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# Abstracts and Insights From AAN 2011: Update on Developments in MS Treatment CME


***Mark S. Freedman, MD***
***Bruce Cree, MD, PhD***
***Amy Perrin Ross, APN, MSN, CNRN***
***Andrew N. Wilner, MD***



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## Goal

The goal of this activity is to discuss recent conference data related to the treatment of MS.

## Learning Objectives

Upon completion of this activity, participants will be able to:

1. Review data on the safety and efficacy of evolving/emerging MS therapies
2. Evaluate a patient's risk tolerance to aid treatment initiation or modification
3. Assess early treatment to slow disease progression
4. Identify factors that may hinder or promote treatment adherence

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## Authors and Disclosures

## Author(s)

**Mark S. Freedman, MD**
Professor of Neurology, University of Ottawa; Director, Multiple Sclerosis Research Unit, The Ottawa Hospital, General Campus, Ottawa, Ontario, Canada

Disclosure: Mark S. Freedman, MD, has disclosed the following relevant financial relationships:
Received grants for clinical research from: Bayer HealthCare Pharmaceuticals; Genzyme Corporation; EMD Canada
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## Author(s)

**Bruce Cree, MD, PhD**
Assistant Professor of Clinical Neurology, University of California, San Francisco

Disclosure: Bruce Cree, MD, PhD, has disclosed the following relevant financial relationships:
Served as an advisor or consultant for: Biogen Idec Inc.; sanofi-aventis; Genzyme Corporation; Teva Pharmaceuticals USA
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**Amy Perrin Ross, APN, MSN, CNRN**
Neuroscience Program Coordinator, Loyola University Health System, Oakbrook Terrace, Illinois

Disclosure: Amy Perrin Ross, APN, MSN, CNRN, has disclosed the following relevant financial relationships:
Served as an advisor or consultant for: EMD Serono, Inc.; Pfizer Inc.; Novartis Pharmaceuticals Corporation; Bayer HealthCare Pharmaceuticals; Teva Pharmaceuticals USA; Genzyme Corporation; Acorda Therapeutics, Inc.; Questcor Pharmaceuticals, Inc.; Allergan, Inc.

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**Andrew N. Wilner, MD**
Neurohospitalist, Lawrence and Memorial Hospital, New London, Connecticut

Disclosure: Andrew N. Wilner, MD, has disclosed the following relevant financial relationships:
Owns stock, stock options, or bonds from: GlaxoSmithKline

Dr. Wilner does intend to discuss **off-label** uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

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Scientific Director, Medscape LLC

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Scientific Director, Medscape LLC

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## CME Reviewer

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CME Clinical Director, Medscape, LLC

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## Intoduction

Multiple sclerosis (MS) is an autoimmune disease that occurs in genetically susceptible individuals exposed to specific environmental triggers. Approximately 85% of patients suffer from relapsing-remitting MS.[1] However, this descriptive term is misleading because ultimately signs and symptoms of MS tend to progress, highlighting the need for prompt and consistent therapy. Early treatment has been advocated, including for clinically isolated syndrome (CIS), often a precursor to MS.

Until recently, the only US Food and Drug Administration (FDA)-approved treatment options for initial therapy for MS have been injectable beta interferons and glatiramer acetate. These treatments boast a long, proven safety record without life-threatening adverse events, but they may be associated with nuisance symptoms such as fatigue, fever, and myalgias. Patient acceptance and adherence to injectable therapy has been less than optimal. Although most patients submit to conventional treatment for lack of a better alternative, some patients eschew needle-based therapy altogether. The lack of more effective, better-tolerated therapy has unfortunately led many people with MS to seek alternative and potentially dangerous treatments such as venoplasty for possible chronic cerebrospinal vascular insufficiency.

The first oral agent for MS, fingolimod, received FDA approval in 2010, and at least half a dozen new molecules, both oral and parenteral, are racing toward FDA approval. Attendees at the American Academy of Neurology (AAN) 63rd Annual Meeting witnessed the release of phase 3 clinical trial data for laquinimod and teriflunomide: 2 promising oral disease-modifying monotherapy agents. These therapies were effective for both clinical and MRI endpoints. In addition, phase 2 results from a trial of intravenous (IV) ocrelizumab, a humanized anti-CD20 monoclonal antibody, demonstrated a high proportion of relapse-free patients at 48 weeks, although treatment was associated with 1 patient death due to brain edema. Results of studies of a third oral agent, BG-12, have recently been announced via a press release.

In addition to these drugs, the following report includes data on several other medications that have not yet been approved by the FDA.

**In your opinion, which of the following is the most significant barrier to patients' adherence to existing disease-modifying therapies (DMTs) for MS?**

- Mediocre efficacy of the existing DMTs
- Risks for serious side effects among the more potent DMTs
- Reluctance to use injectable DMTs for the long term
- Poor understanding of the risks of delaying treatment for MS
- Unrealistic expectations of treatment leading to disappointment in efficacy of DMTs
- Physical inability to inject medications
- Cannot always remember to take/inject because of busy schedules

**In your opinion, which of the following characteristics is most important in a new DMT for MS?**

- Oral administration
- Mild side effects
- Superior efficacy
- Infrequent dosing

## Emerging Therapies for MS

### Oral Therapies

Teriflunomide, a new oral disease-modifying agent administered once daily, is a dihydroorotate dehydrogenase inhibitor that blocks pyrimidine synthesis in T and B cells. It also inhibits protein tyrosine kinase and cyclooxygenase-2 and decreases the ability of antigen-presenting cells to activate T cells.[2] In the recently completed randomized, double-blind, placebo-controlled TEMSO trial, teriflunomide reduced annualized relapse rate at both trial doses compared with placebo: placebo (0.539), 7 mg (0.370, 31.2% relative risk reduction), and 14 mg (0.369, 31.5% relative risk reduction) ($P = .001$ for both doses vs placebo).[3] TEMSO included 1088 patients (18-55 years of age) with relapsing MS who were followed for 108 weeks. Inclusion criteria were an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 and ≥ 1 relapse in the previous year or ≥ 2 in the previous 2 years. Disability progression at 12 weeks was reduced only in patients who received the 14-mg dose ($P = .0279$). The higher dose also reduced the burden of disease (total lesion volume) by 67% ($P = .0003$). On average, treatment with teriflunomide reduced relapse rates from 1 every 2 years to 1 every 3 years. One in 4 patients were free of gadolinium-enhanced T1 lesions at 108 weeks, and 1 in 10 patients were progression free.

A subgroup analysis that characterized patients by baseline demographics (age, race, sex) and disease characteristics (EDSS, number of relapses, MS subtype, MRI parameters, and prior treatment) did not find significant differences in the annualized relapse rate or risk for disability progression between subgroups.[4] Both doses reduced the mean change from baseline in z4 score (sum of individual z scores derived from gadolinium-enhancing T1 lesion volume, burden of disease, T1 hypointense lesion volume, and proportion of parenchymal intracranial content) over the 108 weeks relative to placebo ($P = .0008$ for 7 mg and $P < .0001$ for 14 mg).[5] In addition, the 14-mg dose significantly reduced the mean loss from baseline volume of white matter compared with placebo: (+) 2.406 for 14 mg vs (-) 3.741 for placebo ($P = .0002$). The change in volume of grey matter from baseline was similar in all 3 groups. The number of adverse events, serious adverse events, and adverse events leading to study discontinuation were similar in both the treatment and placebo groups, including serious infections or hepatic disorders.[3]

Giancarlo Comi, MD, Director, Department of Neurology, Scientific Institute San Raffaele, Milan, Italy, presented the results of ALLEGRO, a phase 3, double-blind, 2-year, randomized study of oral laquinimod 0.6 mg/day vs placebo. The study included 1106 patients between the ages of 18 and 55 years with relapsing-remitting MS and an EDSS ≤ 5.5.[6] Five hundred fifty patients were randomly assigned to laquinimod with 437 (79%) completing the study, and 556 patients were randomly assigned to placebo with 427 completers (77%). Compared with placebo, the annualized relapse rate was reduced by 23% in patients taking laquinimod ($P = .0024$) with a 36% reduction in rate of sustained disability progression ($P = .0122$). On MRI, the laquinimod group had a 37% decline in gadolinium-enhancing lesions ($P = .003$), a 30% decrease in new T2 lesions ($P = .0002$), a 27% decrease in new T1 hypointense lesions ($P = .0039$), and a 32.8% reduction of brain volume loss relative to placebo ($P < .0001$). In regard to adverse events, abdominal pain was more frequent in the patients receiving laquinimod (5.8%) than those taking placebo (2.9%). Liver enzyme elevations occurred in 32.4% of the laquinimod group vs 21.6% of the placebo group.

Liver enzymes were elevated during the first few months of treatment. Risk factors predisposing to liver toxicity could not be identified. Laquinimod was discontinued if liver function tests were > 5 times the upper limit of normal on 2 separate occasions 2 weeks apart. No patients in the laquinimod group had overt liver failure, and no patients in the laquinimod group died; 2 patients in the placebo group died, unrelated to the study. Of the laquinimod group, 7.6% discontinued the study due to adverse events compared with 5.8% of the placebo group. A second phase 3 study, which includes an interferon beta-1a comparison arm, is ongoing with results expected later in 2011.[7]

**Of the following choices, which do you think is the greatest unmet need in MS therapeutics?**

- Treatment of patients with primary progressive MS
- Treatment of women with MS who are pregnant or want to become pregnant
- Treatment of patients with MS that is unresponsive to existing therapies
- Development of a neuroprotective therapy for patients with MS
- Development of a preventive therapy for patients at risk for MS
- Development of a DMT that is both safe and effective

## Monoclonal Antibodies

Ocrelizumab, a humanized anti-CD20 monoclonal antibody, has a similar mechanism of action to rituximab. In the phase 2, 48-week study of 220 patients with relapsing-remitting MS, IV ocrelizumab was administered at doses of 600 mg and 2000/1000 mg.[8] During the first 24 weeks, patients received 2000 mg, and during the second 24 weeks, they received 1000 mg. This was a 4-armed trial: Three arms were double blind (placebo, ocrelizumab 600 mg, and ocrelizumab 2000/1000 mg), and the interferon beta-1a (30 µg/week) arm was open label. At week 48, 80% of the patients taking ocrelizumab 600 mg and 72.7% taking 2000/1000 mg were relapse free. During the last 24 weeks, the efficacy of placebo and interferon beta-1a was similar. Between weeks 24 and 48, rates of serious adverse events in each group were: 1.9% (placebo), 2.0% (600 mg), 4.3% (1000 mg), and 6.0% (interferon beta-1a). Infusion-related events were more common on first exposure to ocrelizumab. One patient on ocrelizumab died at 14 weeks due to brain edema after occurrence of a systemic inflammatory response syndrome. No opportunistic infections were reported.

Enrollment has begun for ORATORIO: a 120-week, phase 3, double-blind, randomized, placebo-controlled trial of ocrelizumab for patients with primary progressive MS. This 24-week trial will consist of 5 treatment cycles of IV ocrelizumab 600 mg.[9] Eligible patients must be between 18 and 50 years of age, have an EDSS between 3 and 6.5, have positive oligoclonal bands or an elevated immunoglobulin (Ig)G index, have Functional Systems Scores of ≥ 2 for pyramidal symptoms of the lower extremities, and have a disease duration of < 15 years for patients with an EDSS > 5 or disease duration < 10 years for patients with an EDSS ≤ 5. The primary outcome measure is time to onset of sustained disability progression over the treatment period. Sustained disability progression is defined as an increase in EDSS score sustained for > 12 weeks. Anticipated enrollment is 630 patients from 210 countries.

Daclizumab is a humanized monoclonal antibody specific for the interleukin-2 receptor alpha chain. Investigators reported a trial[10] of daclizumab in 2 adolescent patients (15- and 17-year-old girls) with highly active MS that was unresponsive to other immunotherapies. The first patient had the onset of MS at 12 years of age and 53 contrast-enhancing lesions on MRI. Previous treatment with IV and oral steroids and glatiramer acetate had failed in this patient. The second patient had MS diagnosed at 15 years of age and had received corticosteroids, glatiramer acetate, interferon, IVIg, and mitoxantrone, with little or no response. Courses of plasmapheresis had produced transient improvements. Both patients received IV daclizumab (1 mg/kg every 4 weeks) for 24 months and experienced complete cessation of relapses and MRI activity with no apparent adverse effects.

Alemtuzumab is another humanized monoclonal antibody that has completed phase 2 trials. In a study[11] of 334 patients with relapsing-remitting MS, the effects of alemtuzumab and interferon beta-1a on visual outcomes were assessed with Pelli-Robson contrast sensitivity. Patients received alemtuzumab 12 or 24 mg/day (2-3 annualized cycles) or interferon beta-1a 44 µg subcutaneously (SC) thrice weekly. Alemtuzumab patients were more likely to have better responses than those treated with interferon beta-1a ($P = .0054$). The probability of sustained improvement at 36 months was 39.3% for pooled alemtuzumab patients vs 27.7% for those on interferon beta-1a.

### Expert Insight and Analysis From Mark S. Freedman, MD

These are exciting times because we now have evidence supporting 4 oral agents — fingolimod, cladribine, teriflunomide, and laquinimod — as potential new therapies for MS; only 2 are licensed in various countries, and only 1, fingolimod, is licensed in the United States. Patients with MS have long sought a reprieve from their injections, and those who have given up completely on them because of adverse events or intolerance will soon have various oral options. In addition, several specialized monoclonal antibody therapies will allow us to treat MS very differently, with alemtuzumab looking much like the treatment of choice as an "induction" agent: one that can be given as, perhaps, a single dose with sustained efficacy lasting for several years. The other, newer, and highly promising monoclonal antibodies, daclizumab and ocrelizumab, are entering phase 3 trials.

Although we are pleased to have alternatives to interferon beta and glatiramer acetate, we nevertheless need to appreciate how safe these latter 2 agents are compared with the newer agents whose long-term safety has not been similarly established. With the exception of low-dose once-weekly interferon beta, which was found to be inferior to fingolimod in the 5-year follow-up of the TRANSFORMS and FREEDOMS studies,[12] and high-dose thrice-weekly interferon beta, which was inferior to alemtuzumab in the study by Balcer and colleagues,[11] we have no indication whether the newer agents are superior to interferon beta or glatiramer acetate. We eagerly await the results of comparator studies that are under way with several of the new agents to enable us to position these various treatments in terms of true benefit to risk.

Your patient is a 38-year-old former book editor who has MS that has been unresponsive to several trials with different injectable and oral DMT regimens. He is unable to walk unassisted and has difficulty feeding himself because of sensory loss in his fingers. He can no longer read because his visual loss and memory problems have made reading more difficult than pleasurable. Suppose there is a treatment that has been proven to show significant symptomatic improvements for similar patients; however, the risk for a fatal complication is about 1 in 3.

**Putting yourself in this patient's shoes, which of the following outcomes do you think would outweigh the potential risk for this fatal complication?**

- Painless death
- Complete cure
- Reversal of disability
- No new disability
- Maintenance of cognitive status

## Determining Risk Tolerance

In order to assess how well patients with MS understand the risks of therapy, which may include serious complications, 10,259 patients in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry's online cohort were asked to participate in a survey.[13] A total of 5446 (53.1%) patients (mean age, 52.7 years; disease duration, 13.9 years; 78% women; 22% men; 74% on therapy; Patient Defined Disease Steps [PDDS] score of 3.2) completed the Web-based questionnaire. The patients were presented with 2 scenarios to assess the logical consistency of patients when making decisions about risks of treatment. The first identified their risk tolerance to completely cure MS, and the second examined their risk tolerance to prevent a 1-step progression of disability on the EDDS. An illogical response was defined as a lower risk tolerance for a cure than to prevent disease progression. On the basis of their responses, 34% responded illogically, suggesting — according to the investigators — a poor understanding of the meaning of risk related to serious complications associated with MS therapies. This group was more likely to be female ($P < .001$) and have higher education ($P < .05$). Age, disability, smoking, and betting behavior were not associated with illogical responses.

The same group of patients also completed a different questionnaire that assessed risk tolerance on the basis of 2 standard gamble paradigms.[14] In the first paradigm, the risk of a cure was pitted against the risk for "immediate painless death." In the other, benefits of natalizumab were opposed to the risk for progressive multifocal leukoencephalopathy (PML). The median risk tolerance was 1:10,000 for both scenarios. Patients who were male or disabled had higher risk tolerance ($P < .0001$ for both). Betting behavior, education, recent relapses, and smoking were not associated with risk tolerance. Only one third of the respondents demonstrated a risk tolerance consistent with natalizumab treatment or a potential cure. Risk tolerance for a cure was higher in those not currently receiving MS treatment ($P < .01$): a group that also had greater disability ($P < .0001$).

In another study[15] conducted from 2007 to 2009, a series of standardized questions in regard to the risk and benefits of new therapies were posed to clinically stable patients with relapsing-remitting MS who were taking interferon beta or glatiramer acetate. Patients were divided into 2 groups: those with disease duration and treatment of less than 5 years (n = 100) or more than 5 years (n = 100). Patients with more than 5 years of disease and who were using self-injectable therapy were more likely to consider new treatments with greater risks and requiring vigilance ($P < .0001$) as well as new oral therapies with significant risk and vigilance ($P < .0001$).

## Natalizumab Risks

A retrospective review of 2150 patients enrolled in the natalizumab (Tysabri®) Observation Program (TOP) revealed no significant difference in infection rates or serious adverse events whether patients were therapy naive or had taken interferon or glatiramer acetate injections or immunosuppressive therapy prior to starting natalizumab.[16] The annualized relapse rate was lowest in therapy-naive patients (0.19); higher in patients treated with interferon beta (0.21), glatiramer acetate (0.24), or both interferon beta and glatiramer acetate (0.30); and highest in patients previously treated with immunosuppression (0.37). Three cases of PML were reported occurring after 23, 27, and 29 infusions. Two cases occurred among 1834 (0.3%) patients who had not previously received immunosuppressive therapy, and 1 case was reported among the 316 (0.1%) who had previously received immunosuppression.

Patients taking natalizumab, a monoclonal antibody directed against alpha-4 integrin, have an increased risk of developing PML, which appears related to the duration of therapy. A retrospective review[17] of 140 patients taking natalizumab for MS compared 25 patients who took a drug holiday for more than 6 months with 22 patients who took natalizumab every other month for more than 6 months. Of the 25 patients on drug holiday, 14 felt worse, and 9 of the 14 received steroids for relapses. Of the 9 MR images available, 4 showed enhancing lesions. Of the 22 patients on alternating-month therapy, 9 felt worse, but only 2 were determined to have relapses and received steroids. Of the 8 MR images available, only 1 showed an enhancing lesion. The study authors concluded that every-other-month therapy was better tolerated than a drug holiday.

A study[18] designed to lay the groundwork for examining whether higher serum concentrations of natalizumab are associated with the risk for PML assessed the kinetic stability of long-term natalizumab therapy. Natalizumab serum concentration increased from 17.30 g/mL at 24 weeks to 31 g/mL at 196 weeks (79%) in 270 patients currently taking natalizumab. Similar results were observed with an increase from 14.9 g/mL at 12 weeks to 25.4 g/mL at 120 weeks (70% increase) in AFFIRM and an increase from 16.6 g/mL at 12 weeks to 33.1 g/mL at 120 weeks (99% increase) in SENTINEL.[18] Higher serum concentrations of natalizumab correspond with higher alpha-4B1 and alpha-4B7 receptor inhibition on the lymphocyte and diminished cell trafficking to the brain and spinal cord. The study authors theorized that greater receptor inhibition may correlate with a higher risk for PML.

## Expert Insight and Analysis From Bruce Cree, MD, PhD

Some MS therapies are associated with serious risks. Mitoxantrone can cause congestive heart failure and promyelocytic leukemia, and natalizumab can cause PML. Because of the serious nature of these complications, these medications typically are used in patients who experienced ongoing disease activity despite treatment with interferon beta or glatiramer acetate. Because mitoxantrone and natalizumab pose a risk for treatment-related death, patients must be adequately informed about their risks in order to make knowledgeable therapeutic decisions. With the development of several new therapies that may carry similarly serious risks, the discussion taking place between patients with MS and their treating physicians about therapeutic risk and benefit will grow in complexity.

Understanding patient risk tolerance will help neurologists better serve their patients. Recent presentations from the AAN annual meeting provided insight into how patients with MS assess risk. Using the NARCOMS registry,[14] patients were asked to balance the risk for immediate painless death with the benefit of a complete cure, defined by reversal of disability and permanent prevention of further disease. The median risk tolerance for this scenario was 1:10,000, meaning that 50% of patients were willing to accept no more than a 1:10,000 risk for death caused by a hypothetical cure. Men and those with greater disability tended to be more willing to accept higher risks. Of interest, only 1 in 3 patients were willing to accept a 1:1000 risk for death for a cure. Given that the overall risk of developing PML associated with natalizumab is approximately 1:1000 and that natalizumab does not actually cure the disease, this study suggests that fewer than 1 in 3 patients with MS is willing to accept the inherent risk of natalizumab.

The companion study[13] examined the logic used by patients with MS to assess risk tolerance. This study found that 1 in 3 patients with MS were more willing to accept a risk for death than an increase in disability: a choice that appears to be illogical. Women and those who had achieved a higher educational level were more likely to make this illogical choice. If taken at face value, this study implies that patients may not accurately assess therapeutic risk. Therefore, neurologists should take extra steps to make certain that their patients fully understand the potential risks of treatments that have possibly fatal complications.
Patients contemplating treatment with natalizumab should be aware that the risk for PML increases with duration of exposure to the agent, peaking during the third year of treatment. In addition, previous exposure to immunosuppressive medications increases the PML risk by approximately 4-fold. Further risk stratification includes testing for prior exposure to the JC virus. It appears that PML risk will be lowest for patients who test seronegative for the JC virus, higher for patients who are seropositive for JC virus, and highest for patients who are seropositive and have been treated with immunosuppressants. Given the complexities of natalizumab risk stratification and the findings from the NARCOMS registry, it seems likely that many patients who fall into the highest-risk strata for PML will not be willing to accept the risk of natalizumab treatment. Furthermore, given that some patients may make illogical risk decisions, neurologists should be aware that communicating the complexities of natalizumab risk stratification could require additional effort. Assessment of the risks and benefit for some of the emerging MS therapies will likely be equally complex.

**Of the following strategies, which do you use to promote/improve adherence in your patients with MS? (Select all that apply)**

- Discuss realistic expectations of therapy, emphasizing that no treatment can work if you do not take it
- Discuss potential side effects so that patients are prepared if they occur
- Count pills or check injection sites
- Keep in close contact with the pharmacist to check prescription refill rates
- Encourage use of a reminder device such as a watch or cell phone alarm to prompt the patient when it is time to take the medication

**When thinking of characteristics of new DMTs, which of the following characteristics do you think is a top priority for your patients with MS?**

- Oral administration
- Mild side effects
- Superior efficacy
- Infrequent dosing

## Early Treatment and Adherence

### Does Early Treatment Improve Outcomes?

The impact of early treatment of MS was assessed in 500 patients who received therapy during more than 3 years of the first 5 years after symptom onset.[19] Of 500 patients, the 254 who received early treatment had significantly better scores on all 3 questionnaires used: the Euro Quality of Life-5D, Patient Health Questionnaire-9, and MS Impact Scale. However, clinician-measured timed 25-foot walk did not differ between the early- and late-treatment groups.

In a population of 88 patients with CIS and 44 healthy controls, 51% of the patients demonstrated grey matter pathology on MRI with magnetization transfer ratio mapping.[20] Lesions were widely distributed throughout the brain: in the limbic cortex (37%), temporal cortex (34%), deep grey matter (32%), cerebellum (30%), frontal cortex (30%), occipital cortex (26%), and parietal cortex (19%). Grey matter pathology was significantly associated with EDSS ($P = .028$) and T2 white matter lesion load ($P = .019$).

In a long-term follow-up international study,[21] the investigators examined 21-year mortality data from 366 of 372 (98.4%) patients who participated in a randomized, placebo-controlled trial of 2 doses of interferon beta-1b (50 µg [n = 125] or 250 µg [n = 124]) or placebo (n = 123). Patients received randomized treatment for a median of 3.8 years (maximum, 5.1) during the trial before licensed treatment became available. After a median of 21.1 years, 81 of the 372 patients (21.8%) had died. Treatment with interferon beta-1b 250 µg resulted in less all-cause mortality compared with placebo ($P = .0272$), with a risk reduction of 39.3%. Similar results were seen in patients who received the 50-µg dose.

In a study of 517 patients with CIS,[22] interferon beta-1a 44 µg administered thrice weekly (n = 171) resulted in a lower 2-year probability of conversion to clinically definite MS (20.6%) compared with once-weekly 44-µg injections (n = 173; 21.6%) or placebo (n = 171; 37.5%). Similarly, the 2-year probability of reaching the McDonald criteria for MS was 62.5% for patients on the thrice-weekly regimen, 75.5% for those on the once-weekly dose, and 85.8% for patients on placebo. Risk reductions vs placebo were 51% in the higher-dose group ($P < .000001$) and 31% in the lower-dose group ($P = .008$). Comparing risk reduction of the 2 regimens, the thrice-weekly dose was superior to once weekly ($P = .009$). In addition, the time to conversion to the McDonald criteria for MS was 310 days in the thrice-weekly group, 182 days in the once-weekly group, and 97 days in the placebo group.

A related study showed that the higher-dosage frequency reduced various measures of MRI activity.[23] Combined unique active lesions, defined as either new T1 gadolinium-enhancing lesions or new/enlarging T2 lesions, and new T1 hypointense lesions were lowest with the thrice-weekly regimen (0.5), higher with once-weekly dosing (0.95), and highest with placebo (2.58). This represented a reduction of 81% for the higher dose and 63% for the lower dose vs placebo ($P < .000001$ for both).

### Adherence

Results from an online survey of 433 (79% female; mean age, 46 years) members of the PatientsLikeMe.com Website revealed that 31% of these patients missed at least 1 dose of their DMT.[24] Barriers to adherence rated as either moderately or extremely important included the following: "Did not feel like taking my medication" (38%); "Too busy" (32%); and "Side effects of the injection" (27%). In addition, 29% had difficulty in grasping or holding the injector. Adherence was more closely related to perceived barriers than with clinical or demographic variables.

In a longitudinal analysis of claims data from September 2005 to September 2010, adherence to injectable disease-modifying agents (beta interferons and glatiramer acetate) declined 14% over 5 years in a population of 132 insured patients (80% female, 64% white, 74% married) with relapsing-remitting MS.[25] At the onset of the observation period, 91 (69%) of the patients were using the injectable therapies. After 5 years, this number fell to 72 (55%). The odds of injectable use declined by 16% each year. Adherence was worse in younger patients ($P < .02$) and nonwhites ($P = .05$).

Another study[26] compared claims data of 558 patients with MS who adhered to their DMTs (medication possession ratio [MPR] ≥ 80%) with claims data from 172 nonadherent patients (MPR < 80%). The trends observed during the 6-year comparison period were that relapses (7.6% vs 11.0%, $P = .1421$) and costs ($8217 vs $7398; $P = .2554$) in the subsequent year were not significantly different between the adherent and nonadherent groups.

New York State Multiple Sclerosis Consortium data from 1700 patients with MS (≤ 4 years from symptom onset) revealed that 35.7% suffered from mild, moderate, or extreme negative mood.[27] In addition, severe/moderate fatigue ranged from 26.2% to 30.3%, with the highest proportion of severe/moderate fatigue occurring in African American women (32.2%). Patient perception of anxiety did not significantly differ between race or sex.

### Expert Insight and Analysis From Amy Perrin Ross, APN, MSN, CNRN

Early treatment with DMTs has consistently been shown in the research literature to reduce MS relapses, MRI activity, and disability. Studies now are moving beyond these clinical parameters to include aspects such as quality of life. The impact of MS on the lives of our patients even early in the disease has become increasingly important. Patients are deciding on therapy options on the basis of many factors, including the effects on their daily lives. The survey[24] results from the Website PatientsLikeMe.com found that nearly 40% of patients chose "Did not feel like taking my medication" as a barrier to treatment adherence. As clinicians, our role is to educate our patients about the benefits of therapy on the disease and possible disease progression.

Despite our best attempts to get treatment started early, patients do not always remain adherent to therapy over the long term. Adherence is described as the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior that results in a desired preventive or therapeutic outcome. One key role for clinicians is to work with patients to establish realistic expectations of therapy. MS is a progressive disease that results in symptoms that may not completely resolve. Despite lingering symptoms, patients should not abandon DMTs but rather look for ways to mediate the impact of those symptoms on their daily lives. As clinicians, we must also be aware of the changing functional limitations that our patients experience. A patient who self-injects without outside support may need assistance during an exacerbation that results in tremor, vision changes, or sensory loss in the hands. Without our awareness and support, nonadherence is likely to increase.

Claims data is one way of evaluating adherence to DMT. Although these studies have shown steady declines in adherence to therapy over time, the numbers may be inflated. Changes in insurance coverage, specialty pharmacy providers, patient preferences, and switching to other DMTs may not be captured in the claims data. These studies do, however, show consistency over time with a reduction in the number of patients on therapy. As clinicians, it is incumbent on us to evaluate the reasons behind this drop and develop strategies to address them.

## Conclusions

Promising new options for the treatment of MS are on the therapeutic horizon, including 3 oral agents (BG-12, laquinimod, and teriflunomide). If approved, 1 or more of these drugs may become options for first-line monotherapy, offering an alternative to the injectable beta interferons and glatiramer acetate and fingolimod. Novel parenteral monoclonal antibody therapies such as alemtuzumab, daclizumab, and ocrelizumab are also in development. A phase 3 trial of ocrelizumab for primary progressive MS, a disease with no approved treatment, is currently enrolling patients.

New information presented by Comi and colleagues suggests that more frequent dosing of interferon beta-1a in patients with CIS delays conversion to clinically definite MS and significantly reduces the number of MRI lesions. The urgency for early treatment is supported by the finding of grey matter pathology in more than half of patients with CIS who were evaluated with magnetization transfer ratio mapping by Pelletier and colleagues. The multinational, 21-year, follow-up study of interferon beta-1b revealed lower mortality for patients taking interferon beta-1b relative to placebo.

The observation by Foley that chronic treatment with natalizumab results in significantly increased serum levels over time raises the tantalizing hypothesis that it is not the duration of natalizumab therapy that dictates the risk for PML, but chronically elevated serum levels. Adjustments in dosing may easily stabilize natalizumab levels and potentially reduce the risk for PML. Dosing strategies for natalizumab such as every other month or drug holidays have not been proven to reduce the risk for PML. Butzkueven and colleagues' analysis of postmarketing natalizumab TOP data failed to identify any particular baseline treatment prior to natalizumab as a significant risk factor for later development of PML. Strategies are needed to reduce the risk for PML in order to allow patients to optimally benefit from natalizumab.

As options for the treatment of patients with MS continue to proliferate, head-to-head trials of the "new vs old," as was seen with the ocrelizumab study and "new vs new," will become more important. The ongoing laquinimod BRAVO study and the CONFIRM trial, which is comparing BG-12 with glatiramer acetate, are examples of such head-to-head studies. The potential for combination therapy also exists, and trials for these would be welcome.

Advances in understanding the heterogeneity of MS may also lead to the identification of patient subgroups who are more likely to respond and/or tolerate specific therapies. To date, however, susceptible populations remain elusive, and none were identified in a subgroup analysis of the TEMSO teriflunomide data. Although treatment choice remains a joint decision between the patient and the physician, at least one third of patients do not truly understand the risks of therapy, emphasizing the need for physician guidance and improved patient education. Barriers to treatment include adverse events, patient attitude, depression, distractions, difficulty managing an injector, and memory loss. The common occurrence of negative mood warrants additional therapeutic attention. Physicians, nurses, other healthcare providers, nonprofit organizations, the pharmaceutical industry, and others must continue the struggle to improve adherence in order for patients to maximally benefit from approved therapies that may improve their quality of life.

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