

OPTIMIZING PATIENT OUTCOMES WITH CURRENT AND EMERGING TREATMENTS*

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ABSTRACT

Disease-modifying therapy has been shown to reduce relapses and delay disease progression in patients with multiple sclerosis. This article reviews the 6 agents currently approved for this indication (ie, 3 interferon β products, glatiramer acetate, natalizumab, and mitoxantrone), as well as emerging oral therapeutic options. Several significant clinical trials are discussed, to assess the safety and efficacy profiles of each of these products.

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Designed to slow the progression of MS, disease-modifying therapy (DMT) is considered the mainstay of treatment for individuals suffering from MS. First introduced in 1993, there are currently 6 DMTs approved for the treatment of this disease: 3 interferon (IFN) β products, glatiramer acetate (a biological product), natalizumab (a monoclonal antibody), and mitoxantrone (a chemotherapeutic agent). Each of these agents may be characterized as having immunomodulatory or immunosuppressive properties. Immunosuppressive products (ie, natalizumab and mitoxantrone) alter immune function via direct cytotoxic activity or bone marrow suppression (by either killing cells or decreasing access to the central nervous system [CNS]), whereas immunomodulatory products (ie, IFN β and glatiramer acetate) do so in a non-cytotoxic manner. As such, IFN β and glatiramer acetate are considered first-line therapies, whereas natalizumab is a second-line agent. Due to its toxicity profile, mitoxantrone is generally reserved for worsening or progressive disease.^{1,2}

According to recent recommendations from the National Clinical Advisory Board of the National MS Society, treatment with a first-line DMT should be initiated as soon as possible, following a definitive diagnosis of MS. Because treatment delays disease progression and axonal loss, therapy should be continued indefinitely in the absence of intolerable adverse effects, lack of benefit, or better therapeutic options.³ In addition, corticosteroid therapy should be used to speed functional recovery in patients experiencing acute exacerbations.¹

IFN β PRODUCTS

The IFN β products have been shown to reduce disease activity in patients with relapsing forms of MS, including those with secondary progressive disease

CASE STUDY

RE is a 17-year-old white female who was diagnosed with multiple sclerosis (MS) after magnetic resonance imaging (MRI) scans detected 3 lesions in her brain. Symptoms of numbness and visual disturbances indicate that she is currently experiencing an MS exacerbation. What treatment options are available for RE? Which medication(s) is/are most optimal with regard to safety, efficacy, and ease of administration?

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who continue to experience relapses; they also may delay conversion from clinically isolated syndrome (CIS) to clinically definite MS. These agents reduce MRI disease burden, and also may slow disability progression.¹ They exhibit potent activity at the blood-brain barrier (BBB) and impair the trafficking of inflammatory cells into the CNS, thereby decreasing CNS inflammation. In addition, the IFN β products reduce the activation, expansion, and survival of inflammatory T cells,⁴ and may reduce T-cell migration by inhibiting the activity of T-cell matrix metalloproteinases. Finally, these agents have inhibitory effects on the proliferation of leukocytes and antigen presentation.⁵

Three formulations of IFN β (ie, intramuscular [IM] IFN β -1a, subcutaneous [SC] IFN β -1b, and SC IFN β -1a) are currently available. IM IFN β -1a is a low-dose product (30 μ g administered once weekly), whereas SC IFN β -1b and IFN β -1a are high-dose products (250 μ g and 44 μ g administered every other day and 3 times per week, respectively). Commonly experienced adverse events include menstrual irregularities, injection-site reactions, depression, and flu-like symptoms (which tend to improve over time).⁶⁻⁸ Although many patients prefer the convenience of once-weekly administration, the flu-like symptoms associated with IM IFN β -1a are often more severe than with the other formulations.

Table 1 outlines the findings of 3 pivotal trials designed to evaluate the safety and efficacy of the IFN β

products, in comparison to placebo.⁹⁻¹¹ These studies indicate that the IFN β products reduce the frequency of relapses in patients with relapsing-remitting MS (RRMS) and decrease the probability of developing clinically definite MS in those who are at high risk.⁹⁻¹¹

GLATIRAMER ACETATE

Glatiramer acetate is used to reduce the frequency of relapses in individuals with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with MS.¹² It reduces MRI disease burden and possibly also slows sustained disability progression in patients with RRMS.¹ The immunomodulatory effect of glatiramer acetate may be attributed to its ability to alter T-cell differentiation. Specifically, treatment is believed to promote the development of T-helper 2 (T_H2) cells, which are anti-inflammatory in nature; these cells suppress the immune attack on myelin within the CNS.^{4,13} Additionally, glatiramer acetate is the only DMT with proven evidence of neuroprotection. This agent slows brain atrophy and stimulates T cells to produce brain-derived neurotrophic factor, which protects the brain from axonal damage. It also reduces the formation of chronic black holes, or markers of demyelination/axonal loss.¹⁴

Glatiramer acetate is administered subcutaneously, at a dose of 20 mg once daily. Common adverse events include injection-site reactions, hives, and post-injec-

Table 1. Pivotal IFN β Trials

Name	Agent	Condition	Efficacy Findings	Safety Findings
IFN MS Study Group ⁹	IFN β -1b SC	RRMS	Reduced exacerbation rates; more patients free of relapses over a 2-year period	No serious adverse events
CHAMPS ¹⁰	IFN β -1a IM	Acute clinical demyelinating event and evidence of prior subclinical demyelination	Relative reduction in brain lesion volume, fewer new or enlarging lesions, fewer gadolinium-enhancing lesions at 18 months; reduced probability of developing clinically definite MS over a 3-year follow-up period	Influenza-like syndrome, depression; no serious adverse events attributed to treatment
PRISMS ¹¹	IFN β -1a SC	RRMS	Reduced relapse rate, increased time to first relapse, increased proportion of relapse-free patients, delayed disability progression	Well tolerated

CHAMPS = Controlled High-Risk Avonex MS Study; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; PRISMS = Prevention of Relapses and Disability by IFN β -1a SC in MS; RRMS = relapsing-remitting MS; SC = subcutaneous.

Data from The IFN β Multiple Sclerosis Study Group⁹; Jacobs et al¹⁰; and Ebers and PRISMS Study Group.¹¹

tion reactions (which generally only occur once and subside within 20 minutes). It is crucial for pharmacists to educate patients on the possibility of post-injection reactions, as symptoms (eg, chest tightness, diaphoresis, and dyspnea) may resemble those of a myocardial infarction.¹²

Dr Rich: It may be wise to administer the first injection in the office, in case a post-injection reaction occurs.

Dr Guthrie: Unfortunately, this reaction is not necessarily associated with the first injection and may take place at any time.

A multicenter phase III study of patients with RRMS showed that after 2 years, glatiramer acetate reduced

relapse rates by 29% as compared to placebo. Patients receiving the drug also showed a significant improvement in disability. Treatment was well tolerated; rarely, patients experienced transient, self-limited post-injection reactions.¹⁵ Furthermore, over 80% of patients who continued to receive treatment after 15 years were still able to walk without assistance, and 66% had not yet transitioned to secondary progressive MS.¹⁶

THERAPEUTIC COMPARISONS

Several studies have been conducted to compare these first-line DMTs with one another, and to determine the impact of varying dosage regimens (Table 2).¹⁷⁻²³ Results

Table 2. Studies Comparing First-Line DMTs

Name	Agents/Dosing	Condition	Efficacy Findings	Safety Findings
EVIDENCE ¹⁷	IFN β -1a 44 μ g SC 3 times weekly vs IFN β -1a 30 μ g IM weekly	RRMS	Significantly fewer relapses and active lesions with IFN β -1a SC after 24 weeks	More injection-site reactions, asymptomatic liver enzyme abnormalities, altered leukocyte counts, and neutralizing antibodies with IFN β -1a SC
INCOMIN ¹⁸	IFN β -1b 250 μ g SC every other day vs IFN β -1a 30 μ g IM weekly	RRMS	Significantly fewer relapses and T2 lesions with IFN β -1b after 2 years	More injection-site reactions with IFN β -1b
Clanet et al ¹⁹	IFN β -1a 30 μ g IM weekly vs IFN β -1a 60 μ g IM weekly	RRMS	Equal rates of disability progression after 36 weeks	Higher incidence of flu-like symptoms, muscle weakness, and more neutralizing antibodies with IFN β -1a 60 μ g
BEYOND ²⁰	IFN β -1b 250 μ g SC every other day vs IFN β -1b 500 μ g SC every other day vs glatiramer acetate 20 mg SC daily	RRMS	No difference in relapse rates	More flu-like symptoms with IFN β -1b, more injection-site reactions with glatiramer acetate
REGARD ²¹	IFN β -1a 44 μ g SC 3 times weekly vs glatiramer acetate 20 mg SC daily	RRMS	No significant differences in time to first relapse, number of T2 active lesions, or change in volume of gadolinium-enhancing lesions	Similar between treatments
BECOME ²²	IFN β -1b 250 μ g SC every other day vs glatiramer acetate 20 mg SC daily	RRMS	No significant differences in MRI parameters representing disease activity, or total or new enhancing lesions	—
Haas et al ²³	IFN β products vs glatiramer acetate	RRMS	Relapse rate significantly reduced with glatiramer acetate after 12 and 24 months	—

BECOME = Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3-T MRI Endpoints; BEYOND = Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose; DMT = disease-modifying therapy; EVIDENCE = Evidence of IFN Dose-Response: European North American Comparative Efficacy; IFN = interferon; IM = intramuscular; INCOMIN = Independent Comparison of IFN; MRI = magnetic resonance imaging; REGARD = Rebif vs Glatiramer Acetate in Relapsing Multiple Sclerosis Disease; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.

Data from Panitch et al¹⁷; Durelli et al¹⁸; Clanet et al¹⁹; O'Connor et al²⁰; Mikol et al²¹; Beals²²; and Haas and Firzloff.²³

of the studies by Panitch et al, Durelli et al, and Clanet et al suggest that IFN β products are more effective when dosed more frequently, regardless of dosage strength.¹⁷⁻¹⁹ However, it is important to keep in mind that the formation of neutralizing antibodies may increase with drug dose and frequency; these antibodies may reduce the effectiveness of these products by interfering with their biological activity.²⁴

Dr Lipsy: While the EVIDENCE (Evidence of IFN Dose Response: European North American Comparative Efficacy) trial found that high-dose IFN β therapy was associated with an increased production of neutralizing antibodies, patients receiving high-dose therapy still had better outcomes overall.

Dr Miravalle: On the other hand, some studies suggest that low-dose IFN β therapy has a more favorable impact on brain volume than high-dose therapy; however, such studies were not powered to assess brain volume.

The majority of studies comparing IFN β products with glatiramer acetate found that these agents are similar in efficacy, and that both are generally well tolerated. Thus, any of these products may be a suitable first-line option for patients diagnosed with MS.²⁰⁻²³

CASE STUDY (cont'd)

RE's neurologist opted to place her on IFN β -1b 250 μ g SC every other day. Two years later, she has had no new lesions on MRI and no new symptoms of MS. However, she has been experiencing minor flu-like symptoms from her medication. Is RE a candidate for second-line therapy?

NATALIZUMAB

Natalizumab is a monoclonal antibody used to treat relapsing forms of MS, to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations.²⁵ It prevents leukocyte transmigration through the BBB, resulting in diminished inflammatory activity.²⁶ Natalizumab is administered intravenously every 4 weeks, at a dose of 300 mg. Infusion reactions (eg, rash, drowsiness, fever, nausea, flushing, chest pain, and hypotension), which generally occur within 2 hours of the start of the infusion, are quite common. However, these reactions typically subside when the medication is stopped or the patient is treated with diphenhydramine or epinephrine.

Natalizumab also has a black box warning for progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.²⁵ As of May 6, 2010, 49 cases of PML (and 11 deaths) have been reported among patients treated with this agent.²⁷ Thus, natalizumab is only indicated for patients who have inadequate responses to or are unable to tolerate first-line DMTs.²⁵ Moreover, the product is only available through a restricted distribution program known as TOUCH (Tysabri Outreach: Unified Commitment to Health). According to the TOUCH prescribing program, only prescribers and patients enrolled in the program may prescribe and receive natalizumab, and only certain pharmacies and infusion sites authorized by the program may dispense and infuse this medication. Additionally, patients must be evaluated 3 and 6 months after the first infusion, and every 6 months thereafter.²⁸

Natalizumab was initially approved based on the results of 2 pivotal trials. The AFFIRM (Natalizumab Safety and Efficacy in RRMS) study found that at 2 years, this agent reduced the relapse rate in patients with RRMS by 68%, relative to placebo. Additionally, a sustained progression of disability was significantly less likely among patients receiving natalizumab.²⁹ The SENTINEL (Safety and Efficacy of Natalizumab in Combination with IFN β -1a in Patients with RRMS) study evaluated the addition of natalizumab to IFN β -1a SC in patients with relapsing MS who continued to experience disease activity. Combination therapy resulted in a 54% reduction in the rate of clinical relapses at 1 year; 2 cases of PML occurred in patients treated with natalizumab.³⁰

Dr Miravalle: Some data suggest that infection with the JC virus may place patients at an increased risk of developing PML. As such, 2 clinical trials are being conducted to evaluate JC virus serology in patients being treated with natalizumab.

Dr Guthrie: Yes, research is currently under way. In addition, natalizumab should only be used as monotherapy because the theoretical risk of PML increases when it is combined with another immunomodulatory agent.

Dr Miravalle: This is controversial, and there have been many cases of PML with monotherapy as well.

Dr Rich: From a payer perspective, supporting literature would be required to approve combination therapy.

MITOXANTRONE

Mitoxantrone is a chemotherapeutic agent indicated for patients with secondary progressive, progressive relapsing, or RRMS. It has been shown in vitro to inhibit B-cell, T-cell, and macrophage proliferation and impair antigen presentation. Due to its toxicity profile (eg, cardiotoxicity and leukemia [$\sim 1/145$]), mitoxantrone should not be used early in the course of disease.^{1,31}

CASE STUDY (cont'd)

RE is not a candidate for second-line therapy with natalizumab because she is responding well to IFN β therapy, and her flu-like symptoms are mild. She would like to know about emerging oral medications for the treatment of MS.

EMERGING THERAPIES

RITUXIMAB

In addition to T-cell-mediated inflammation, there is now increasing evidence that autoimmune B cells and humoral immune mechanisms also play key roles in the pathophysiology of MS. As such, rituximab, a monoclonal antibody that depletes B cells, may be an option for treating RRMS. Indeed, a recent phase II study evaluating this agent found that fewer patients receiving rituximab experienced relapses, as compared to placebo; these individuals also had reduced counts of total gadolinium-enhancing lesions over a 48-week period. Infusion-related adverse events were mild to moderate in nature.³²

ORAL AGENTS

Compliance with parenteral medications is often suboptimal, due to the inconvenience of medication administration. Fortunately, many oral therapies, including cladribine, fingolimod, and laquinimod, are currently in phase III trials and show promise as efficacious treatments for MS.³³

Cladribine

Cladribine is an immunosuppressive agent that depletes lymphocytes, thereby preventing damage to the myelin sheath. It is administered as short-course, pulse therapy (ie, 1 tablet daily for 5 days/course, for a total of 10–20 days/year). Although generally well tolerated, cladribine treatment must be considered with caution because it may have carcinogenic, teratogenic, and prolonged myelosuppressive effects; it also impairs fertility, both in males and females.^{33,34}

The CLARITY (Cladribine Tablets Treating MS Orally) study evaluated the effects of oral cladribine in patients with RRMS. After 2 years, patients who received the medication had fewer relapses, decreased disability progression, and a greater reduction in lesions than those who received placebo. Adverse events that were more frequent in patients treated with cladribine included lymphocytopenia and herpes zoster.³⁵

This product has been approved for fast-track status by the US Food and Drug Administration (FDA). A New Drug Application (NDA) was submitted to the FDA in September of 2009, but serious safety concerns have kept it from being filed; the manufacturer is expected to resubmit the NDA after addressing these issues.³⁶

Dr Murphy: The manufacturer resubmitted the NDA to the FDA in June of 2010.

Fingolimod

Fingolimod is a sphingosine-1-phosphate receptor agonist that sequesters circulating lymphocytes into secondary lymphoid organs and prevents T lymphocytes and macrophages from infiltrating the CNS³⁷; it also is believed to have neuroprotective properties.³⁸ It is administered once daily and has been evaluated in 2 doses (ie, 0.5 mg and 1.25 mg). Significant safety concerns include malignancies, opportunistic infections,³⁹ lymphopenia^{37,38} (which may take weeks to reverse), and cardiac issues (ie, bradycardia³⁷ and second-degree Wenckebach atrioventricular block³⁸) with initial dosing.

The FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in MS) and TRANSFORMS (Trial Assessing Injectable IFN vs FTY720 Oral in RRMS) studies were conducted to assess the safety and efficacy of fingolimod in patients with RRMS. The FREEDOMS trial randomized patients to fingolimod (0.5 mg or 1.25 mg) daily or placebo. After 2 years, patients receiving either dose of fingolimod had a reduced relapse rate, decreased risk of disability progression, and improved MRI findings, as compared to placebo. Adverse events related to fingolimod included bradycardia, atrioventricular conduction block, macular edema, elevated liver-enzyme levels, and mild hypertension; events generally occurred more frequently with high-dose therapy.⁴⁰ Patients enrolled in TRANSFORMS were randomized to receive fingolimod (0.5 mg or 1.25 mg) daily or IFN β -1a 30 mg IM weekly. After 1 year, the relapse rate was significantly lower in patients receiving fingolimod than in those receiving IM IFN β -1a. Two

fatal infections occurred in patients treated with the 1.25-mg dose of fingolimod; other adverse events among patients receiving fingolimod were nonfatal herpes virus infections, bradycardia, atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver-enzyme levels.⁴¹ Fingolimod has been granted fast-track status by the FDA, which is currently reviewing the NDA submitted in January 2010.⁴²

Dr Miravalle: Only the 0.5-mg dose of fingolimod will be marketed because the 1.25-mg dose has been associated with too many adverse events.

Laquinimod

Laquinimod is an immunomodulatory agent that appears to reduce CNS inflammation by shifting the immune response from T_H1 cells to T_H2 cells.³³ It is also neuroprotective because it reduces leukocyte infiltration into the CNS, thereby preventing demyelination and axonal loss.⁴³

A phase IIb study designed to evaluate the safety and efficacy of laquinimod in patients with RRMS randomized patients to receive laquinimod (0.3 mg or 0.6 mg) daily or placebo. Compared with placebo, treatment with laquinimod 0.6 mg daily showed a 40.4% reduction in the mean cumulative number of gadolinium-enhanced lesions per scan, on the last 4 scans; treatment with the 0.3-mg dose showed no significant effects. Both doses of laquinimod were well tolerated, with some transient and dose-dependent increases in liver enzymes.⁴⁴

Laquinimod also has been granted fast-track status by the FDA; however, an NDA has not yet been filed because the manufacturer is awaiting the results of 2 phase III clinical trials that are currently under way.⁴⁵

CASE STUDY (cont'd)

RE is told that there are currently no approved oral medications, but that they are likely to become available within the next couple of years.

CONCLUSIONS

Disease-modifying therapy with immunomodulating/immunosuppressive agents is the most effective strategy for altering the course of MS. Immunomodulating products (ie, IFN β therapy and glatiramer acetate) are considered first-line treatment options, due to their relatively favorable safety and

efficacy profiles. Conversely, immunosuppressive products (ie, natalizumab and mitoxantrone) are reserved for patients who have inadequate responses to first-line therapy or for patients with worsening or progressive disease; these products are associated with significant safety issues. Oral therapy is also on the horizon, as various agents (ie, cladribine, fingolimod, and laquinimod) are currently being studied or undergoing FDA review.

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