



eMultipleSclerosis Review VOLUME 1, ISSUE 1

Personalizing DMT Regimens/The Risks of Medication Non-Adherence



Editor's Note: The 67th annual meeting of the American Academy of Neurology provided a platform for important discussions on issues relevant to the treatment of patients with multiple sclerosis (MS). Reports focused on disease-modifying therapies (DMTs) and addressed safety and efficacy considerations. Other reports clearly identified low vitamin D levels as clinical predictors of MS disease progression and provided insights into the range of symptoms reported by patients with MS. Investigations surrounding MRI revealed that processing of data specifically from the infratentorial region yielded fewer false positives (FP) and an improved positive predictive value (PPV) in detecting white matter lesions.

Relapse frequency in early MS is associated with long-term disability. An ad hoc pooled analysis of 2416 patients with MS, using data collected from the FREEDOMS/FREEDOMS II clinical trials,¹ which randomized patients to receive oral fingolimod 0.5 mg or placebo once daily for two years; and the TRANSFORMS clinical trial,¹ which used oral fingolimod 0.5 mg once daily or IFNβ-1a IM 30 μg once weekly for one year, demonstrated that treatment with fingolimod 0.5 mg consistently reduced annualized relapse rates (ARR) compared with placebo and IFNβ-1a in patients with relapse-remitting MS (RRMS). The effect was observed regardless of patients' disease duration and treatment history, which may have important implications for DMT treatment selection early in MS.

Modifiable lifestyle factors such as stress, smoking, and vitamin D levels are important intervention targets for clinicians. The BENEFIT study² showed vitamin D as a predictor of functional deficits in 468 patients, by examining the relationship of serum 25(OH)D concentrations during five years of MS disease progression. It also studied the impact of early versus delayed IFNβ-1b treatment in patients with a first event suggestive of MS. A season-adjusted 25(OH)D was calculated and the 25(OH)D status was characterized using a time-dependent cumulative average. The results showed that the average 25(OH)D levels were associated with higher MS functional composite (MSFC) Z-scores. 50 nmol/L increments were associated with a mean 0.29 higher MSFC Z-score (95% CI: 0.16-0.41, P < .0001). Similar results were observed using quintiles. Over five years, the results support the prognostic importance of vitamin D in patients with RRMS treated with IFNβ-1b.

Symptom management provides both physical and mental relief for patients with MS, because it allows them to function more normally, restoring a sense of control and improving quality of life (QoL). Investigators in Canada³ found that patients with MS who had comorbidities were much more likely to also suffer from pain and fatigue, and identifying and treating comorbidities was essential to avoid life-disrupting symptoms. In 949 consecutive patients from Canadian MS clinics nationwide, 56% had at least one comorbidity, 40% had pain, and the mean DFIS (Fatigue Impact Scale for Daily Use) score was 12.6. Pain that disrupted normal activities was more prevalent in patients with at least one comorbidity (54%) than in those without a comorbidity (30.7%; P < .0001). The mean DFIS score was also higher for persons with at least one comorbidity (15.8) than for those with no comorbidities (10.2; P < .0001). Irritable bowel syndrome, rheumatoid arthritis, and

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fibromyalgia were associated with more disruptive pain. Anxiety, depression, and fibromyalgia were also positively associated with increased fatigue.

Finally, a new study⁴ showed a significant improvement in automated white matter lesion (WML) segmentation from a multichannel MRI that processed the infratentorial region separately, yielding fewer FPs and associated increases in PPV. Using Magnetom® Skyra (Siemens Healthcare GmbH, Erlangen, Germany), with adjustable tissue intensity modeling for different anatomical regions, 20 patients with relapsing (n = 14) and progressive (n = 6) MS, with 12.4 ± 6.4 years' disease duration and EDSS (Expanded Disability Status Scale) scores 2.2±1.8, were examined. The study showed that while infratentorial WML accounted for only 1%-2% of the total lesion burden, the region was responsible for 2%-50% (mean 16% ± 13%) of FPs. The dual-sensitivity approach greatly diminished the number of FPs, and although the overall sensitivity did not change (P = .8), a significant improvement in specificity (P = .0002) was observed and PPV increased by over 50% (P = .0001). Infratentorial lesions predict long-term disability, making reliable morphometry of this region in routine MRI assessments all the more important.

1. Poster P3.248: [Relapse Outcomes in Patients with Multiple Sclerosis Treated with Fingolimod After Previous Treatment with Injectable Disease-modifying Therapies](#). Jacqueline Nicholas, Tobias Derfuss, Daniel Ontaneda, Xiangyi Meng, Kathleen Hawker.
2. Poster P4.014: [Vitamin D as a Predictor of Functional Deficits in Multiple Sclerosis](#). Kathryn Fitzgerald, Kassandra Munger, Mark Freedman, Hans Hartung, David Miller, Xavier Montalban, Gilles Edan, Frederik Barkhoff, Rupert Sandbrink, Ludwig Kappos, Gustavo Suarez, Christoph Pohl, Alberto Ascherio.
3. Poster P1.114: [Comorbidity is Associated with Increased Pain and Fatigue in Multiple Sclerosis](#). Kirsten Fiest, John Fisk, Scott Patten, Helen Tremlett, Christina Wolfson, Sharon Warren, Kyla McKay, Lindsay Berrigan, Ruth-Ann Marrie.
4. Poster P6.116: [Improved Specificity of Multiple Sclerosis Lesion Segmentation from Dual-Sensitivity MRI Morphometry](#). Domonik Meier, Nicola Moscufo, Michele Cavallari, Subhash Tummala, Charles Guttmann, Howard Weiner, Rohit Bakshi

In this Issue...

As the landscape of treatment for MS continues to evolve, clinicians must be aware of the efficacy and safety of newer treatments, strategies for risk stratification, and factors associated with adherence to therapy in order to tailor disease-modifying treatments over the course of the disease.

In this issue, we review recent literature that addresses these issues, including:

- the ADVANCE trial of peginterferon beta-1a
- the TOWER study, the second large, randomized, placebo-controlled trial of teriflunomide in relapsing, remitting multiple sclerosis (RRMS)
- an extension of the FREEDOMS trial, assessing safety and efficacy of fingolimod in RRMS
- a recent study evaluating the utility of the anti-JC virus index to provide further risk stratification for progressive multifocal leukoencephalopathy in the setting of natalizumab administration
- a North American Research Committee on Multiple Sclerosis (NARCOMS) substudy evaluating patient perspectives on switching therapies in MS

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the efficacy of newer disease-modifying therapies (DMTs) for MS.
- Discuss the safety profiles and risks of newly approved DMTs.
- Identify patient perspectives on factors that lead to switching of DMTs.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

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Guest Faculty Disclosure

Dr. Newsome has indicated that he has served as a consultant/advisor for Biogen, Genzyme, and Novartis. He has received grant/research funding from Biogen and Novartis. Dr. Venkatesan has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of his presentation.

Unlabeled/Unapproved uses

The authors have indicated that there will be reference to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

For several decades the "platform" injectable therapies, comprising the non-pegylated interferons and glatiramer acetate, have served as the mainstays of disease-modifying therapy (DMT) for MS.¹ These medications, taken with a frequency ranging from daily to



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once a week and injected either subcutaneously or intramuscularly, have been found to reduce annualized relapse rate by about 30% and have been shown to exhibit favorable long-term safety profiles. However, the relatively modest efficacy of these agents — along with issues surrounding tolerability, side effects, and adherence — has prompted efforts to develop newer treatments. Two new formulations of the platform injectables have been recently approved: pegylated interferon beta-1a, as described by Calabresi et al (reviewed herein), and high-dose glatiramer acetate (GA), based on a recent study that assessed a dosage of 40 mg three times weekly as compared to placebo.² Both newer formulations show efficacy similar to that of the original formulations, allow less frequent injections, and are likely to be used as first-line agents. Although in theory these formulations may be better tolerated, careful long-term studies — several of which are already underway — will be necessary to determine tolerability and adherence and safety.

Over the past 10 years there has been an exponential increase in newer DMTs for MS that have unique mechanisms of action and ease of administration, including those administered by infusion or orally, with several demonstrating increased efficacy when compared head to head with the platform injectable therapies. In general, these newer agents target the inflammatory/immune component of MS and thus either modulate or suppress the immune system with varying degrees of selectivity and potency. Clinicians treating individuals with MS must be aware of the relative efficacy, safety, and side effect profile of these agents to help patients make informed choices regarding starting or switching DMTs. Both the TOWER study by Confraveux et al and the previous large TEMSO trial³ demonstrate that the oral agent teriflunomide is an effective therapy for RRMS, with the 14 mg dose more effective than the 7 mg daily dose. A small phase 3 trial has demonstrated teriflunomide to be at least as effective as interferon-beta-1a⁴, and one phase 2 study has shown that as an add-on to interferon-beta it may have a synergistic therapeutic effect with a reasonable safety profile.⁵ Indeed, the safety profile of teriflunomide appears to be much more favorable than its precursor, leflunomide. As an oral agent with a relatively benign safety profile, it might be predicted that teriflunomide may have better tolerability and adherence than injectables; however, in both TOWER and TEMSO trials, approximately 30% of patients discontinued the trials. Moreover, significant concerns regarding teratogenicity (the drug is pregnancy category X) will likely limit the use of the drug in women of childbearing age. Overall, teriflunomide is a reasonable first-line alternative to the platform injectables and may be more broadly utilized as add-on therapy in the future, but it is unlikely to be the drug of choice in women with childbearing potential.

The report by Kappos et al (discussed in this issue) confirms that fingolimod is also an efficacious oral agent for treating RRMS. Indeed, when compared head to head with intramuscular interferon-beta 1a, fingolimod was superior with respect to annualized relapsed rate and MRI disease activity, although disability progression was similar.⁶ Fingolimod is a sphingosine-1-phosphate (S1P) analog that functionally antagonizes S1P receptors, resulting in sequestration of lymphocytes within lymph nodes with a corresponding decrease in circulating lymphocytes in the peripheral blood.⁷ Because of the presence of S1P receptors in multiple cell types and organs, a number of side effects may occur with treatment, as pointed out in the article reviewed. Side effects such as bradycardia and/or atrioventricular conduction block with the initial dose, macular edema, transaminase elevations, hypertension, basal cell carcinoma, and increased risk of infections including fatal herpes viral infections are well-recognized. Moreover, two cases of PML have been associated with fingolimod in people with MS. Thus, although fingolimod has the benefit of oral administration, its safety concerns warrant a serious consideration of the risks and benefits prior to initiation. In practice, fingolimod is typically used as second-line therapy in patients with high disease activity despite treatment with a platform injectable, or as first-line therapy in severe, rapidly evolving disease.⁸

Almost a decade ago, natalizumab was reported to reduce the annualized relapse rate by 68%, disability progression as measured by EDSS by 42%, and brain MRI activity by 80%-90%, thus positioning it as a highly effective treatment in RRMS.⁹ As a humanized monoclonal antibody directed against alpha4-integrin, natalizumab inhibits lymphocyte migration across the blood-brain barrier, thus limiting CNS inflammation and accompanying relapses but also reducing immune surveillance of pathogens.¹⁰ PML has emerged as the major risk in the setting of natalizumab use, and JCV antibody serostatus is now widely used to stratify a patient's risk for PML.¹¹ Adoption of the JCV antibody

index data, as reported herein by Plavina et al, will allow for more refined risk stratification. Overall, natalizumab is typically used in patients with disease profiles similar to those of fingolimod—in patients with aggressive MS natalizumab is used as a first-line agent, and as a second-line agent it is used in patients with unacceptable breakthrough disease while on first-line treatments. In all patients in whom natalizumab is being considered, current risk stratification tools should inform the treatment decision.

The explosion of newly approved DMTs for MS raises the possibility of truly individualized DMT regimens for patients. Factors such as relative efficacy, side effects, tolerability, and safety are important for physicians to consider. Moreover, an understanding of the patient perspective is critical to allow informed and shared decision-making regarding DMTs. The recently published study by Salter et al discussed herein provides important data on patient perspectives regarding switching DMTs — providing new insight into the role of patients in initiating discussions regarding switching, and highlighting patient concerns such as dislike of injections or infusions, perceived lack of efficacy, and unfavorable side effect profiles as reasons for switching medications. Future studies will undoubtedly capitalize on such approaches to further explore the process of shared decision-making between physicians and patients in the treatment of MS.

Overall, we believe that a reasonable approach to treatment of relapsing MS over the disease course includes, in most individuals, early initiation of agents such as the interferons, glatiramer acetate, dimethyl fumarate, or teriflunomide. Natalizumab can also be considered early if an individual's JCV antibody testing is negative, especially in those patients who are at higher risk for long-term disability. With injectable treatments, if adherence is limited by injection site reactions, then peginterferon or thrice weekly high dose glatiramer acetate can be used. Patients should be monitored for side effects and adherence, and if necessary DMTs should be changed to minimize the former and optimize the latter. If patients develop breakthrough disease while compliant with an injectable treatment or one of the aforementioned oral therapies, consideration should be given to agents such as fingolimod (efficacy of this therapy is considered very similar to that of dimethyl fumarate), natalizumab, or alemtuzumab. These agents should also be considered in those who are naïve to DMT but have evidence of severe, aggressive disease activity at onset. The development of these newer, more potent treatments with significant but often monitorable risks makes the use of mitoxantrone, an agent with potentially severe side effects including leukemia and cardiotoxicity less appealing in our opinion. In all patients in whom natalizumab is being considered, JCV antibody testing should be performed, and the JCV antibody index should be quantified to inform treatment decisions. In patients with further breakthrough disease despite several different treatment trials with the above DMTs, experimental therapies can be considered (to be discussed further in the accompanying podcast). Importantly, the use of more potent agents mandates increased surveillance for opportunistic infections and other side effects.

References

1. Oh J and O'Connor PW. [Established disease-modifying treatments in relapsing-remitting multiple sclerosis](#). *Curr Opin Neurol*. 2015 28:220-229.
2. Khan O, Rieckmann P, Boyko A, et al. [Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis](#). *Ann Neurol*. 2013 73:705-713.
3. O'Connor PW, Wolinsky JS, Confravreux C, et al. [Randomized trial of oral teriflunomide for relapsing multiple sclerosis](#). *N Engl J Med*. 2011 365:1293-1303.
4. Vermersch P, Czonkowska A, Grimaldi LM. [Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial](#). *Mult Scler*. 2014 20:705-716.
5. Freedman MS, Wolinsky JS, Wamil B, et al. [Teriflunomide added to interferon-beta in multiple sclerosis: a randomized phase II trial](#). *Neurology*. 2012 78:1877-1885.
6. Cohen JA, Barkhof F, Comi G et al. [Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis](#). *N Engl J Med*. 2010 362:402-415.
7. Massberg S, von Andrian UH. [Fingolimod and sphingosine-1-phosphate--modifiers of lymphocyte migration](#). *N Engl J Med*. 2006 355:1088-1091.
8. Sorenson PS. [New management algorithms in multiple sclerosis](#). *Curr Opin Neurol*. 2014 27:246-259.
9. Polman C, O'Connor PW, Havrdova E, et al. [A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis](#). *NEJM*. 2006 354:899-910.
10. Bielekova B and Becker B. [Monoclonal antibodies in MS](#). *Neurology*. 74 S31-40.
11. Chalkley JJ and Berger JR. [Progressive multifocal leukoencephalopathy in multiple sclerosis](#). *Curr Neurol Neurosci Rep*. 2013 13:408.

PEGYLATED INTERFERON BETA-1A IN RRMS

Calabresi PA, Keiseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol*. 2014 13:657-665.



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The non-pegylated beta interferons, along with glatiramer acetate, have been the mainstays of first line treatment for RRMS for over two decades because of their proven track records of safety and efficacy. However, associated side effects including flu-like reactions and local injection site reactions, along with perceived poorer compliance of injectable medications than to oral formulations, have had a negative impact on patient compliance and adherence.¹ Thus, recent efforts have focused on improving formulations of the injectable medications to optimize tolerability and compliance.

The covalent linkage of polyethylene glycol to bioactive molecules, termed pegylation, has been known for decades to improve the delivery and bioavailability of therapeutic agents. Pegylation increases the resistance of agents to proteolytic degradation, extends the systemic half-life of the drug, and may result in fewer fluctuations in drug levels. In addition, pegylation may reduce the immunogenicity of a drug, an important consideration for beta interferons, whose efficacy is known to be adversely affected by the generation of neutralizing antibodies.

The ADVANCE trial assessed the safety, efficacy, and tolerability of interferon beta-1a pegylated at the α -amino group of the N terminus of interferon beta-1a, a site that is not involved in binding of interferon beta to its receptor. This formulation had previously been shown to be bioactive in animals, and in phase 1 human studies had demonstrated improved pharmacodynamic and pharmacokinetic properties in healthy people.² Calabresi and colleagues performed a randomized trial in which patients were assigned either placebo or subcutaneous peginterferon beta-1a at a dose of 125 μ g every two weeks or every four weeks. Patients were followed for a total of two years, in which the first 48 weeks were placebo-controlled and the annualized relapse rate (ARR) was used as the primary outcome measure. At 48 weeks, the ARR was substantially lower in both peginterferon groups (0.397 in the placebo group; 0.256 in the peginterferon every two weeks group [P = .0007], representing a 35% decrease; and 0.288 in the peginterferon every 4 weeks group [P = .0114], representing a 27.5% decrease). Several secondary endpoints, including 12-week sustained disability progression at 48 weeks and new or newly enlarging T2 lesions on MRI, also favored the peginterferon group and suggested that the drug was most effective when given every two weeks.

The generation of neutralizing antibodies was also assessed in the study and occurred in less than 1% of patients in either peginterferon group, as compared to 5% in weekly administered non-pegylated 22 μ g interferon beta-1a and over 20% in non-pegylated interferon beta-1a at a dose of 44 μ g administered three times weekly.³ Adverse events were more common in the peginterferon groups compared to placebo, with the most common adverse events including injection-site erythema, influenza-like symptoms, and pyrexia. Leukopenia (defined as less than $3 < 10^6$ white blood cells/mL) occurred more frequently in the peginterferon groups, as did elevations in hepatic transaminases (elevations greater than five-fold of normal occurred in 1% of patients on placebo and 2% of each of the peginterferon groups), although the overall incidence for each was low. Adverse events leading to discontinuation occurred in 5% of each of the peginterferon groups, compared to only 1% of the placebo group.

Overall, these data suggest that peginterferon beta-1a is an effective and viable alternative to the non-pegylated versions of beta interferon, adverse events do not appear to be more common, and the incidence of sustained neutralizing antibodies that could limit efficacy of the drug is lower with pegylation.

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References

1. Nikfar S, Rahmini R, Abdollahi M. [A meta-analysis of the efficacy and tolerability of interferon-beta in multiple sclerosis, overall and by drug and disease type](#). *Clin Ther*. 2010; 32:1871–1888.
2. Hu X, Miller L, Richman S, et al. [A novel PEGylated interferon beta-1a for multiple sclerosis: safety, pharmacology and biology](#). *J Clin Pharmacol*. 2012; 52:789–808.
3. Hemmer B, Stüve O, Kieseier B, et al. [Immune responses to immunotherapy: the role of neutralizing antibodies to interferon beta in the treatment of multiple sclerosis](#). *Lancet Neurol*. 2005; 4:403–412.

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TERIFLUNOMIDE IN RRMS

Confavreux C, O'Connor P, Comi G et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo controlled, phase 3 trial. *Lancet Neurol*. 2014 13:247-256.



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Teriflunomide is a once-a-day, orally administered medication that reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, thereby interfering with pyrimidine synthesis in rapidly proliferating cells such as B and T cells.¹ The proliferation of activated immune effector cells is suppressed by teriflunomide, although homeostatic immune functions such as responses to infection do not appear to be significantly disrupted. In the first large phase 3 study evaluating the effects of teriflunomide in MS (TEMSo; Teriflunomide in Multiple Sclerosis Oral trial), patients were randomly assigned to receive 7 mg or 14 mg daily teriflunomide, or placebo for two years. Teriflunomide (either group) was found to reduce the annualized relapse rate by just over 30% compared to placebo, while progression of disability was reduced by 24% for the 7 mg teriflunomide group and 30% for the 14 mg teriflunomide group compared to placebo.² Based largely on the TEMSo study, teriflunomide was approved by the U.S. FDA for treating adults with relapsing remitting multiple sclerosis in 2012, and approval by the European Medicines Agency soon followed in 2013.

In a recent report in *The Lancet Neurology*, results of the second large randomized placebo-controlled phase 3 trial of teriflunomide in MS are reported by the TOWER trial group. Over 1,000 patients with RRMS were randomly assigned to either daily placebo, 7 mg of teriflunomide, or 14 mg of teriflunomide, and over 800 patients completed the study. Treatment duration was variable (48-152 weeks), since this study ended 48 weeks after the last patient was enrolled. Time from first MS symptoms at enrollment was approximately 7-8 years, and about 70% of enrollees were women. Slightly over 30% of patients had used other MS DMTs in the previous two years, largely accounted for by interferon beta-1a, interferon beta-1b, and glatiramer acetate. Similar to the TEMSo trial, patients receiving teriflunomide experienced a reduction in the annualized relapse rate (22% reduction in the 7 mg daily group [P = .183], and 36% reduction in the 14 mg daily group [P = .0001]). Moreover, sustained disability, as defined by a persistent increase in Expanded Disability Status Scale score, was decreased by approximately 30% in the teriflunomide 14 mg group as compared to placebo (P = .0442). Thus, these findings largely confirmed the results of the TEMSo study regarding efficacy of the 14 mg daily dose.

Notably, the safety profile of teriflunomide was reported as quite favorable. Serious adverse events were equivalent in all groups (about 12%). Elevations in transaminases (defined as greater than one time the upper limit of normal) occurred more frequently in the teriflunomide groups than in the controls, although profound increases (greater than five times the upper limit of normal) occurred at a similar frequency in all study groups. Profound neutropenia occurred in five patients, all in the teriflunomide groups, although all patients were asymptomatic and the neutropenia recovered in several, despite continuing on study treatment. Hair thinning and headache occurred more frequently in the teriflunomide groups, while b infections and serious infections occurred at similar frequencies across treatment groups.

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Overall, the safety profile in both TOWER and TEMSO was found to be far more benign than that of its precursor, leflunomide, a drug mainly used for treating rheumatoid arthritis. Thus, teriflunomide appears to be a safe, efficacious oral medication for the treatment of RRMS.

References

1. Oh J, O'Connor PW. [Teriflunomide](#). *Neurol Clin Pract*. 2013 3:254-260.
2. O'Connor PW, Wolinsky JS, Confraveux C, et al. [Randomized trial of oral teriflunomide for relapsing remitting multiple sclerosis](#). *N Engl J Med*. 2011 365:1293-1303.

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EXTENSION STUDY OF FINGOLIMOD IN RRMS

Kappos L, O'Connor P, Radue EW, et al. Long-term effects of fingolimod in multiple sclerosis: The randomized FREEDOMS extension trial. *Neurology*. 2015 84:1282-1291.



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The arrival several years ago of fingolimod, the first oral disease-modifying drug approved for MS, ushered in a new era in MS therapy. The efficacy of fingolimod was confirmed in three separate double-blind randomized phase 3 trials in patients with RRMS: TRANSFORMS (Trial Assessing Injectable Interferon vs. FTY720 Oral in Relapsing Remitting MS), FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in MS, and FREEDOMS II.¹⁻³ In all three trials, fingolimod significantly reduced the annualized relapse rate (ARR) with respect to the comparator group; in FREEDOMS, the comparator group was placebo, while in TRANSFORMS the comparator group was interferon beta-1a. Moreover, MRI outcomes, including number of new or enlarging T2 lesions, gadolinium-enhancing lesions, and brain atrophy were improved in the fingolimod 0.5 mg group compared to the comparator group. Kappos et al now report on an extension of the FREEDOMS trial, in which longer-term efficacy, safety, and tolerability of fingolimod in patients with RRMS are characterized.

For the extension trial, patients who received fingolimod continued on the same blinded dose (continuous group), while those who had received placebo were rerandomized to either fingolimod 0.5 mg or 1.25 mg daily (switch groups). Of the 1272 patients randomized in the original FREEDOMS study, 1033 were eligible for the extension study; 920 patients entered the extension study, and 773 of these patients completed the study. Although the time spent in the extension trial varied by patient enrollment date, over 90% completed 12 months of treatment in the extension, while just under half (44%) reached 24 months. Principal conclusions of the study were: 1) ARR in the continuous fingolimod groups was lower than in the switch groups; and 2) in the switch groups, ARR was reduced after the extension as compared to before the extension phase. Additional findings included less brain volume loss in the continuous fingolimod group than in the switch groups, as well as fewer new or newly enlarged T2 lesions or gadolinium-enhancing T1 lesions in the continuous group. The most common adverse events included nasopharyngitis, upper respiratory tract infections, lymphopenia, headache, and influenza. Adverse events that led to discontinuation of the study drug, including lymphopenia, elevations in hepatic transaminases, basal cell carcinoma, and dyspnea, were rare with each occurring in less than 1.4% of patients in any treatment group. Notably, there were three instances of macular edema, none of which was classified as serious; symptomatic first-dose bradycardia was observed in two patients; and there were no deaths.

Overall, both efficacy and safety signals were similar to those observed in prior studies, thus confirming fingolimod to be a useful option as an oral therapy for MS albeit with potentially serious side effects that need specific monitoring.

References

1. Cohen JA, Barkhof F, Comi G, et al. [Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis](#). *N Engl J Med*. 2010 362:402-415.

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2. Kappos L, Radue EW, O'Connor P, et al. [A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis](#). *N Engl J Med*. 2010 362:387-401.
3. Calabresi PA, Radue EW, Goodin D, et al. [Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis \(FREEDOMS II\): a double-blind, randomized, placebo-controlled, phase 3 trial](#). *Lancet Neurol*. 2014:545-556.

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NEW STRATIFICATION OF PML RISK IN NATALIZUMAB-TREATED PATIENTS

Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 2014 76:802-812.



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Natalizumab has been shown to be a highly effective treatment for patients with relapsing-remitting multiple sclerosis, reducing the rate of clinical relapse by 68% and resulting in 92% fewer lesions than in the placebo group in the pivotal AFFIRM trial.¹ However, it is well-recognized that treatment with natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an infection caused by the JC (John Cunningham) virus that can result in substantial morbidity and mortality and for which there is no specific treatment.² In recent years, extensive effort has been devoted to stratifying patients for PML risk treated with natalizumab. Prior immunosuppressant use, duration of natalizumab treatment, and presence of antibodies against the JC virus in serum or plasma using a two-step enzyme-linked immunosorbent assay (ELISA) have been shown to stratify such a risk.³

The current study aimed to address the question of whether the risk of PML in JCV AB positive patients could be further stratified by antibody index levels. Plavina and colleagues from Biogen examined the association between the anti-JCV antibody index and PML risk in patients enrolled in clinical studies and from postmarketing settings. Data were available from 71 patients with PML who were treated with natalizumab at least six months prior to the diagnosis of PML and from over 2500 anti-JCV antibody positive patients who did not have PML. Analysis of the data demonstrated that patients who developed PML had substantially higher JCV antibody indices than patients without PML. PML risk estimates were then generated for anti-JCV index levels of ≤ 0.9 , ≤ 1.1 , ≤ 1.3 , ≤ 1.5 , and > 1.5 in patients with no history of prior immunosuppressant use. The authors calculated that an antibody index at or below 0.9 to 1.5 was associated with a risk of PML of about 0.1 per 1000 (1 in 10,000) for the first two years of treatment. For patients who maintained an antibody index level of ≤ 0.9 after two years, the risk of PML increased modestly over time (0.3 per 1000 from months 25-48 [1 in 3333], and 0.4 per 1000 from months 49 to 72 [1 in 2500]). For patients with an index of > 1.5 , on the other hand, the risk was substantially higher; it was calculated to be 1 per 1000 during the first two years of treatment and over 8 per 1000 from month 25 onward (around 1 in 100). Moreover, up to 97% of individuals who were negative for the JCV antibody at baseline either remained negative or, if they converted, had an index value below 1.5.

Overall, this is a very important study because the data presented appear to help further stratify the risk of PML in patients treated with natalizumab who are positive for JCV antibody, thus enabling more informed choices on the part of both patients and physicians with respect to initiation and continuation of the drug. Some important limitations of this study include the relatively short duration of follow-up and the relatively small numbers of patients with PML, thus highlighting the importance of conducting follow-up studies with larger groups of patients and over a longer time. Moreover, the biological underpinnings relating JCV antibody index to PML risk remain to be discovered.

References

1. Polman CH, O'Connor PW, Havrodva E, et al. [A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis](#). *N Engl J Med*. 2006 354:899-910.

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2. Chalkley JJ, Berger JR. [Progressive multifocal leukoencephalopathy in multiple sclerosis](#). *Curr Neurol Neurosci Rep*. 2013 13:408.
3. Bloomgren G, Richman S, Hotermans C et al. [Risk of natalizumab-associated progressive multifocal leukoencephalopathy](#). *N Engl J Med*. 2012 366:1870-1880.

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PATIENT PERSPECTIVES ON SWITCHING DMTS

Salter AR, Marrie RA, Agashivala N, et al. Patient perspectives on switching disease-modifying therapies in the NARCOMS registry. *Patient Prefer Adherence*. 2014 8:971-979.



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The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a voluntary, self-reported registry of patients with MS and comprises predominantly data from people within the United States. Several studies that have used the NARCOMS registry have provided extremely helpful insights into how patients with MS perceive major topics in MS care, including medication risk tolerance, discontinuation of treatments, and the influence of comorbidities on quality of life and overall health.¹⁻⁵

In light of the evolving landscape of DMTs for MS treatment, an understanding of reasons from both physician and patient perspective for switching DMTs is important. To address patients' perspectives, a supplemental survey of NARCOMS registry participants performed in 2011 assessed reasons for switching DMTs and factors that influenced the decisions. The authors' hypotheses were that there would be differences from a clinical and/or sociodemographic standpoint between patients who initiated a switch as compared to those in which the physician initiated a switch, and such differences might depend upon the DMT to which the patient switched. All NARCOMS patients who had reported a DMT switch in 2011 and had a relapsing-remitting course were included in the study. Both primary and secondary reasons for switching were asked for, and choices included the following: Efficacy of medication, Side effects, Safety, Medication tolerance, and Other.

Of the 308 study patients who were ultimately included in the analyses, the majority were female (over 80%), and the averages duration of MS was 14 years. About one-third were taking first-line injectable DMTs (interferons, glatiramer acetate), about one-quarter received infusions (natalizumab, rituximab, alemtuzumab, daclizumab), and about took 40% oral drugs (fingolimod). Most patients had switched from a first-line injectable DMT to their current drug. The discussion to switch originated equally between the patient (49%) and the physician (48.7%), with a few cases in which both answer choices were selected. Although there were no associated demographic or clinical factors, a higher proportion of patients initiated the discussion when switching to an oral DMT. Of the patients who initiated the discussion to switch, adverse effects was the most common reason (39%), followed by perceived lack of effectiveness (33%). Regarding factors associated with the switch itself, physician's recommendation was the most frequently reported main reason (25%), followed by perceived lack of efficacy, dislike of injections/infusions, and side effect profile. Patient-initiated switches were more likely associated with dislike of injections/infusions and drug convenience. Finally, the main reasons for switching among patients with no disease activity were doctor's recommendation (21%) and dislike of injections/infusions (18%), while the main reasons for switching among those with some disease activity were doctor's recommendation (28%) and adverse effects (16%).

Overall, these findings demonstrate that patients play important roles in initiating the discussion to switch DMTs, regardless of sociodemographic factors. Moreover, reasons for switching DMTs were similar, regardless of whether the switch was initiated by the patient or the physician and were dominated by adverse effects or intolerance of medications. In this study population, recommendations provided by treating physicians were a major factor in the choice of DMT.

References

1. Fox RJ, Salter A, Alster JM, et al. [Risk tolerance to MS therapies: Survey results from the NARCOMS registry](#). *Mult Scler Relat Disord*. 2015 May;4(3):241-9.

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2. Fox RJ, Salter A, Tyry T, et al. [Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database](#). *Int J MS Care*. 2013 Winter;15(4):194-201.
3. Marrie RA, Horwitz R, Cutter G, et al. [Cumulative impact of comorbidity on quality of life in MS](#). *Acta Neurol Scand*. 2012 Mar;125(3):180-6.
4. Marrie RA, Cutter G, Tyry T, et al. [A cross-sectional study of bone health in multiple sclerosis](#). *Neurology*. 2009 Oct 27;73(17):1394-8.
5. Marrie R, Horwitz R, Cutter G, et al. [High frequency of adverse health behaviors in multiple sclerosis](#). *Mult Scler*. 2009 Jan;15(1):105-13

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KEY TAKEAWAYS

- Newer formulations and therapies have greatly expanded the choice of disease modifying treatments in multiple sclerosis.
- A variety of factors, including treatment efficacy, side effect profiles and routes of administration, inform a rational approach to MS therapy over the disease course.
- Newer methodologies for risk stratification, such as calculation of JCV antibody index in patients treated with natalizumab, are being developed.

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