ABSTRACT

Many patients with multiple sclerosis (MS) will eventually experience significant disease progression and worsening of neurologic function, despite therapy with interferon beta or glatiramer acetate. MS is characterized by considerable patient-to-patient variability in presentation, long-term progression, and response to treatment, making it difficult to identify these patients. Mitoxantrone is the only agent approved for progressive forms of MS. Mitoxantrone was superior to placebo on several outcome measures for patients with worsening MS, and the combination of mitoxantrone and methylprednisolone was more effective than methylprednisolone alone in patients with very active MS. Natalizumab, a monoclonal antibody against a cell-surface adhesion molecule that facilitates the migration of lymphocytes from the circulation to the central nervous system, has also been shown to reduce the likelihood of persistent neurologic deterioration in patients with worsening MS. Pulsed intravenous methylprednisolone, although often used for worsening MS, has no proven effect on MS relapse rates in clinical studies. Agents that are currently being evaluated for worsening or progressing MS in controlled clinical trials include cladribine, teriflunomide, and daclizumab. (Adv Stud Pharm. 2007;4(11):324-329)

IDENTIFYING PATIENTS WITH WORSENING MULTIPLE SCLEROSIS

Multiple sclerosis (MS) typically progresses from an initial state of alternating relapses and remissions (relapsing-remitting MS [RRMS]) to an eventual progressing form of MS that is characterized by a gradual and irreversible decline in neurologic function. The median time to progression to an Expanded Disability Status Scale (EDSS) score of 6 (indicating the need for ambulatory assistance) is approximately 15 years. This suggests that a large proportion of patients will eventually progress to the point in which treatments for relapsing-remitting forms of the disorder are no longer effective. However, it is difficult to identify these patients. MS is a disease that is characterized by significant patient-to-patient variability in clinical presentation, long-term course, and response to disease-modifying therapy, which may reflect the presence of more than one underlying disease process. In addition, disease-modifying therapies may become ineffective at any time point during the course of MS, and it can be difficult to determine the point when therapy is no longer working. Possible measures to identify treatment failure include increased frequency of clinical relapses, increasing severity of relapses, worsening scores on rating scales of disability, cognitive decline, or evidence of increased disease burden or contrast-enhancing lesions on conventional magnetic resonance imaging (MRI). The identification of treatment failure is especially important due to the high cost of MS treatments and the potential for clinically significant adverse events. However, criteria to identify treatment failure are not well defined, and the relative advantages and disadvantages of the available methods to identify progression remain controversial.
**Therapeutic Approach to Suboptimal Responders**

There are several potential approaches to the treatment of patients with suboptimal response to disease-modifying therapy, including increasing the dose of the currently used agent, changing from one formulation to another (e.g., from intramuscular [IM] interferon beta-1a to a subcutaneous formulation), or changing to a different medication. Combination therapy is often used in clinical practice, but the combinations employed are unproven and lack consideration for the different mechanisms of action of the individual therapies and the potential for unpredictable toxicity or drug interactions.

Mitoxantrone is the only medication currently approved for progressive forms of MS. It is specifically indicated for the reduction of neurologic disability and/or the frequency of relapses in patients with secondary (chronic) progressive MS (SPMS), progressive relapsing MS, or patients with RRMS who have significant residual symptoms between episodes. It is not indicated for the treatment of primary progressive MS. Mitoxantrone is an anthracenedione that is used in the treatment of various types of cancer, and that produces several immunosuppressive effects, including disruption of the function of T cells, B cells, and macrophages. A phase II clinical trial of 42 patients with very active MS (24% with SPMS, 76% with RRMS) compared mitoxantrone plus methylprednisolone versus methylprednisolone alone for 6 months. The mean number of relapses was significantly lower with combination therapy than with methylprednisolone alone (7 vs 31; \( P < .01 \)). This finding is probably due primarily to the effects of mitoxantrone in patients with continued relapses. Methylprednisolone alone did not significantly improve the relapse rate. On the EDSS clinical rating scale, combination therapy was associated with significantly greater improvement than methylprednisolone monotherapy (mean improvement of 1.1 point vs mean worsening of 0.3 points with methylprednisolone; \( P < .001 \)).

The phase III Mitoxantrone in MS trial compared mitoxantrone versus placebo for 24 months in 194 patients with worsening MS (46% with SPMS, 54% with RRMS). As shown in Figure 1, the proportion of patients who remained relapse-free over 24 months was greater for patients who received mitoxantrone 12 mg/m² than patients who received placebo (\( P = .004 \)). Patients who received a lower mitoxantrone dose (5 mg/m²) also tended to have a lower relapse rate than the placebo group; this group was included for exploratory purposes, and the statistical significance was not reported. Analysis of data from 124 of the patients who received the US Food and Drug Administration (FDA)-approved dose of 12 mg/m² demonstrated significant improvement with mitoxantrone on a composite endpoint that included individual measures of clinical disability, ambulation, neurologic function, and relapse rate (\( P < .001 \)). This composite endpoint result was largely driven by a reduction in the mean number of relapses (76.77 vs 24.08 for the mitoxantrone and placebo groups, respectively; \( P = .002 \)). Adverse events included mild alopecia, gastrointestinal discomfort, mild febrile episodes, and malaise. Current concerns about mitoxantrone include cardiotoxicity and post-treatment malignancies. Patients with MS receiving mitoxantrone require quantitative testing of cardiac output (multigated acquisition scan and echocardiography) prior to each treatment.

Natalizumab is a monoclonal antibody directed against \( \alpha_4 \) integrin, one component of a leukocyte cell-surface adhesion molecule that regulates interac-
tions between leukocytes and other cells. Blockade of this molecule reduces the infiltration of T cells from the vasculature and into the central nervous system (CNS). Natalizumab is approved as monotherapy for relapsing forms of MS. It was recently evaluated in 2 large, randomized, placebo-controlled, phase III clinical trials for the treatment of worsening MS, with a combined population of more than 2000 patients. In both studies, patients were randomized to natalizumab 300 mg intravenously or placebo infusion once monthly for 116 weeks. In the SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing-Remitting Multiple Sclerosis) trial, natalizumab or placebo was administered in combination with interferon beta-1a IM. Natalizumab was associated with a significant relative risk reduction of 54% in the annualized rate of relapse (P < .001), a 50% reduction in the number of patients with at least 1 relapse (P < .001), and reduction in disability on both the EDSS and the Multiple Sclerosis Functional Composite rating scales (Figure 2). Natalizumab also produced robust reduction in MS activity on MRI, including both the number of gadolinium-enhancing lesions and new or enlarging T2 lesions. In the AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) trial, in which patients were randomized to monotherapy with natalizumab or placebo, natalizumab was associated with significant improvement on several MS outcomes. The percentage of patients with sustained disability on the EDSS rating scale was significantly lower in the group of patients who received natalizumab (Figure 3). The annualized relapse rate was 0.26 relapses per year with natalizumab and 0.81 per year with placebo (P < .001). Natalizumab-treated patients also reported better ratings of physical and mental quality of life. In general, natalizumab was well tolerated by patients, with a low risk of adverse events. No differences were observed in the incidence of severe adverse events between patients who received natalizumab alone versus natalizumab plus interferon beta-1a. During the open-label extension phase of the SENTINEL trial, 2 patients developed a rare and often lethal viral infection of the CNS, progressive multifocal leukoencephalopathy (PML). After a voluntary withdrawal of the medication and a careful survey of treated individuals, no additional infections were discovered. Based on the number of individuals exposed to natal-

Figure 2. SENTINEL Trial

![Figure 2](https://example.com/figure2)

In the SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing-Remitting Multiple Sclerosis) trial, patients with worsening multiple sclerosis (MS) were treated with interferon beta-1a and were randomly assigned to receive placebo or natalizumab. The proportion of patients with sustained progression of MS disability (defined as a worsening of MS disability that persisted for at least 12 weeks) was significantly reduced by the addition of natalizumab (P = .02).


Figure 3. AFFIRM Trial

![Figure 3](https://example.com/figure3)

In the AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) clinical trial of patients with worsening MS, patients were randomly assigned to treatment with natalizumab or placebo. The proportion of patients with sustained progression of disability was significantly lower for patients in the natalizumab group (P = .001).

izumab in clinical trials, the risk of PML is estimated to be 1:1000.\textsuperscript{13} In order to monitor for the development of rare adverse events, including PML, the manufacturer has developed the Tysabri Outreach: Unified Commitment to Health (TOUCH) risk minimization plan. This program includes signed consent by the patient and neurologist, a pretreatment MRI scan, and screening and documentation of the patient’s symptoms before each monthly natalizumab treatment.

Pulsed intravenous methylprednisolone (IVMP) is often used for worsening MS, although there is little evidence that it is effective. Only one well-designed clinical trial has examined the efficacy of this strategy. This 5-year study compared treatment only during MS attacks (pulse therapy) to treatment on a regular schedule (frequency therapy; administered every 4 months for the first 3 years, and then every 6 months for the next 2 years).\textsuperscript{14} No difference was noted in relapse rates or lesion volume using T2-weighted imaging between the 2 groups. The mean EDSS score was significantly lower with pulse therapy than with regular therapy (3.4 vs 1.7 points, respectively; \( P < .001 \)), and pulsed therapy was also associated with a 32% reduction in the proportion of patients with sustained disability (\( P < .001 \)). The change in T1 lesion volume over the course of the study was also significantly less with pulsed therapy than with regular therapy (1.3 vs 5.2 mL; \( P < .001 \)), suggesting that IVMP may have suppressed the conversion of inflammatory lesions to irreversible axonal injury and neurodegeneration.

**INVESTIGATIONAL AGENTS**

Several investigational agents for the treatment of progressing MS are currently being evaluated in clinical trials. Cladribine is a synthetic nucleotide analogue that specifically disrupts DNA synthesis and proliferation of lymphocytes while sparing other cell types.\textsuperscript{15} Phase II clinical trials have demonstrated dose-dependent clinical improvement and MRI evidence of reduced inflammation with intravenous cladribine, with a relatively low incidence of adverse events.\textsuperscript{16-18} Studies of an oral cladribine formulation are in progress. Clinical improvement with cladribine was observed in a clinical trial of patients with SPMS,\textsuperscript{16} but not in a trial that included patients with both SPMS and primary progressive MS (PPMS),\textsuperscript{17} perhaps due to the relative absence of an inflammatory component in patients with PPMS. A second inhibitor of DNA synthesis, teriflunomide, was examined in a recent phase II clinical trial that compared the effects of 2 teriflunomide doses versus placebo on MRI outcomes after 36 weeks.\textsuperscript{19} Both teriflunomide doses produced approximately 60% reduction in the number of new or enlarging T2 lesions per scan (\( P < .03 \)). Teriflunomide was well tolerated, with laboratory elevations of liver enzymes, minor paresthesias, nasopharyngitis, and alopecia.

Daclizumab is an immunosuppressive monoclonal antibody against one component of the receptor for the cytokine interleukin-2 (CD25).\textsuperscript{20} It is currently US FDA approved for acute renal transplant rejection, and it has been shown to reduce neurologic injury in an animal model of MS and 2 preliminary clinical trials.\textsuperscript{21-23} In a study of 10 patients with incomplete response to interferon beta, daclizumab reduced new contrast-enhancing lesions by 78% (\( P = .004 \)), and also improved clinical outcomes compared to baseline.\textsuperscript{21} In the second study, 21 patients with RRMS or SPMS received daclizumab for 5 to 25 months.\textsuperscript{23} Infusion of daclizumab was associated with significantly improved scores on the EDSS disability rating scale (mean improvement of 1.5 points from baseline; \( P < .004 \)), and significant reduction in MRI lesion activity. The annualized relapse rate decreased from 1.03 relapses per year before treatment to 0.32 per year after treatment (\( P < .05 \)). Daclizumab was well tolerated, and was discontinued by only 2 of the 21 patients due to side effects. The most common adverse events included paresthesias, leukopenia, rash, liver enzyme elevation, and upper respiratory infections.\textsuperscript{23}

**CONCLUSIONS**

Most patients with MS will eventually experience increased disease activity, despite ongoing treatment. Clinicians require better methods to identify and treat patients with MS who progress despite therapy. Mitoxantrone is approved for progressing MS, but most of the benefit of this agent in clinical trials appears to be related to a strong reduction in the number of relapses. Natalizumab is approved for worsening or relapsing forms of MS, but may be used at the physician’s discretion for monotherapy in initial forms of relapsing MS for those who are intolerant of injectable therapies. The use of natalizumab in combination therapy or as induction therapy requires further study. No data support the use of pulsed methylprednisolone with the goal of relapse rate reduction. Several new agents are being developed for relapsing or worsening forms of MS.
**DISCUSSION HIGHLIGHTS**

*Dr Guthrie:* I get many questions from patients about low-dose naltrexone. Are any clinical trials coming out soon?

*Dr Tallian:* In the United States, naltrexone is currently being studied in a trial that is blinded right now. At present, it’s a totally unproven therapy. There is a lot of hope that’s engendered by testimonial Web sites that doesn’t ring true for those who are treating patients with MS.

*Dr Guthrie:* What about the statins?

*Dr Bennett:* There are some combination therapy trials in progress. The idea that we can have a highly prescribed drug that we like for one reason that may have benefits for another is appealing. However, the experimental autoimmune encephalomyelitis animal (EAE) model of MS is a highly inflammatory model, and it is easy to see drug effects using that model that are not seen in patients with MS. And, there are drugs such as the anti-TNFα (tumor necrosis factor alpha) drugs or interferon γ that work very well in EAE, but make MS worse.

*Mr Watkins:* Do you ever find it helpful if we restrict use of some of these drugs, for example, in which patients are asking for a treatment based on Internet testimonials but for which really there is no evidence of efficacy?

*Dr Cook:* For example, if we were to put impediments in which we have coverage determinations or preservice review, is it helpful to treating physicians to be able to say, “Not only do I not recommend it, but your plan won’t cover it.”

*Dr Bennett:* I’m not in favor of restrictions of that type. As a physician, I would try to educate other physicians about considering the issue of why they are using a particular drug. If they are using steroids because someone is having a lot of relapses, and they think that this is going to reduce relapse rates, the data would say that they are wrong. If they say, “I’m using it on top of this therapy because it looks like there is a reduction in progression of disability, T1 black hole formation, and I’m treating the progressive form of the disease,” then the data are unclear and possibly in favor. However, for a “hot” patient with MS who is frequently relapsing, the next step in my armamentarium is certainly not the introduction of pulse methylprednisolone. I’m going to switch to something that’s proven to really have a big effect on frequent relapses, as with the addition of an agent such as mitoxantrone. Or, I would consider increasing the dosage of switching single agents. I also have trouble obtaining approval for some treatments that I truly believe have significant benefits and that are supported by data, such as plasma exchange for worsening MS or severe relapses.

**REFERENCES**


