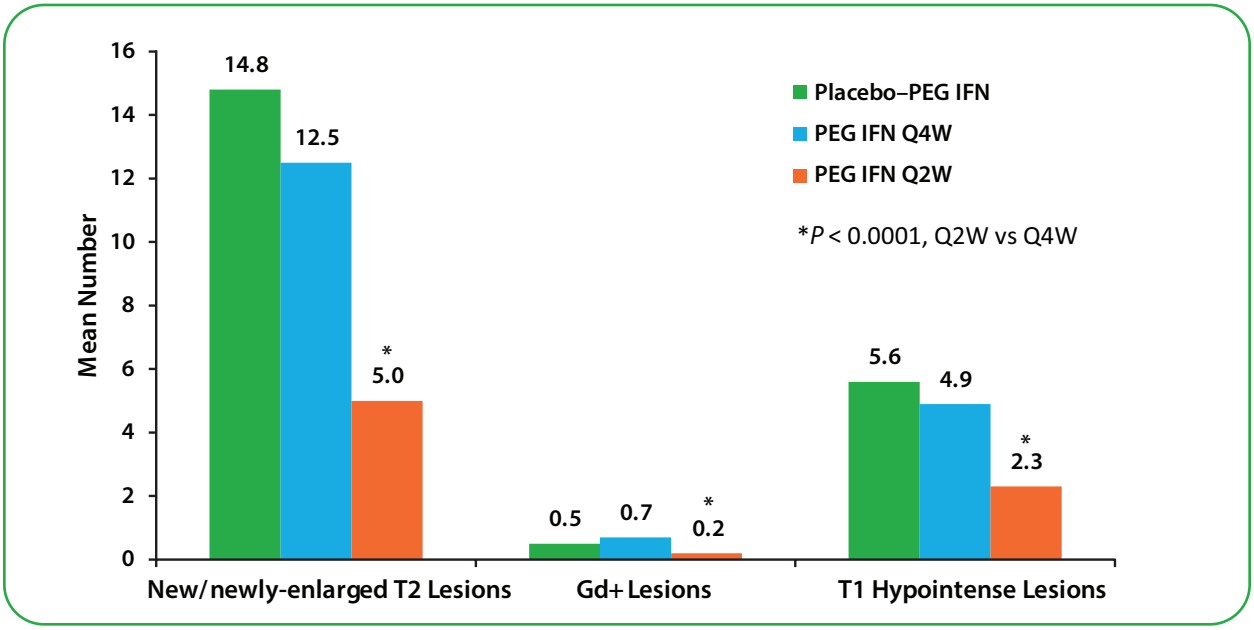


Table 3: ADVANCE: Freedom from Measured Disease Activity[46]

Timeframe	Placebo (n = 484)	PEG IFN Q4W (n = 469)	PEG IFN Q2W (n = 466)
Baseline to Week 48	15.1%	21.5%‡	33.9%*†
Week 24 to Week 48	28.9%	38.6%‡	60.2%*†

Values represent percent of patients; *$P < 0.0001$ vs placebo; ‡$P = 0.01$ vs placebo; †$P < 0.0001$ vs Q4W

$P = 0.0960$). Over 2 years, the PEG IFN Q2W treatment group had the least new or newly enlarged T2-weighted hyperintense lesions, Gd+ lesions, and T1 hypointense lesions **(Figure 3)**. The most common adverse events associated with PEG IFN were injection site erythema (59%–64%), influenza-like illness (50%–51%), pyrexia (41%–43%), and headache (41%–42%). Less than 1% of patients treated with PEG IFN developed IFN neutralizing antibodies over the 2-year study. Collectively, the 2-year results provide evidence of greater treatment effects with the PEG IFN Q2W compared with the Q4W schedule.

Kieseier et al presented a retrospective analysis of the first year of the ADVANCE trial, to determine whether treatment with PEG IFN was associated with improved recovery following relapse in patients with RRMS.[45] Baseline demographic and clinical characteristics were well balanced among the 3 treatment groups. Baseline EDSS scores were 1.18, 1.24, and 1.26 for the placebo, PEG IFN Q4W, and PEG IFN Q2W groups, respectively. In the first year of the study, 55 patients had disability progression associated with a relapse and 57 patients experienced disability progression not associated with relapse. A lower proportion of patients treated with PEG IFN had confirmed disability progression associated with a relapse compared with placebo (30% and 22% reduction for the Q2W and Q4W groups, respectively). In addition, fewer patients treated with PEG IFN had sustained disability progression due to incomplete recovery after a relapse (12% and 16% for PEG IFN Q2W and Q4W, vs 27% for placebo).

Arnold et al presented a post hoc analysis of the first year of the ADVANCE trial, evaluating the composite endpoint, freedom from measured disease activity or FMDA, also referred to as "no evidence of disease activity".[46] FMDA was defined as the absence of clinical activity (no relapses and no sustained accumulation of disability) and absence of MRI disease activity (no Gd+ lesions and no new or newly-enlarging T2 lesions). The investigators looked at FMDA from baseline to week 48 and from week 24 to week 48 of the study. Significantly higher proportions of patients in the PEG IFN Q2W treatment group had FMDA from baseline to week 48 and from week 24 to week 48 as compared with PEG IFN Q4W and placebo groups **(Table 3)**.

These results provide additional evidence supporting the beneficial effects associated with PEG IFN Q2W compared with placebo and PEG IFN Q4W.

GLATIRAMER ACETATE

A new preparation of GA with less frequent dosing (40 mg SC 3 times a week vs 20 mg SC daily) was FDA approved in early 2014.[47] In the 12-month placebo-controlled GALA trial, treatment with GA 40 mg SC TIW was associated with a 34% reduction

Table 4: GALA: Glatiramer Acetate (40 mg TIW) ARR at 12 and 24 months[49]

Treatment	ARR	Percent Reduction
Placebo-controlled Phase at 12 Months		
Placebo (n = 461)	0.505	---
GA 40 mg TIW (n = 943)	0.331	34% ($P < 0.0001$)
Open-label Phase at 24 Months		
Placebo to GA 40 mg TIW Delayed Start (n = 419)	0.257	---
GA 40 mg TIW Early Start (n = 834)	0.177	31% ($P = 0.0002$)

in confirmed relapses and improvements in MRI endpoints compared with placebo.[48] In May, Khan et al presented 24-month efficacy and safety results from the open-label extension study.[49] Patients treated with GA 40 mg TIW in the placebo-controlled phase of GALA continued with this treatment regimen in the extension phase or "early start." Patients in the placebo arm were switched to GA 40 mg TIW at month 12 or "delayed start." Continued treatment with GA 40 mg was associated with a 31% reduction in ARR at 24 months compared with patients in the placebo→GA (delayed start) group (Table 4). The authors reported that the safety profile observed for the 40 mg GA dose was consistent with the 20 mg GA formulation.

Wolinsky et al presented results of GLACIER, an open-label, randomized, multicenter study to evaluate the safety and tolerability of GA 40 mg TIW compared with GA 20mg QD in patients with RRMS.[50] Eligible patients for GLACIER had been stable on GA 20 mg QD for at least 6 months prior to screening, then were randomized to either continuing on GA 20 mg QD or switching to GA 40 mg TIW for the core phase (4 months) of the trial. A total of 209 patients were enrolled and randomized. All patients were offered the GA 40 mg TIW during the extension phase. Baseline characteristics were balanced between groups; patients were approximately 50 years of age, 82% were female, they were ~11.5 years from MS diagnosis, and had 0.2 relapses in the 1 year before the study. The primary endpoint was the rate of injection-related adverse events (IRAEs). IRAEs included injection site reactions (ISRs) and symptoms/events related to immediate post-injection reactions, such as flushing, chest pain, palpitations, anxiety, dyspnea, throat constrictions, and urticaria. Treatment with GA

Table 5: Injection-Related Adverse Events (IRAE): GA 40 mg TIW vs GA 20 mg QD[50]

Treatment	Adjusted Mean Annualized IRAE	Percent Reduction
GA 20 mg QD (n = 101)	70.4	---
GA 40 mg TIW (n = 108)	35.3	50% ($P = 0.0006$)

40 mg TIW was associated with a significant reduction in IRAEs compared with daily treatment with GA 20 mg (Table 5).

When looking only at injection site reactions, there was also a 50% reduction in the adjusted annualized rate for the GA 40 mg TIW treatment arm compared with GA 20 mg QD. There were no significant differences between treatment arms in patient reported outcomes. Collectively, the results from GALA and GLACIER provide additional information about GA that may be useful in discussions with patients about therapeutic options for RRMS.

ESTRIOL PLUS GA

Interest in sex hormones as factors in MS relapse rates goes back to the observation in 1998 that in women with MS, the relapse rate declines during pregnancy.[51] The relapse rate is 3 to 4-fold lower in the third trimester than in the year prior to pregnancy. These changes are opposite to the fluctuations in sex hormones, which may exert protective effects. Estriol is unique to pregnancy, was protective in multiple EAE models (reviewed by Spence and Voskuhl52), and showed positive effects in a pilot trial in women with MS.[53] Neural estrogen receptor knock-out experiments in mice implicate direct neuroprotection as a mechanism of action.[52]

Voskuhl and colleagues presented results of a combination trial of estriol plus GA in RRMS.[54,55] The study was a double-blind, placebo-controlled study of 164 women with RRMS. The treatment period was 2 years and the primary endpoint was relapse rate. Subjects were randomized to treatment with GA plus 8 mg estriol daily or GA plus placebo. Blood levels of estriol reached mid-pregnancy levels in the active treatment group. The most common adverse event was irregular menstrual spotting. Estriol has a good safety record, which was confirmed by the safety monitoring in this study. At 12 months the GA plus estriol group had a statistically significant reduction in relapses vs placebo; at 2 years the GA plus estriol group had a lower relapse rate than the GA plus placebo group but the difference was no longer significant. Cognitive improvement was assessed with the Paced Auditory Serial Addition Task at 3 seconds (PASAT3) and PASAT2. At 1 year there were significant increases in the cognition scores in the treatment group but no change in the GA plus placebo group. At 24 months the GA plus estriol group's improvement over baseline was still significant and there was a trend toward improvement in the placebo group. In summary, this combination study shows that addition of estriol to GA was associated with improvement in relapse rate and cognition at 12 months and some continued benefit on cognition seen at 24 months. Combination with other DMTs and possible use in men remain to be investigated.

ATX-MS-1467

ATX-MS-1467 is a mixture of 4 T cell epitopes from myelin basic protein (MBP). Wraith et al showed that treatment with ATX-MS-1467 after induction of EAE in mice resulted in a dose-dependent suppression of the mean EAE score.[56] The authors also presented a phase 1 open-label, ascending-dose study in patients with relapsing MS. Treatment with 800 mcg intradermal ATX-MS-1467 every 2 weeks from week 8 to week 16 resulted in a significant reduction in newly enhancing MRI lesions (maximum effect was 78% reduction at week 16). The effect was lost 12 weeks after therapy cessation. There was also a reduction in

the total volume of Gd+ lesions during the treatment period.

VITAMIN D WITH IFN OR GA

Results of a study designed to determine the effect of vitamin D levels on clinical and MRI outcomes in patients with RRMS treated with interferon and GA were presented by Rotstein et al in both oral and poster sessions.[57] Patients in this prospective, longitudinal cohort were enrolled in the CLIMB study. All patients had EDSS < 5.0, and were initiating their first disease-modifying therapy (monotherapy) with either GA or interferon β (IFNβ-1a SC, IFNβ-1a IM, or IFNβ-1b SC). Vitamin D (25-hydroxy—vitamin D) levels were determined by chemiluminescent assay from blood samples collected within 18 months of treatment initiation. A standard random effects model was used to adjust vitamin D levels for seasonality. Outcome measures included time to first relapse or T1 Gd+ lesion; time to first relapse; and time to disability progression. The patient population included 151 patients treated with GA and 96 treated with IFN; 69% of each group were female; and disease duration was a mean of 4.5 and 3.3 years for the GA and IFN groups, respectively. Patients were categorized using seasonally adjusted vitamin D level tertiles: > 28.7 ng/mL; > 20.6 ng/mL and ≤ 28.7 ng/mL; and ≤ 20.6 ng/mL. The time to the first inflammatory event (relapse or T1 Gd+ lesion) was longest for patients in the highest vitamin D tertile.

Using the Cox model, the hazard ratios for the composite endpoint of clinical and MRI events adjusted for age, gender, and disease duration were 0.75 overall ($P = 0.028$); 0.87 for the GA group ($P = 0.375$); and 0.58 for the IFN group ($P = 0.013$), suggesting that the benefit for the cohort overall was driven by effects of vitamin D in the IFN group. A similar trend was noted for time to relapse alone; however, the effect did not reach significance. The authors speculate that the effects of IFN and vitamin D may be complementary, contributing to the beneficial effect on inflammatory endpoints observed in this study, whereas greater redundancy exists in the immunomodulatory effects of GA and vitamin D.

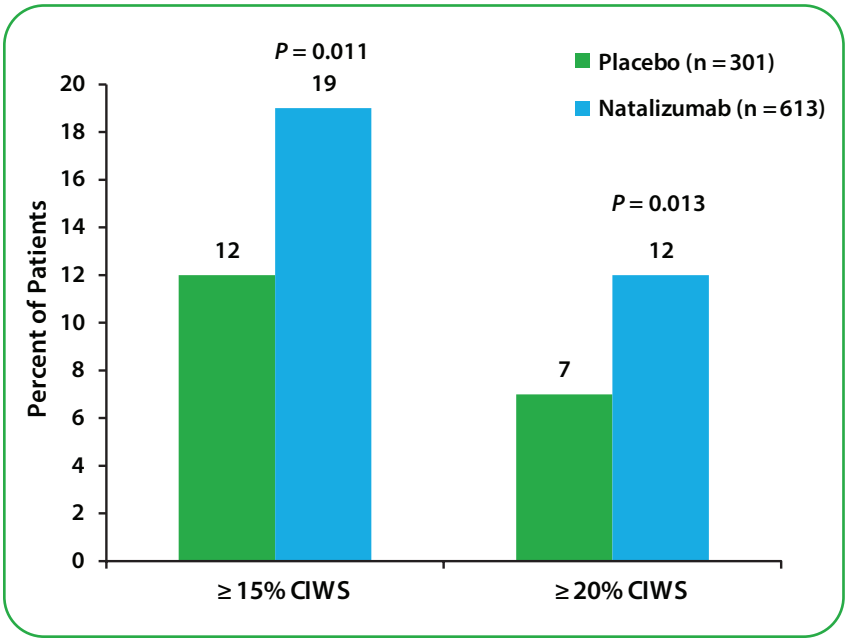
MONOCLONAL ANTIBODIES

Natalizumab

In the double-blind, placebo-controlled AFFIRM trial, treatment with natalizumab reduced the risk of disability progression by 42% over 2 years in patients with RRMS.[58] Recently, Rudick et al presented the results of a post hoc analysis of AFFIRM to determine the effect of natalizumab on improvement in walking speed.[59] The baseline characteristics of patients in the natalizumab and placebo groups of the AFFIRM trial were well balanced. EDSS and T25-FW were performed at baseline and every 3 months during the study; SF-36 was reported at baseline and then at months 6, 12, and 24. For the current analysis, the authors looked at the percentage of patients who had ≥ 15% or ≥ 20% confirmed improvement in walking speed (CIWS) from baseline on the T25-FW. The analysis showed that a greater proportion of patients treated with natalizumab had CIWS over 2 years than placebo controls **(Figure 4)**.

CIWS was associated with improvement in physical component scores of the SF-36 (SF-36 PCS). Patients with ≥ 20% CIWS had a mean change of 2.7 on the SF-36 PCS compared with -0.3 for patients without CIWS ($P = 0.002$). The largest

Figure 4: Natalizumab and Walking Speed[59]



treatment-related effects of natalizumab on CIWS occurred in those patients with higher EDSS scores (≥ 4.0) at baseline.

While natalizumab has demonstrated efficacy for reducing annualized relapse rates, disability progression, and MRI endpoints, its use is limited by the risk for progressive multifocal leukoencephalopathy (PML) caused by the JC virus.[58,60,61] The presence of anti-JC virus antibodies, prior immunosuppressant use, and natalizumab exposure beyond 24 months are risk factors for the development of PML.[61] As a result, patients effectively treated with natalizumab may be switched to other disease-modifying therapies due to increasing risk for PML. There is great interest in strategies for the management of patients with MS during a transition, due to the risk of disease recurrence with natalizumab treatment interruption. Fox et al recently published results from the RESTORE study; a prospective, randomized, partially placebo- controlled study designed to examine the course of MS disease activity in patients undergoing an interruption of natalizumab treatment for up to 24 weeks compared with those continuing on natalizumab.[62] Of the 175 patients in the RESTORE study, 45 were randomized to continue on natalizumab, 42 to placebo, and 88 to treatment with other therapies (IFNβ-1a, GA, or methyl prednisolone). MRI disease recurrence occurred in none of the patients who continued treatment with natalizumab compared to 7%–53% of patients in the other treatment groups. Relapses were reported in 4% of patients who continued on natalizumab and in 15%–29% of patients in the placebo and other treatment groups. Following the last dose of natalizumab, MRI activity recurred as early as 12 weeks, and relapses as early as 4–8 weeks.

In May, Clerico et al presented a poster on the TY-STOP study, an observational, prospective Italian multicenter study of patients with RRMS followed for 1 year after receiving 24 doses of natalizumab.[63] The primary outcome was the mean annualized relapse rate (ARR) at the end of the year of observation; secondary outcomes were annual MRI activity and EDSS. One hundred thirty RRMS patients who had received 24 doses of natalizumab and had clinical and MRI stability were enrolled in the study; 124 completed follow-up. In the

intention-to-treat (ITT) population, 43 patients (34.7%) chose to continue treatment with natalizumab and 81 (65.3%) elected to interrupt natalizumab treatment. The treatment interruption group includes those patients who stopped natalizumab for part of the observation year then restarted, and also patients who switched among other therapies. The ARR in the ITT population was 0.24 for patients continuing natalizumab treatment and 0.73 for those interrupting treatment ($P = 0.004$); the presence of MRI activity in the year of observation was 25.6% and 48.2% for the natalizumab continuation and interruption groups respectively ($P = 0.018$). There were no significant differences between groups on the EDSS.

In another study related to the transition following treatment with natalizumab, Capobianco et al presented a poster with the results of a retrospective single center study looking at the effects of different therapeutic approaches on recurrence of disease activity 12 months following discontinuation of natalizumab.[64] Of 196 patients identified who had received at least 1 infusion of natalizumab, 79 discontinued treatment and follow-up data were available. Thirty-five patients were switched to fingolimod following at least 3 months of washout; 24 patients received no treatment; and 19 patients received other treatments including monthly pulsed steroids, GA, IFNβ, azathioprine, and cyclophosphamide. Survival curves and log-rank test of the percentage of relapse-free patients showed no significant difference between the 3 groups (fingolimod, other treated, and untreated). Clinical relapses occurred in 31.4% of patients treated with fingolimod and in 41.8% of the patients who were untreated or treated with other agents (non-significant difference). There were no differences between groups for change in EDSS at the end of follow-up. Two recently published studies of patients treated with fingolimod after natalizumab highlight the importance of the washout period during this switch, namely that a shorter washout period (less than 3 months) was associated with lower risk for relapse.[65] Further study in this area will be important to inform decisions about the optimal therapeutic approach for patients discontinuing treatment with natalizumab.

Alemtuzumab

The safety and efficacy of the humanized anti-CD52 antibody, alemtuzumab, have been demonstrated in 2 phase 3 studies in patients with RRMS.[66,67] In the CARE-MS I and CARE-MS II trials, conducted in treatment-naïve and treatment-experienced patients (relapsed on prior therapy), treatment with alemtuzumab (IV, 12 mg/day for 5 days at baseline, then 3 days at 12 months) was associated with significant benefits in clinical and MRI endpoints compared with IFNβ-1a (44 µg SC 3x/week) over the 2-year studies. Arnold et al presented MRI outcomes at 3 years of follow-up for the CARE-MS I and II studies.[68] Patients entered into the extension study included 349 from the CARE-MS I trial (previously treatment-naïve) and 393 from CARE-MS II (previously treatment-experienced). Approximately 80% of patients who were treated with alemtuzumab during the core studies did not require additional treatment during year 3. The investigators showed that most patients (treatment-naïve and treatment-experienced) were free of MRI activity in the third year of follow-up. In addition, treatment with alemtuzumab appeared to slow the rate of brain volume loss over 3 years **(Table 6)**.

Table 6: CARE-MS Trials: Brain Volume Loss[73]

Patients	Median Yearly Brain Parenchymal Fraction Change (%)		
	Year 0-1	Year 1-2	Year 2-3
Treatment-Naïve Patients (CARE-MS I)	-0.59	-0.25	0.19
Treatment-Experienced Patients (CARE-MS II)	-0.48	-0.22	-0.10

Collectively, these results support the efficacy of alemtuzumab in patients with RRMS, and help to characterize the durability of the treatment effects for both treatment naïve and those patients who have relapsed on prior therapy.

In the CARE-MS trials, thyroid-associated adverse events and immune thrombocytopenia (ITP) were noted as risks with alemtuzumab treatment.[66,67] Cuker et al presented a poster at a neurology conference summarizing the experience in the alemtuzumab phase 2, phase 3, and extension studies with regard to the development of ITP in patients with RRMS.[69] Overall, 1486 patients were treated with alemtuzumab across these studies, with a mean follow-up of 54.4 months. Across all patients, the incidence of protocol-defined ITP was 2.0%, corresponding to 20/1217 (1.6%) treated with the 12 mg alemtuzumab dose, and 10/269 (3.7%) who received 24 mg alemtuzumab. All cases of ITP were identified through the ITP safety monitoring program, which was initiated during the CAMMS223 phase 2 study, and continued during the phase 3 and extension studies. Of those patients who developed ITP following treatment with alemtuzumab, a mean of 29 months (range 4-51) elapsed between the first alemtuzumab dose to ITP onset, and a mean of 16 months (range 1-34) from the last alemtuzumab dose. The treatment-related cases of ITP were successfully managed with medical therapy or self-limiting.

Hunter et al presented data on treatment of alemtuzumab in treatment-refractory patients with MS and high disability scores.[70] The patient cohort included 29 patients with a mean ARR of 1.6 in the 2 years prior to current alemtuzumab treatment, baseline EDSS of 5.1, and mean MS severity score (MSSS) of 6.6. The patients were all treatment-experienced with approved disease-modifying therapies. After receiving 2 or more cycles of alemtuzumab (60 mg total in the first cycle over 5 days, a second cycle 12 months later of 30–36 mg over 3 days, and subsequent 3-day cycles 12 months apart as needed for ongoing disease activity), 72% of patients showed improvement in EDSS compared to baseline. The mean change in MSSS was -1.8. For patients who were stable or worsened on the EDSS, the change in MSSS was -0.2. The ARR was 1.1 for Year 1, 0.97 for Year 2, and 0.92 for Year 3, compared with 1.6 in the 2 years prior to alemtuzumab treatment. This small study demonstrates benefit associated with alemtuzumab treatment in a cohort of patients with MS characterized by greater disability than those included in the CARE-MS phase 3 studies.

Graves et al presented a poster with visual outcomes data from the CARE-MS II study.[71] Binocular and monocular Sloan visual acuity testing was performed every 6 months over the 2-year study, and outcomes included the proportions of patients who improved, remained

stable, or worsened according to the visual measures. In this population of patients with RRMS who had relapsed on prior therapy, treatment with alemtuzumab was associated with improvement in Sloan visual metrics compared with IFNβ-1a. The authors suggest that monitoring visual dysfunction in MS clinical trials may shed light on an important dimension of disability in this patient population.

Ofatumumab

Ofatumumab (OFA) is a fully human anti-CD 20 monoclonal antibody that depletes B cells via antibody dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[72] Bar-Or et al presented results of the phase 2 MIRROR study of ofatumumab in patients with RRMS at AAN.[73] MIRROR is an international, randomized, double-blind, placebo-controlled, parallel group trial designed to determine the MRI efficacy and safety of SC ofatumumab at doses of 3 mg, 30 mg, and 60 mg compared to placebo in patients with RRMS. Patients (n = 231) were randomized to placebo (placebo for 12 weeks followed by ofatumumab 3 mg at 12 weeks), ofatumumab 3 mg every 12 weeks, ofatumumab 30 mg every 12 weeks, ofatumumab 60 mg every 12 weeks, or ofatumumab 60 mg every 4 weeks. The 24-week double-blind treatment phase was followed by 24 weeks of follow-up. The primary endpoint was the cumulative number of new Gd+ T1 brain lesions over 12 weeks compared with placebo. The treatment arms were well balanced in terms of demographic and clinical parameters at baseline, and 85%–97% of patients completed week 24 of the study. Ofatumumab treatment resulted in dose-dependent depletion of B cells, and a significant reduction in new Gd+ lesions over 12 weeks compared with placebo **(Figure 5)**.

Figure 5: MIRROR: Ofatumumab and New T1 Gadolinium-Enhancing Lesions (Weeks 4–12)[73]

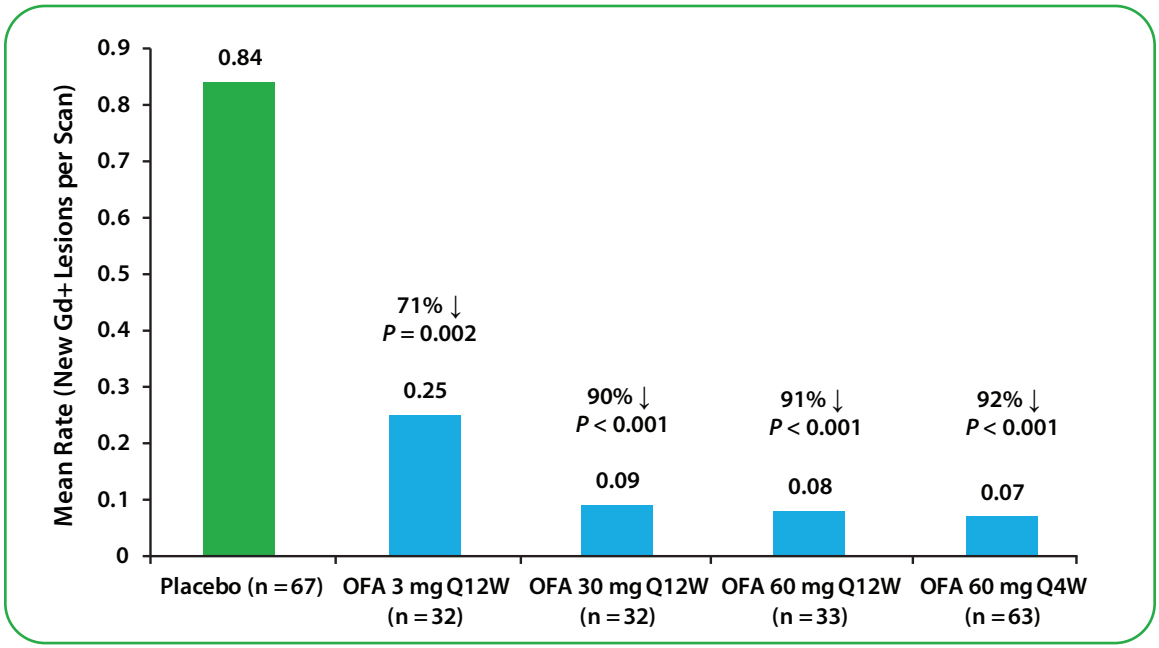


Table 7: MIRROR: Common Adverse Events Weeks 0–12[73]

Adverse Event	Placebo (n = 67)	OFA 3 mg Q12W (n = 34)	OFA 30 mg Q12W (n = 32)	OFA 60 mg Q12W (n = 34)	OFA 60 mg Q4W (n = 64)
Injection-related reaction	15	47	41	44	66
Nasopharyngitis	6	3	6	18	9
Dizziness	0	0	3	0	6
Urinary tract infection	3	3	9	0	0
Anxiety	3	3	6	0	0
Pyrexia	0	3	6	0	2
Respiratory tract infection	1	3	0	6	0
Ecchymosis	0	6	0	0	0
Neuralgia	0	0	6	0	0

Values represent %

Over 24 weeks, 79% of patients in the placebo arm had any adverse event, compared with 74%–86% of patients in the ofatumumab treatment arms. Adverse events led to study withdrawal for a total of 6 patients, from the 3 mg, 30 mg, and 60 mg (every 4 weeks) ofatumumab groups. Six serious adverse events were reported, all from ofatumumab treatment arms. A summary of common adverse events is shown in Table 7.

In a related presentation, Austin et al reported on the relationship between peripheral B-cell levels and MRI disease activity with ofatumumab in the MIRROR study.[74] This analysis demonstrated that there was a threshold of B-cell depletion to levels of 32–64 cells/µL, below which there is no added benefit with regard to effects on new Gd+ MRI lesions in patients with RRMS. These results may help to inform optimal dosing of ofatumumab for additional studies in patients with RRMS.

Daclizumab

Daclizumab is a humanized monoclonal antibody specific for the alpha subunit (CD25) of the human interleukin-2 receptor. SELECT was a 52-week, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of daclizumab high-yield process (DAC HYP) (150 mg or 300 mg every 4 weeks) in adults with RRMS.[75] SELECTION was a 1-year extension, where patients in the SELECT placebo group were randomized to receive 150 mg or 300 mg DAC HYP and those in treatment groups were randomized to continue the same dose or to a 24-week washout followed by 24 weeks of the original dose.[76] Radue et al presented a poster with a post hoc analysis of T1 hypointense lesion volumes at the conclusion of SELECT (1 year) and SELECTION (2 years).[77] At year 1, the treatment groups had a 15% decrease in lesion volume while the placebo group had a 16% increase ($P < 0.0001$). During year 2, the continuous treatment group had

an additional 15% decrease in volume while the patients who were switched from placebo in year 1 to treatment in year 2 had a 6% decrease in volume. The authors conclude that DAC HYP treatment resulted in a sustained reduction in the volume of total and new T1 hypointense lesions over 2 years of treatment. This radiologic effect is consistent with the clinical effects on disability progression observed in the clinical trials.

Rituximab in Progressive MS

While mitoxantrone is approved for progressive forms of MS, its use is limited by risk for cardiotoxicity and treatment-related leukemia.[78] The lack of safe and effective treatment options for patients with progressive MS is a significant unmet need. Perrone et al presented a poster with results of a retrospective, single center analysis of rituximab therapy in patients with secondary-progressive MS.[79] This analysis included 80 patients with secondary progressive MS, 40 treated with rituximab and 40 controls. Patients in the rituximab group received at least 4 cycles of treatment (each cycle 1 g rituximab IV, 2 weeks apart), with 2 years of pretreatment and posttreatment follow-up. Patients in the control group had at least 4 years of monitoring on second-line therapies or on no medication. Baseline characteristics were relatively similar between the 2 groups; disease duration was 16.4 and 17.1 years for the rituximab and control groups, respectively. After 2 years of rituximab treatment, the mean change in EDSS score was significantly improved compared with controls ($P = 0.016$). Categorizing response based on the EDSS, 45% of patients treated with rituximab showed improvement, 38% were stable, and 18% progressed. There were no severe adverse events associated with rituximab treatment. Urinary tract infections, fatigue, infusion reactions, rash, bronchitis, headache, serum sickness disease, and nausea were reported in ≥ 5% of patients. These results suggest that B cell depletion may be a beneficial treatment strategy for patients with secondary-progressive MS and worthy of additional study.

ORAL DISEASE-MODIFYING THERAPIES

Fingolimod

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated at a dose of 0.5 mg orally once daily for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[80] Brain volume loss (BVL) is a natural part of aging but is accelerated in patients with MS. Correlations have been reported between BVL and cognitive performance in patients with MS[81] as well as RIS.[82] The rate of BVL in healthy adults has been assessed by several investigators. A meta-analysis of multiple MRI studies in healthy control subjects found that the brain volume is stable until 35 years of age, and decreases by approximately 0.2% per year afterwards.[83] De Stefano et al presented unpublished data at a Neurology conference from a smaller study of healthy adults over a period up to 12 years. Using the Structural Image Evaluation using Normalization of Atrophy (SIENA) algorithm, adults less than 35 years (n = 15) lost brain volume at 0.2% per year while subjects ≥ 35 years (n = 22) lost brain volume at a rate of 0.35% per year. He also referred to several studies of healthy adults who lost brain volume at a rate of approximately 0.24% per year, assessed with the SIENA algorithm.

Patients with MS in the placebo groups from the FREEDOMS and FREEDOMS II studies had BVL of approximately 0.66% per year, while this loss was reduced to 0.44% in the 0.5 mg fingolimod treatment groups.[84] Another way to approach the data is by asking what percentage of the treated patients in these two trials exceeded a threshold of 0.2% BVL per year. This categorical analysis showed that 20.0% of placebo-treated patients lost less than 0.2% of brain volume per year (N = 580) while 29.1% of patients at the 0.5 mg dose and 32.9% of patients at the 1.25 mg dose lost this amount of brain volume (N = 623 and 581; $P = 0.0003$ and $P < 0.0001$, respectively). Analysis with a threshold value of 0.4% gave a qualitatively similar result. Since 0.2% BVL per year is a good approximation of the rate in healthy adults, this threshold approach to BVL could constitute part of a definition of "no evidence of disease activity" that is evolving as a metric for success of MS therapy.

Radue et al reported BVL in three fingolimod studies (FREEDOMS, N = 1272, FREEDOMS II, N = 1083, and TRANSFORMS, N = 1280).[85] They analyzed each patient individually to account for treatment discontinuation by some participants. The TRANSFORMS extension study included IM IFNβ-1a as an active comparator and did not have a placebo arm. All these studies had extension phases where all patients were switched to fingolimod. Their BVL findings are consistent with values reported for the individual studies and support fingolimod's activity in slowing the rate of BVL for patients with MS. The lowest rate of BVL (approximately 0.2% per year) was observed in TRANSFORMS patients who switched from IM IFNβ-1a after 12 months to fingolimod.

A post-hoc analysis of pooled data from FREEDOMS and FREEDOMS II patients who had been treated previously with glatiramer acetate (subgroup GA1) was presented in a poster by Jeffery et al.[86] Seventy-six patients received 0.5 mg/day fingolimod and 90 patients received placebo. High disease activity (GA1-DA) was defined as relapse in the year before screening and with either at least 1 Gd-enhancing T1 lesion or at least 9 T2 lesions at baseline and/or equal or more relapses in this 1 year before screening than 2 years before screening. GA1-DA patients benefited from fingolimod treatment compared to placebo in a number of key measures:

- The ARR was reduced by 53% (0.250, 95% CI: 0.166; 0.376) compared to placebo (0.529; 95% CI: 0.393; 0.712)
- There was a higher proportion of relapse-free patients after fingolimod treatment (68.1%) than with placebo (49.4%, odds ratio: 2.20, $P = 0.042$)
- There was higher proportion of patients free of 3-month disability progression compared to placebo (81.7% vs 64.2%, HR = 0.423, $P = 0.042$)
- All subgroups had highly significant reductions in the number of new/newly enlarged T2 lesions as well as the number of Gd+ T1 lesions at month 24 compared to placebo
- Treatment with fingolimod resulted in a significant reduction in percent change from baseline in normalized brain volume at month 24 compared to placebo in both, group GA1 and subgroup GA1-DA

Fingolimod has been associated with a decrease in heart rate and/or atrioventricular conduction after

the first dose. The FDA-approved labeling includes 6 hours of monitoring for bradycardia after the first dose, and overnight monitoring of patients at risk of bradycardia or heart block or those with a prolonged QTc interval.[80] These cardiovascular effects would be of special concern for patients taking other drugs with similar effects. One example is the selective serotonin reuptake inhibitors (SSRIs) that are used to treat depression and other conditions; bradycardia and prolongation of QT interval have been observed with SSRIs.[87,88] Bermel et al evaluated safety data from phase 2 and phase 3 studies of fingolimod to evaluate first dose effects in patients with RRMS who were receiving concomitant SSRIs.[89] The data set included all patients randomized to receive fingolimod 0.5 mg or 1.25 mg or placebo in the core, controlled phases of all phase 2 and 3 fingolimod studies (FREEDOMS, FREEDOMS II, TRANSFORMS and a phase 2 study). Although the SSRI citalopram is associated with a dose-dependent increase in QTc,[90] the current study found no indication of added effect on QTc interval during treatment initiation in over 400 patients treated with fingolimod and SSRIs. The possibility remains that rare patients may be sensitive to both SSRI and fingolimod effects on QTc.

The 2-year FREEDOMS II study showed that fingolimod reduced the ARR by 48% compared with placebo and increased the percentage of patients free from relapse.[91] A study in Southern California found that African American (AA) women have a higher risk of MS than white women.[92] It has been proposed that African Americans have a poorer response to DMTs than whites.[93] Coyle et al analyzed the FREEDOMS II results for evidence of racial differences in response to fingolimod.[94] There were 77 African American subjects in the study distributed in the placebo, fingolimod 0.5 mg, and fingolimod 1.25 mg groups (n = 28, 24, and 25, respectively). The ARRs were 0.26 and 0.17 in the fingolimod 0.5 mg and 1.25 mg treatment groups, respectively, versus 0.36 for placebo in AA patients. This translates into 29% and 54% relative reductions in the two treatment groups. There were fewer Gd+ lesions in the fingolimod groups than in the placebo group at 6, 12, and 24 months, and a higher proportion of patients were free from Gd+ lesions in the fingolimod groups than in the placebo group at these times. The numbers of new/newly enlarged T2 lesions during months 0–6, 0–12 and 0–24 were lower in the fingolimod groups than in the placebo group and proportionately more patients were free from new/newly enlarged T2 lesions in the fingolimod groups than in the placebo group during each period. The overall incidence of adverse events was similar in the three arms. The authors conclude that the efficacy and safety of fingolimod in African American patients in FREEDOMS II are consistent with results from the overall study population. This study with fingolimod does not support the proposal that African Americans respond differently to DMTs.

Siponimod

Siponimod is an oral sphingosine 1-phosphate receptor modulator being developed for secondary progressive MS (SPMS).[95] In the phase 2 BOLD study siponimod treatment reduced combined unique active MRI lesions (CUAL) up to 80% versus placebo in RRMS patients. The MRI dose-response curve indicated near-maximal efficacy at 2 mg and the ARR was reduced versus placebo (0.20 vs. 0.58; $P = 0.041$).[96] Kappos et al presented a poster with

24-month results of a BOLD dose-blinded extension study.[97] In this phase, BOLD patients continued on the siponimod dose from the core study; patients on placebo were randomized to active treatment groups. The final phase is an open-label extension study where all patients receive siponimod 2 mg. At the end of the core study, the mean number of Gd+ T1 lesions was reduced in all treatment groups. At extension month 24, the mean number of Gd+ T1 lesions was reduced in the higher dose groups. Similarly, the mean number of new/newly enlarged T2 lesions was lower at higher doses. The therapeutic effect appears to plateau at the 1.25 mg dose. Approximately 90% of the subjects experienced adverse effects. Nasopharyngitis and headache were the most common effects and the authors said that in general the treatment was well-tolerated.

Ceralifimod (ONO-4641)

Ceralifimod is also an emerging oral sphingosine 1-phosphate receptor modulator under development for RRMS. The 26-week DreaMS multidose phase 2 study showed positive efficacy results in 2012[98] and a poster presentation by Bar-Or et al shows interim results from the first 26 weeks of the 229 week extension trial.[99] Patients entering the extension study continued on their core study dose of ceralifimod or were randomized from placebo to active treatment (0.05 mg, 0.10 mg, or 0.15 mg per day). During the extension period patients originally on placebo had a decrease in the mean number of new/enlarging T2 lesions and patients continually receiving drug maintained a low number of these lesions. Over the 6-month extension study, ARRs decreased in patients who had switched from placebo to ceralifimod, while patients who had continued on treatment had consistently low ARRs. The safety and tolerability findings were similar to the core study, and approximately 70% of patients in the extension group experienced an adverse event.

A poster presentation by Huang et al described work with the Dark Agouti (DA) EAE rat model.[100] Ceralifimod was administered daily beginning at the peak of disease, 13 days after induction with full length myelin oligodendrocyte glycoprotein in a Complete Freund's Adjuvant emulsion. In vehicle-treated animals, quantitative MRI analysis demonstrated that inflammation and demyelination continued to develop throughout the course of disease, correlating with clinical score. Levels of inflammation and demyelination were reduced to baseline levels in animals treated with ceralifimod. Spinal cord T2 and MT MRI measurements in the DA rats correlated with clinical assessments of the animals.

Teriflunomide

Teriflunomide, an inhibitor of dihydroorotate dehydrogenase (de novo pyrimidine synthesis inhibitor), is an FDA-approved therapy for RRMS with once daily oral dosing at either 7 mg or 14 mg.[101] In a clinical trials plenary session, Miller et al presented data from TOPIC, an international, randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of teriflunomide (7 mg or 14 mg) in patients with a first clinical episode consistent with MS.[102] Patients (n = 618) were randomized to 1 of 3 treatment arms (teriflunomide 14 mg, teriflunomide 7 mg, or placebo), and the core study duration was 108 weeks. The primary endpoint was time to new clinical relapse confirming clinically definite MS

Table 8: Teriflunomide in Patients with CIS: TOPIC Outcomes[102]

Outcome Measure	Teriflunomide (7 mg) [n = 203]	Teriflunomide (14 mg) [n = 214]
Risk for Conversion to CDMS	HR: 0.628 (95% CI: 0.416, 0.949) *P* = 0.0271	HR: 0.574 (95% CI: 0.379, 0.869) *P* = 0.0087
Risk for New Clinical Relapse or MRI Lesion	HR: 0.686 (95% CI: 0.540, 0.871) *P* = 0.0020	HR: 0.651 (95% CI: 0.515, 0.822) *P* = 0.0003
Percent Change from Baseline in Total Lesion Volume	18% vs 28% for placebo *P* = 0.7789	5% vs 28% for placebo *P* = 0.0374
Adjusted Gd+ T1 Lesions	21% RRR vs placebo *P* = 0.4366	59% RRR vs placebo *P* = 0.0008

(CDMS), and a key secondary endpoint was the occurrence of a new clinical relapse or MRI lesion (Gd+ or new T2). The patient demographic and baseline disease characteristics were well balanced among treatment groups. Mean patient age was 32 years, 68% of patients were female, and 59% had a monofocal presentation. Treatment with teriflunomide resulted in a 37% and 43% reduction in the risk for conversion to CDMS for the 7 mg and 14 mg doses, respectively, compared with placebo (Table 8).

Treatment with both doses of teriflunomide was superior to placebo in risk for either new clinical relapse or MRI lesion, and the 14 mg dose was associated with a significantly lower total lesion volume and number of Gd+ T1 lesions per scan compared with placebo. The occurrence of side effects was similar to results observed in other MS clinical trials with teriflunomide; the most common treatment-emergent adverse events occurring at greater frequency in the teriflunomide arms included increased ALT, headache, hair thinning, diarrhea, paresthesia, and upper respiratory tract infection. Overall, these results suggest that teriflunomide may have beneficial effects very early in the MS disease course, as has been demonstrated for IFNβ-1a/1b and GA in patients with CIS.[103,104,105,106,107]

Pooled safety data from 4 placebo-controlled teriflunomide studies (phase 2 proof-of-concept, TEMSO, TOWER, and TOPIC) were presented in posters at a conference in May.[108,109] The combined core studies included data from 1002 patients treated with teriflunomide 14 mg, 1045 patients in teriflunomide 7 mg arms, and 997 patients who received placebo. Overall, this analysis did not identify any new safety signals associated with teriflunomide treatment. Information related to selected adverse events is summarized in Table 9.

Teriflunomide has a Pregnancy Category X rating, and the product label recommends that if a woman becomes pregnant while being treated, teriflunomide should be discontinued immediately and an accelerated elimination procedure implemented.[101] Henson et al presented a poster providing updated pregnancy outcomes in patients and partners of patients in the

Table 9: Teriflunomide Safety Data from Placebo-Controlled Studies[108,109]

Treatment-Emergent Adverse Event	Teriflunomide 7 mg (n = 1045)	Teriflunomide 14 mg (n = 1002)	Placebo (n = 997)	Comments
Hepatic	19.8	21.5	15.2	• Most increases in ALT occurred during the initial 6 months of treatment, then normalized • ALT > 3X ULN occurred in 8%, 7.8%, and 6.6% of patients in the teriflunomide 14 mg, 7 mg, and placebo groups, respectively • Discontinuations due to ALT elevation were infrequent, largely a result of protocol requirements
Hair thinning	10.0	13.9	5.1	• Hair thinning typically occurred in the first 6 months of treatment, and remained low with continued exposure
Diarrhea	13.2	13.6	7.6	• Greatest incidence occurred during the first 3 months of treatment • Most patients did not require corrective treatment
Serious Infections	2.2	2.7	2.3	• 5 serious opportunistic infections were reported (2 for 14 mg teriflunomide, 1 for 7 mg teriflunomide, and 2 in the placebo group) • Infection TEAEs leading to permanent discontinuation occurred in 0.6%, 0.5%, and 0.3% of the teriflunomide 14 mg, teriflunomide 7 mg, and placebo groups, respectively

Values represent %

teriflunomide clinical trial program.[110] Of 1591 female patients randomized to teriflunomide (14 or 7 mg doses), 724 in placebo treatment groups, and 71 treated with IFNβ-1a, 83 pregnancies were reported. Of these 83 pregnancies, 70 were in patients treated with teriflunomide, with fetal teriflunomide exposure reported from 229 to 318 days. Outcomes of the 70 pregnancies in patients treated with teriflunomide were 26 live births, 29 induced abortions, 13 spontaneous abortions, 1 ongoing pregnancy, and 1 outcome unknown. Outcomes for patients in other treatment arms included 2 live births (IFNβ-1a); and 2 live births, 8 induced abortions, and 1 spontaneous abortion in women from placebo-treatment groups. The authors also reported 22 pregnancies in female

partners of male patients from the teriflunomide trials. Of the 18 live births from these pregnancies, 16 were to partners of men treated with teriflunomide. Collectively, there were no structural or functional abnormalities reported in the 42 infants born to mothers or fathers treated with teriflunomide. Pregnancy outcomes are being collected on an ongoing basis through global teriflunomide pregnancy registries.

Dimethyl fumarate

Dimethyl fumarate (DMF, BG-12) was originally used as an anti-inflammatory agent in Europe for treating psoriasis.[111] It has since been investigated for MS and gained FDA approval in 2013 for the treatment of patients with relapsing forms of MS.[112] DMF has immunomodulatory and antioxidative effects. Keap1 is a protein that binds Nrf2, a nuclear transcription factor. DMF modifies Keap1, disrupts the interaction with Nrf2, and permits accumulation of Nrf2 in the nucleus with subsequent up-regulation of antioxidant genes.[113,114] DMF is not a specific agent, and Nrf2 is not the only affected pathway. For example, the side effect of flushing is mediated by the nicotinic acid receptor.

The most common side effects of DMF are flushing and GI symptoms,[115] though the incidence of these effects decreased with ongoing treatment.[111] Tornatore et al speculated that the GI symptoms were related to a transient increase in eosinophil counts during the first 2 months of DMF therapy.[116] They performed a study of 21 patients with persistent DMF-related GI symptoms to see if a leukotriene receptor antagonist would reduce the symptoms. Patients were treated with 10 mg of montelukast each morning. The Gastrointestinal Symptom Rating Scale (GSRS) was used to measure the change in the gastrointestinal symptoms both prior to and one month after the introduction of montelukast. The GSRS questionnaire includes 15 questions, and assess severity of GI symptoms in 5 domains: indigestion, diarrhea, constipation, abdominal pain, and reflux. Most patients improved during the month of treatment: 8/21 patients were symptom free, 8/21 patients had attenuation of symptoms (62% reduction from baseline), and 5/21 patients had no response to montelukast.

DEFINE[117] and CONFIRM[118] were pivotal phase 3 studies of delayed-release DMF. Both trials met their primary endpoints, proportion of patients relapsed at 2 years and ARR at 2 years, respectively. Havrdova et al presented a poster with a post-hoc analysis of these studies looking at the absence of measured disease activity at 6 months, 1 year, and 2 years.[119] This endpoint (aka No Evidence of Disease Activity, NEDA; or Freedom from Measured Disease Activity, FMDA) is receiving considerable interest as a clinical goal as the number, variety, and efficacy of MS therapies increases. Havrdova and colleagues defined overall absence of measured disease activity as meeting all of these criteria:

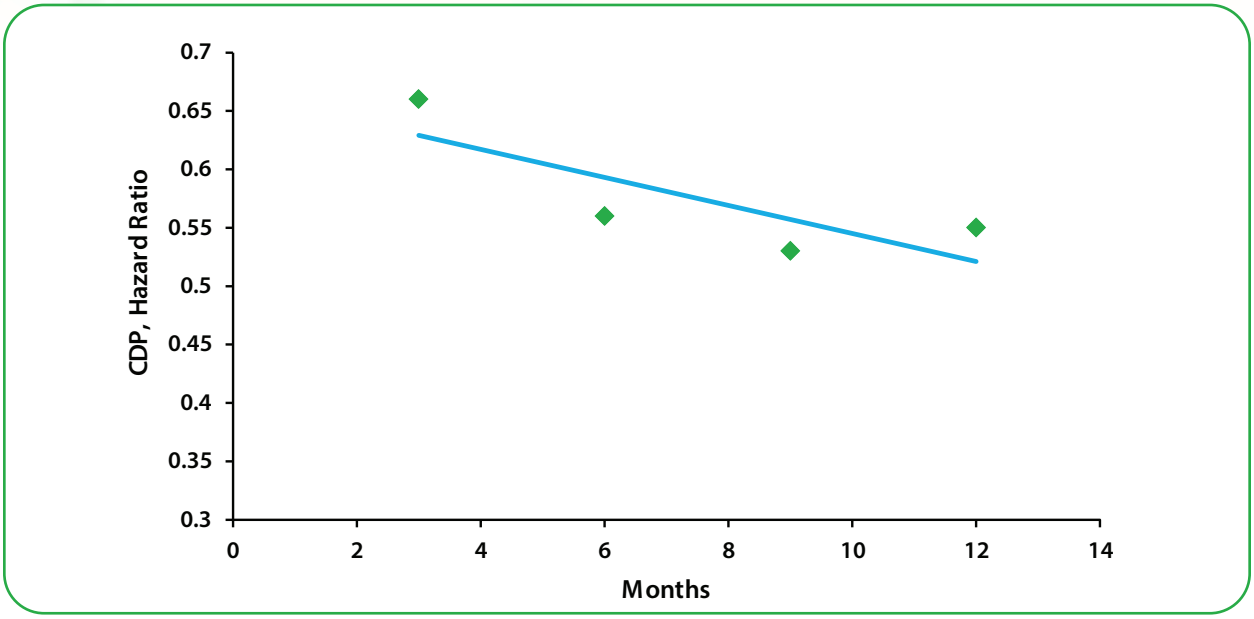
- No relapses (confirmed by an independent neurology evaluation committee)
- No EDSS progression (progression was a > 1.0-point increase in patients with a baseline score of > 1.0 or a > 1.5-point increase in patients with a baseline score of 0, sustained for 12 weeks)
- No brain MRI activity (no new or newly enlarging T2 lesions and no Gd+ lesions)

The ITT population comprised 2301 patients randomized and treated with DMF BID (n = 769), delayed-release DMF TID (n = 761), or placebo (n = 771); the MRI cohort included 1046 patients. Patients treated with DMF were approximately twice as likely to have no measured overall disease activity at 6 months, 1 year, and 2 years, as well as between year 1 and year 2 of treatment. The proportions of patients in the delayed-release DMF BID and TID groups with no measured clinical disease activity at 2 years were 69% and 71%, respectively, versus 53% in the placebo group (both $P = 0.0001$). The proportions of patients with no measured brain MRI activity at 2 years were 34% and 35%, respectively, versus 20% in the placebo group (both $P = 0.0001$). The proportion of patients with no measured overall disease activity at 2 years was 23% for both BID and TID versus 11% in the placebo group (both $P = 0.0001$); and between Year 1 and Year 2 the proportions were 48% and 47% for BID and TID groups, respectively, versus 19% in the placebo group (both $P = 0.0001$). Patients in all subgroups analyzed by demographics and disease characteristics benefited from DMF treatment, compared with placebo. These findings of this combined analysis are similar to individual results of the DEFINE and CONFIRM studies.

Since many MS patients are females of child-bearing age, reproductive safety is of concern for MS therapies. Gold et al presented an overview of reproductive toxicology observations from preclinical animal studies as well as clinical trials with DMF.[120] Rats and rabbits exposed to high doses of DMF had reduced maternal body weight gain. Rat fetal alterations and an increased rate of abortion in rabbits were observed at high doses. These animals received high doses throughout pregnancy, unlike human subjects, so the relevance to treating patients with DMF is unknown. Gold also presented an analysis of humans receiving DMF, including 2665 subjects with MS, 320 subjects with psoriasis, 101 subjects with RA, and 338 healthy volunteers. Postmarketing outcomes from MS patients in the United States, Canada, and Australia were also included. There were 44 pregnancies in DMF clinical trials and 45 pregnancies in women treated with DMF after approval (according to protocol DMF was discontinued after the pregnancy was discovered). Outcomes are known for 38 of these pregnancies. No fetal abnormalities have been reported and three-quarters of the live births were full term. Two of the 13 (15%) of the women receiving placebo in the clinical trials and three of the 44 (7%) of the women receiving delayed-release DMF experienced spontaneous abortions early in the first trimester, rates similar to those reported in the general population.[121] Gold and colleagues concluded that there is no evidence that exposure to DMF increases the rate of fetal abnormalities, adverse pregnancy outcomes, or spontaneous abortion.

EXPLORE[122] was a safety/tolerability study of DMF as add-on therapy for RRMS patients with disease activity currently being treated with IFNβ or GA monotherapy for at least 1 year.[123] Disease activity was defined as at least 1 relapse in the 12 months prior to enrollment or a Gd+ MRI lesion within 6 weeks of enrollment. Approximately 40% of the patients had a prior therapy before the current IFNβ or GA regimen. Patients continued on their prescribed MS therapy for 2 months, then received delayed-release DMF 240 mg 3 times daily (TID) in addition to their prescribed MS therapy for 6 months.

Figure 6: Confirmed Disability Progression (CDP) in the Pooled Analysis of ALLEGRO and BRAVO[125]



One hundred four patients completed the monotherapy period and were dosed with delayed-release DMF/IFNβ (n = 57) or delayed-release DMF/GA (n = 47). During the add-on therapy period the overall incidence of AEs was 95% and 100%; the most common AEs were flushing (42% and 53%), diarrhea (32% and 15%), and abdominal pain (21% and 6%). There were 3 patients with serious AEs (2 in the DMF/IFNβ group and 1 in the DMF/GA group); most AEs were mild or moderate in severity and 14% and 17%, respectively, of the patients discontinued DMF. There was no overall increased risk of infection and no malignancies were reported. Both groups showed a decrease in mean white blood cell and lymphocyte counts, which both remained within normal limits. The authors concluded that the overall safety profile of delayed-release DMF in combination with IFNβ or GA was similar to the known safety profile of delayed-release DMF monotherapy.

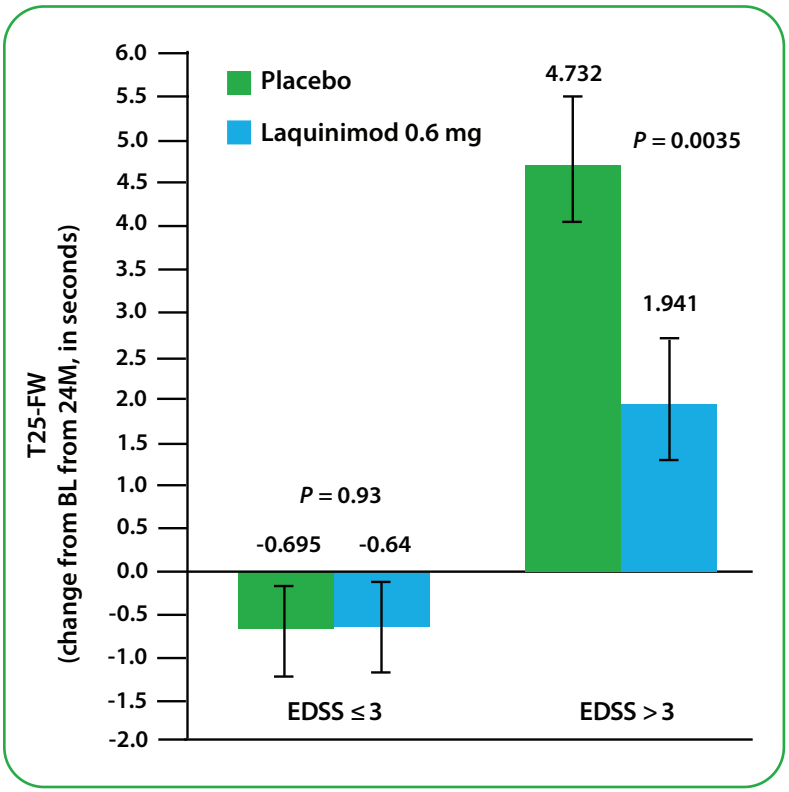
Laquinimod

Laquinimod is an orally available immunomodulatory drug with multiple effects. Laquinimod has been suggested to reduce leukocyte migration into the CNS, modulate B-cell activity, augment T-regulatory cells, and modulate dendritic cells' antigen presentation capacity.[124] Comi[125] presented a pooled analysis of the ALLEGRO[126] and BRAVO[127] phase 3 trials. Laquinimod 0.6 mg was associated with a consistently lower Confirmed Disability Progression (CDP) for one year **(Figure 6)**. Laquinimod reduced whole brain tissue loss over 24 months 30% from 1.19% in the placebo group (n = 1006) to 0.84% in the treatment group (laquinimod 0.6 mg, n = 984, $P < 0.0001$). This protection was evident in white matter, grey matter, and thalamus.[128]

A meta analysis by Sormani et al suggests that CDP can be predicted from the annualized relapse rate.[129] This model predicts that laquinimod's

modest impact on ARR would translate into a 5% reduction in disability progression; the observed pooled risk reduction rate in the 2 trials was actually 29%. In the 1220 patients without relapse during the trials there was a 39% reduction in the rate of CDP with laquinimod (4.8% vs 7.6% with placebo, $P = 0.032$). The reduction was more modest in the 770 patients who experienced a relapse (18.9% with laquinimod, 22.1% with placebo, NS). In the subgroup of 655 patients with baseline EDSS scores > 3, laquinimod had a pronounced positive impact on the T25-FW **(Figure 7)**. The modest effect of laquinimod on inflammatory relapses and its disproportionate effect on disability progression suggest a role for laquinimod in managing progressive forms of MS.

Figure 7: Laquinimod Effect on the Timed 25 Foot Walk Test[125]



Zilkha-Falb et al presented a poster on gene expression in peripheral blood mononuclear cells (PBMC) of 25 RRMS patients in the ALLEGRO trial (half on treatment).[130] Gene expression was performed at baseline and after 1 month and 6 months of treatment. Most informative genes (MIGs) were defined as those that differentiated between groups with $P < 0.01$. Laquinimod suppressed inflammatory cytokine expression as well as gene products involved in cellular adhesion and migration. This effect was observed after one month of treatment in 52 of the 354 MIGs ($P = 0.0003$). Down-regulated genes included integrin family members like ITGB1, 5, 6, and 8 (*P*-values: 1.72E-03- 3.48E-10). After 6 months of treatment 310 of the 1562 differentially expressed MIGs were related to mechanisms of cellular movement, including cell migration and chemotaxis. Laquinimod down-regulated metalloproteinases like MMP16, 24, 26, 28 and integrin family members (ITGB1, 5, 6, 8, ITGA8, and GPIIB-III3). Studies such as this may be useful for characterizing different responses to medication and for differentiating the various mechanisms of drug action. Gene expression could give an early read-out of drug efficacy and help guide treatment decisions.

TREATMENT DISCONTINUATION IN PATIENTS WITH PROGRESSIVE MS

A prospective study presented by Dr. Birnbaum followed 72 patients with progressive MS for at least 1 year following discontinuation of disease

modifying therapy.[131] Patients in Group 1 discontinued treatment on the advice of their physicians and based on > 10 years without evidence of acute inflammatory disease (clinical or MRI activity), and Group 2 were patients who elected to stop disease-modifying therapy on their own (due to treatment-related side effects or for financial reasons). Both groups were largely female (Group 1, 80.6%; Group 2, 90.0%), and the median age was 61.5 years for Group 1 and 50.5 years for Group 2 ($P \leq 0.0001$). The median time on disease-modifying therapy was 10 and 8 years for Group 1 and Group 2 patients, respectively. Of the 62 patients in Group 1, 94% remained stable; patients who worsened in this group were significantly younger than those who remained stable (53.5 years vs 62 years, $P = 0.004$). In contrast, fewer patients in Group 2 remained stable (6/10) and 40% worsened following treatment discontinuation (age was not associated with increased risk for active disease in Group 2). Overall, 89% of this patient cohort were stable following treatment discontinuation, however higher relapse rates were observed in those patients who independently decided to discontinue therapy.

Symptom Management

VITAMIN D

Fatigue is a common symptom of MS, occurring in 30%–80% of patients. Dr. Anat Achiron presented the results of an efficacy trial with the synthetic analog alfacalcidol (1α-hydroxy vitamin D3).[132] Alfacalcidol is hydroxylated in the liver to the active form of vitamin D, calcitriol. A small 6-month pilot study in patients with MS suggested that alfacalcidol had few side effects and may have had a positive impact on relapse rate.[133] In vitro experiments showed that PBMC from MS patients had a lower level of apoptosis than cells from healthy subjects. Stimulation of MS PBMC by vitamin D3 restored the normal level of apoptosis, mainly through an increase of NR4A1 and to a lesser extent BAX, while in cells from healthy subjects both pathways were stimulated.[134] In the current trial 158 patients were randomized to receive alfacalcidol 1 mcg/day or placebo for 6 months. These subjects were selected from 600 random patients from the Sheba MS registry on the basis of a Fatigue Severity Scale question ("Fatigue interferes with my work, family, or social life" answer ≥ 3). Patient fatigue was evaluated with the Fatigue Impact Scale (FIS), a 40-item questionnaire with subscales in physical, cognitive, and social areas. The primary endpoint was the difference in the FIS score between alfacalcidol and placebo groups at 6 months.

Both groups showed improvement (decreases) in the FIS scores, and the treatment group was significantly lower than the placebo group (relative decreases of 41.6% and 27.4%, respectively, $P = 0.007$). Among the secondary endpoints, the change in EDSS was not significant but more patients remained relapse-free in the treatment group (89.5% vs 67.1%, $P = 0.007$). No serious

adverse events were reported in the trial and the frequencies of patients in each group who experienced any adverse event were not different (treatment, 15.8%, placebo, 16.7%). These positive findings are notable as the first prospective therapeutic trial results of vitamin D in MS.

EXERCISE

In addition to evidence that exercise is associated with improvement in physical parameters, recent studies indicate that exercise may also have benefits on cognitive function in patients with MS.[135,136] In a poster, Mandelbaum et al presented the results of a small study of salsa dancing in persons with MS.[137] This pilot study included 8 individuals with MS who participated in a 4-week dance program (dance sessions twice per week, 40 minutes each) and independent physical activities (30 minutes/week). Compared with pre-intervention values, participation in the dance program was associated with significant improvement in 3-month follow-up measures on the Timed Up and Go ($P = 0.05$), Dynamic Gait Index ($P = 0.04$), and MS Walking Scale ($P = 0.05$). The investigators indicated that a larger controlled study of dance intervention for patients with MS is underway.

CONSTRAINT-INDUCED THERAPY

Patients with neurologic disorders who suffer limb disability frequently favor their stronger side, reduce the use of the weaker limb, and thereby exacerbate the disability. Victor Mark presented a small randomized controlled trial of constraint-induced (CI) movement therapy.[138] Core elements of CI therapy include the following:

- Massed practice with the paretic limb 3 hours/day
- Physical restraint to the less-affected arm 90% of waking hours
- Shaping of training exercises (incrementally increased task difficulty)
- Transfer package of behavioral techniques
  - Behavioral contract with patient
  - Home practice assignments
  - Daily activity diary
  - Daily review of activities with therapist, using the Motor Activity Log (MAL)

The MAL is a structured interview where the patient rates the use of the paretic hand. It uses a 0-5 scale covering 30 activities of daily life. MAL has excellent test/retest reliability and has been validated with activity counts with an accelerometer. The reported trial consisted of 20 patients with chronic non-relapsing progressive MS and upper limb hemiparesis who had MAL scores less than 3/5. Patients were randomized to CI therapy or complementary and alternative medicine (CAM), which included a package of aquatic therapy, yoga, relaxation exercises, music therapy, and massage. Patients in the CI therapy group had their less-affected hand restrained in a mitt for the 35 hours of therapy over 10 days. The more-affected hand was used to perform training tasks such as transferring tennis balls between containers under the guidance and encouragement of a therapist. CI therapy resulted in significant improvement in MAL score compared to the CAM group (changes of 2.7 and 0.5, respectively) and all patients in the CI therapy group showed improvement. The CI group showed cortical gray matter growth by 3T MRI voxel-based morphometry ($P < 0.02$) while the CAM group showed no change. These results are consistent with previous findings in stroke patients[139] and children with cerebral palsy treated with CI therapy.

Future Challenges

Ongoing advances in the diagnosis and management of MS are reflected in the research presented at recent neurology conferences. Choice of DMT is a process that must be custom tailored for each individual patient. One of the biggest remaining challenges is that it is still not possible to predict which patient will have an optimal response (ie no relapses and no new or inflammatory MRI lesions) to any one medication. This is an emerging area where biomarkers and genetic information will be very valuable. Other considerations include side effect profile, lifestyle, and comorbidities. Changing to another therapeutic agent when response to the first agent is deemed suboptimal is complicated. In addition to the inability to predict response to any one agent, there are very few head-to-head trials between agents, and therefore comparisons of efficacy may only be inferred. The data on combinations of DMTs as a safe and effective strategy are very limited at the current time, but this may prove to be an effective and feasible treatment approach in the future.

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Notes

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