

# A Review of Current and Emerging Therapeutic Strategies in Multiple Sclerosis

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## Management of Acute Multiple Sclerosis Exacerbations

High-dose intravenous corticosteroids hasten recovery from, but do not appear to affect the degree of improvement from, acute multiple sclerosis (MS) exacerbations. A typical regimen consists of a 3- to 5-day course of 1000 mg of intravenous methylprednisolone with or without an oral prednisone taper. Because treatment does not appear to affect long-term outcome, not every MS exacerbation (eg, mild sensory symptoms) requires treatment. Based on the results of the Optic Neuritis Treatment Trial (ONTT), low-dose oral corticosteroids have no role as a treatment for MS exacerbations. In the ONTT, prednisone 1 mg/kg/day for 14 days had no effect on the rate of recovery from optic neuritis and was associated with an increased risk of subsequent optic neuritis.<sup>1,2</sup> Corticosteroids are well tolerated by most MS patients. Side effects of short pulsed doses include insomnia, behavioral disturbances, elevated blood glucose, risk of infection, and aseptic necrosis of bone. Plasma exchange may be considered for the treatment of exacerbations that result in significant disability despite high-dose intravenous corticosteroid therapy.<sup>2</sup>

## Symptomatic Therapies

Most patients with MS experience symptoms on a daily basis. Many of these symptoms can be disabling and socially distressing, and they often interfere with personal relationships and impact quality of life (QOL).<sup>3</sup> Common symptoms include fatigue, spasticity, depression, bowel and bladder dysfunction, pain, weakness, impaired mobility, cognitive problems, and sexual dysfunction. Disease-modifying drugs (DMDs) have no effect on preexisting symptoms, so therapies to alleviate the daily symptoms of MS are an integral part of patient care. Successful treatment often requires a combination of pharmacotherapy with nonpharmacologic measures, such as rehabilitation, exercise, and/or lifestyle and environmental modifications.

There are many therapies available for the symptoms of MS; several are described below.<sup>1,3</sup> Fatigue is one of the most common and disabling MS symptoms. Modafinil and amantadine are the most commonly used medications to treat MS-related fatigue.<sup>1,3</sup> Walking impairment has been reported in up to approximately 60% to 85% of patients with MS. Dalfampridine (previously referred to as fampridine) is a broad-spectrum potassium channel

## Abstract

Multiple sclerosis (MS) is a chronic immune-mediated disease that potentially requires symptomatic and disease-modifying therapies. Numerous symptoms (eg, fatigue, spasticity, depression, bowel and bladder dysfunction, pain, and impaired mobility) are associated with the neurologic damage that results from MS. Several therapies (eg, modafinil, dalfampridine, baclofen, diazepam, gabapentin, opioids) are used for symptomatic treatment of disability and symptoms, but these do not improve disease outcome. Intravenous corticosteroids (with or without an oral corticosteroid taper) are used in the management of MS exacerbations, but do not appear to affect the degree of improvement from acute exacerbations. A more definitive therapy for MS should reduce relapse rate, prolong remission, limit the onset of new MS lesions, and postpone the development of long-term disability. The currently available MS disease-modifying therapies have been shown to reduce relapse rate, have beneficial effects on magnetic resonance imaging measures, and delay accumulation of disability. In addition, a number of agents are in development, but thus far no beneficial agent has been established in primary-progressive MS.

(*Am J Manag Care. 2013;19:S21-S27*)

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blocker that enhances conduction across demyelinated axons and improves walking in some MS patients.<sup>4-7</sup> Spasticity occurs in up to 75% of patients with MS. Treatment should begin with, or at least include, physical therapy and stretching exercises. Medication, which is often necessary for optimal management, commonly includes baclofen and tizanidine, alone or in combination.<sup>1,3</sup> Other agents that may also be effective include onabotulinum toxin (especially for focal spasticity), diazepam, or gabapentin. Pain is reported in more than 80% of patients with MS at some point during the course of the disease and it is usually ameliorated with anti-convulsants and/or antidepressants. Opioids may be necessary for some patients.<sup>1,3</sup> Cognitive impairment affects approximately 40% to 60% of patients. Attention concentration, short-term memory, information processing, verbal intelligence, and visuospatial skills are the domains most commonly affected.<sup>8</sup> To date, there is no clearly effective treatment for MS-related cognitive impairment. Some patients may benefit from cognitive remediation and strategies to compensate for deficits. Donepezil improved memory in 1 small controlled trial in patients with MS and mild to moderate cognitive impairment. However, the results could not be duplicated in a larger multicenter study. DMDs that minimize lesion development, tissue destruction, or brain atrophy may limit cognitive decline.

Depression occurs in 50% to 75% of patients with MS; patients respond well to psychotherapy and antidepressants, either alone or in combination. Pseudobulbar affect, involuntary and uncontrollable episodes of laughing and/or crying, may respond to dextromethorphan with quinidine sulfate.<sup>1,3</sup> Other MS symptoms that should be identified and treated as appropriate include bladder, bowel, and sexual dysfunction, paroxysmal symptoms, and tremor.<sup>9-12</sup>

### Disease-Modifying Drugs

There are currently 9 DMDs approved by the US Food and Drug Administration (FDA) for MS. All of these agents reduce relapse rate and have a beneficial effect on a variety of magnetic resonance imaging (MRI) measures, and most have been shown to delay the accumulation of disability in short-term clinical trials. Current and some potential MS therapies for relapsing-remitting or relapsing forms of MS are described in the [Table](#). The treatment of progressive forms of MS is challenging, with no proven therapy for the primary-progressive form of the disease, and discussion of this is beyond the scope of this article.<sup>13-15</sup>

The beta interferons and glatiramer acetate are considered first-line therapies for relapsing-remitting MS (RRMS). Studies have also shown these agents to be effective (and

possibly even more so) when initiated at the time of a clinically isolated syndrome (CIS) in patients with at least several asymptomatic MRI brain lesions. Delaying treatment results in irreversible neurologic deficit. The interferons and glatiramer acetate clearly alter the short-term course of MS. Anecdotes, along with retrospective and prospective open-label studies, suggest a long-term treatment effect, but controlled studies are lacking.<sup>14-17</sup>

The therapeutic effects of interferon may be due to its anti-proliferative action, down-regulation of co-stimulatory molecules, or decrease of pro-inflammatory cytokines, or may occur through effects on matrix metalloproteinases and adhesion molecules, which reduce the permeability of the blood-brain barrier and limit trafficking of T lymphocytes into the central nervous system. The beneficial effects of glatiramer acetate, a synthetic polypeptide composed of the 4 amino acids L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, may result from reactive Th2 cells that cross the blood-brain barrier and increase the secretion of suppressor-type cytokines and down-regulate inflammatory activity within the CNS, a process known as bystander suppression.<sup>14-17</sup>

Interferon beta-1a is administered at a dosage of 30 mcg intramuscularly once weekly or usually 44 mcg subcutaneously 3 times a week. The standard dose of interferon beta-1b is 250 mcg subcutaneously every other day. Glatiramer acetate is given as a daily 20-mg subcutaneous injection. Most evidence suggests an interferon dose/frequency effect; however, the results of a recent large double-blind study that compared a double dose of interferon beta-1b with the standard dose were disappointing and indicated a ceiling dose effect.<sup>18,19</sup>

In head-to-head studies, the clinical effectiveness of glatiramer acetate was similar to that of high-dose interferons (ie, interferon beta-1b 250 mcg administered subcutaneously every other day or interferon beta-1a 44 mcg administered subcutaneously 3 times weekly) in patients with RRMS.<sup>20-32</sup> Effects on MRI measures of disease were inconsistent. In a recently completed randomized, double-blind, placebo-controlled, multicenter study, the combination of interferon beta-1a 30 mcg once weekly and glatiramer acetate was no better than either agent alone.

However, the annualized relapse rate was approximately 30% lower in patients who received glatiramer acetate monotherapy compared with patients who received interferon beta alone. There were no significant differences on any other clinical or MRI outcome measures between the glatiramer acetate- and interferon-treated groups.

The main interferon-related side effects include flu-like symptoms, injection site reactions, and laboratory abnormalities. Injection site reactions, which include local redness and

■ **Table.** Disease-Modifying Agents in MS<sup>13-15</sup>

Agent	Mechanism	Dose/Route	Frequency	Adverse Effects (most common and concerning)	Place in Therapy
<b>Approved by the FDA</b>					
Interferon beta-1a	Decreases MHC-II expression, upregulates IL-10, and decreases Th1 and Th17 production	30 mcg, IM	Once weekly	Flu-like symptoms, depression, thyroid dysfunction, liver enzyme abnormalities	First-line therapy for RRMS, SPMS, PRMS, and CIS; slow/delay disability
Interferon beta-1a	Decreases MHC-II expression, upregulates IL-10, and decreases Th1 and Th17 production	44 mcg, SC; typical dose	Three times per week	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzyme abnormalities	First-line therapy for RRMS, SPMS, PRMS; slow/delay disability
Interferon beta-1b	Decreases MHC-II expression, upregulates IL-10, and decreases Th1 and Th17 production	250 mcg, SC; typical dose	Every other day	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzyme abnormalities	First-line therapy for RRMS, SPMS, PRMS, and CIS
Glatiramer acetate	Consists of antigen-presenting cells, which present to lymphocytes, and limits ability of lymphocytes to respond to myelin basic protein	20 mg, SC	Daily	Skin site reactions, immediate post-injection reaction, lipatrophy	First-line therapy for RRMS and CIS
Fingolimod	Sphingosine 1-phosphate receptor modulator, retains lymphocytes in the lymph nodes, preventing them from crossing the blood-brain barrier into the central nervous system and causing consequent damage	0.5 mg, oral	Daily	First degree AV block with first dose (rare), bradycardia, macular edema, shingles, pulmonary dysfunction, skin cancer, back pain	First- or second-line therapy for RRMS, SPMS, and PRMS
Mitoxantrone	Inhibits topoisomerase II to prevent lymphocyte proliferation	12 mg/m <sup>2</sup> , IV; typical dose	Every 3 months, up to 140 mg/m <sup>2</sup> cumulative lifetime dose	Hair loss, cardiotoxicity, leukemia, infertility, infection risk, leucopenia, anemia, nausea, vomiting, thrombocytopenia	Second-line therapy for SPMS, PRMS, and worsening RRMS
Natalizumab	Blocks α4 integrins, which inhibits adhesion and migration of leukocytes into the brain	300 mg, IV	Every 4 weeks	Transient headache, fatigue, recurrent UTIs, PML, hypersensitivity	Second-line therapy for RRMS, SPMS, and PRMS
Teriflunomide	Pyrimidine synthesis inhibitor, inhibits a key enzyme in lymphocytes—which reduces the proliferation of T and B cells, and T cell messaging.	7 mg or 14 mg, oral	Once daily	Nasopharyngitis, headache, diarrhea, fatigue, back pain, influenza, hair thinning, LFT elevation, nausea, UTI	Second-line therapy for RRMS and SPMS
<b>Investigational</b>					
Alemtuzumab	Humanized monoclonal antibody that binds to CD52 on lymphocytes and monocytes and results in prolonged T-cell depletion	12 mg, IV	Daily for 5 consecutive days, followed by daily for 3 consecutive days 12 months later	Immune thrombocytopenic-purpura, autoimmune thyroid problems, headache, flushing	Phase 3 studies
Daclizumab	Humanized monoclonal antibody that binds to CD25 and increases CD56 bright natural killer cells, which target activated immune cells	150 mg, SC	Every 2 weeks	Infusion reaction, skin rash, lymphadenopathy, LFT abnormalities, diarrhea, constipation	Phase 3 studies
Dimethyl fumarate (BG-12)	Anti-inflammatory and potential neuro-protective properties mediated through the Nrf2 pathway	240 mg, oral	Two times daily	Diarrhea, cramps, LFT elevation, nausea, flushing	Phase 3 studies
Laquinimod	Reduces inflammation, demyelination, and axonal loss	0.6 mg, oral	Daily	LFT elevation	Phase 3 studies
Ocrelizumab	Humanized anti-CD20 monoclonal antibody that results in B-cell depletion	600 mg, IV	Every 24 weeks	Systemic inflammatory response, infusion reactions	Phase 3 studies

AV indicates atrioventricular; CIS, clinically isolated syndrome; FDA, US Food and Drug Administration; IL, interleukin; IM, intramuscular; IV, intravenous; LFT, liver function test; MHC, major histocompatibility complex; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PRMS, progressive-relapsing MS; RRMS, relapsing-remitting MS; SC, subcutaneous; SPMS, secondary-progressive MS; TH, T helper; UTI, urinary tract infection.

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swelling, are less common when interferon is given intramuscularly. Interferon is frequently given at night to limit flu-like symptoms during wakefulness, which may be worse in the first few weeks after starting treatment.<sup>20-25</sup> Flu-like symptoms can often be managed with nonsteroidal anti-inflammatory medications or acetaminophen, and typically lessen after 2 to 3 months of therapy. However, the flu-like symptoms are occasionally severe enough to warrant discontinuation of treatment and commencement of an alternative therapy. Skin necrosis is a rare side effect associated with subcutaneously administered interferons. Thrombocytopenia, anemia, leukopenia, or an increase in liver enzymes may develop at any time during therapy. Reports of liver damage are rare. Thyroid dysfunction, which is usually subclinical, may also occur. Interferons may cause or worsen depression, and it is probably best to avoid their use in patients with a history of severe depression.<sup>20-25</sup>

Neutralizing antibodies (NAbs) develop in 15% to 25% of patients treated with subcutaneous interferon beta-1a (44 mcg 3 times a week), and in 25% to 40% of those treated with interferon beta-1b. Intramuscular interferon beta-1a (30 mcg) is clearly less immunogenic, with NAbs occurring in only 2% of patients. NAbs typically develop between 6 and 18 months after the initiation of treatment, and only rarely after more than 2 years of therapy. Although potentially transient, persistent high-titer NAbs (>100 NU/ml) are associated with a reduced therapeutic effect.<sup>22</sup>

The most common adverse effects related to glatiramer acetate include injection site reactions, which typically consist of itching, redness, or induration. Lipoatrophy occurs less frequently. A systemic reaction characterized by a combination of chest tightness, flushing, shortness of breath, palpitations, and anxiety occurs in a small percentage of patients within seconds to a few minutes after an injection. The reaction is self-limited, lasts for several minutes, resolves without sequelae, and rarely recurs.<sup>26-32</sup>

Mitoxantrone is an anthracendione with immunosuppressive and immunomodulatory properties that is effective in aggressive MS. However, it is no longer widely used because of safety concerns (mainly irreversible cardiotoxicity and treatment-associated leukemia) and the availability of newer agents (eg, natalizumab, fingolimod).<sup>33-43</sup>

Natalizumab is a humanized monoclonal antibody indicated for relapsing forms of MS. Although head-to-head studies are lacking, natalizumab appears to be more effective than the interferons or glatiramer acetate. In the natalizumab monotherapy pivotal trial, there was a 67% reduction in the annualized relapse rate in the natalizumab-treated patients compared with the placebo group (in the interferon beta and

glatiramer acetate pivotal trials, the interferons or glatiramer acetate reduced the annualized relapse rate by up to 18% to 34% compared with placebo).<sup>39</sup> Natalizumab also reduced the accumulation of disability by 42%, the mean number of new or enlarging T2 hyperintense brain MRI lesions by 83%, and new gadolinium-enhancing brain MRI lesions by 92%.<sup>40</sup> However, because it is associated with a risk of progressive multifocal leukoencephalopathy (PML), natalizumab is currently most often used as a second- or third-line agent.<sup>41</sup> Natalizumab likely exerts its therapeutic effects by blocking the binding of the  $\alpha_4$ -subunit of  $\alpha_4\beta_1$  integrin expressed on the surface of activated T cells with its receptor vascular cell adhesion molecule 1 (VCAM-1) on the vascular endothelial surface at the blood-brain barrier. The interaction between  $\alpha_4$  and VCAM-1 is critical for T cells to gain access into the CNS. The recommended dose of natalizumab is 300 mg intravenously every 4 weeks.

Treatment with natalizumab was generally well tolerated, with 5% of patients reporting a headache during infusion. Hypersensitivity reactions occurred in 2% to 4% of patients and anaphylactic reactions occurred in fewer than 1% of individuals. Three known risk factors for PML include anti-JC virus seropositivity, longer duration of treatment (especially more than 2 years), and prior immunosuppressive therapy.<sup>41</sup> Among confirmed cases of PML in patients treated with natalizumab (2.1 cases per 1000), all patients with samples available before diagnosis of PML had anti-JC virus antibodies. The risk of PML is lowest among patients who were negative for anti-JC virus antibodies (0.09 cases or less per 1000). Patients who were anti-JC virus antibody positive with immunosuppressant exposure prior to natalizumab and received therapy for 25 to 48 months had the highest risk of PML, with an estimated risk of 11.1 cases per 1000, suggesting that the risk of PML can be stratified.<sup>44</sup> In addition to PML, there are rare reports of atypical herpes and other opportunistic infections, primary CNS lymphoma, and liver damage in patients treated with natalizumab. Six percent of patients develop persistent anti-natalizumab antibodies, which are associated with a clear loss of efficacy and an increased risk of infusion-related hypersensitivity reactions.<sup>41</sup>

Fingolimod is an oral DMD that was approved by the FDA in 2010. It is a sphingosine-1-phosphate receptor modulator that, once phosphorylated, acts as a superagonist of the sphingosine-1-phosphate-1 receptor on thymocytes and lymphocytes, preventing egress from secondary lymphoid tissues and sequestration of lymphocytes in lymph nodes.<sup>32</sup>

The efficacy of fingolimod 0.5 mg daily was demonstrated in 2 large placebo-controlled 24-month studies and in a head-to-head 12-month study comparing it with

interferon beta-1a 30 mcg once weekly in patients with relapsing-remitting MS. Fingolimod reduced the annualized relapse rate by 54% and 48% in the 2 placebo-controlled trials and by 52% when compared with interferon beta-1a.<sup>34-36</sup> Fingolimod reduced the risk of disability progression in the first placebo-controlled trial, but not in the second placebo-controlled study or when compared with interferon beta-1a. Fingolimod also demonstrated a superior effect on a variety of brain MRI measures, including new T2 and gadolinium-enhancing lesions and brain volume, compared with placebo or interferon beta-1a.<sup>34-36</sup>

The most common adverse reactions associated with fingolimod include influenza, cough, bronchitis, and liver enzyme elevations. Initiation of fingolimod results in a reduction in heart rate and is associated with a risk of bradyarrhythmias and atrioventricular blocks, which necessitates patient monitoring for at least 6 hours at the time of the first dose. Fingolimod is also associated with an average increase in systolic and diastolic blood pressure of approximately 2 mm Hg and 1 mm Hg (respectively), a low risk of macular edema, an approximately 75% reduction in peripheral lymphocyte counts, and a reduction in pulmonary function studies (clinical significance is unclear and may or may not be reversible). There were 2 cases of fatal herpes infections (herpes simplex encephalitis and disseminated primary herpes zoster) in the fingolimod phase 3 clinical trials. Both patients were treated with fingolimod 1.25 mg daily, which is higher than the 0.5-mg dose approved by the FDA. There is a paucity of data regarding the long-term safety profile of fingolimod.

Teriflunomide was approved by the FDA for relapsing forms of MS in September 2012. It inhibits the enzyme dihydroorotate dehydrogenase, which is involved in de novo pyrimidine synthesis, and decreases T- and B-cell proliferation and activation. In placebo-controlled phase 3 studies, teriflunomide 7 mg daily and 14 mg daily (vs placebo) produced beneficial and consistent effects in regard to clinical (ARR and disability) and MRI (T2 and gadolinium-enhancing lesions) measures of disease.<sup>45,46</sup> The ARR was 0.54 for placebo vs 0.37 for teriflunomide at either 7 or 14 mg.<sup>45</sup> The higher dose appeared to be superior because the proportion of patients with confirmed disability was only statistically lower relative to placebo in the teriflunomide 14 mg group.<sup>45</sup>

The most common adverse effects of teriflunomide include hair thinning, elevated liver function tests, diarrhea, and nausea.<sup>45</sup> Severe liver failure has been reported in patients treated with leflunomide (used for rheumatoid arthritis) and a similar risk is expected in association with teriflunomide, because the recommended doses of both drugs result in a similar range of plasma concentrations of teriflunomide.

Due to its risk of teratogenicity, teriflunomide is considered pregnancy category X. It is also found in human semen, and therefore may be associated with male-mediated fetal toxicity. Teriflunomide may also reduce white blood cell count and cause peripheral neuropathy, severe skin reactions (very rare and expected based on experience with leflunomide), increased blood pressure, infections, acute renal failure, and hyperkalemia; however, these effects are relatively uncommon. Teriflunomide is eliminated very slowly from the plasma; as such, certain patients (eg, women who discontinue teriflunomide and wish to become pregnant) may require an accelerated elimination procedure using either cholestyramine or activated charcoal.<sup>47</sup>

### Treatment Guidelines

There are no current evidence-based guidelines in the United States for DMDs in MS. Clinical practice guidelines from the American Academy of Neurology were published in 2002, prior to the availability of natalizumab, fingolimod, and teriflunomide. Treatment decisions should be individualized, considered in the context of the risks of the disease, and based, at least partially, on a combination of efficacy and potential side effects. Route and frequency of administration, as well as anti-JCV antibody status, may also be factors to consider in making treatment decisions.

### Treating Beyond Approved Therapy and Emerging Agents

Several agents are used off label for MS.<sup>14</sup> Agents which are in, or have completed, phase 3 MS trials are summarized in the Table. Ongoing studies will determine their efficacy and safety, and ultimately, whether they are approved by the FDA.

### Conclusion

The goals of therapy for MS are to prevent relapses and disease progression. When acute exacerbations occur, high-dose intravenous corticosteroids speed recovery, but do not affect the extent of recovery. Because symptoms are present in most patients on a daily basis, symptomatic therapies have an important role in improving quality of life. The DMDs are used to postpone disease progression. Recently, therapies beyond interferon and glatiramer acetate have become available, providing clinicians and patients with more therapeutic choices. However, treatment guidelines for MS are lacking in the United States, making treatment decisions (from among the numerous available DMDs) complex. Clinicians and managed care professionals should rely on available evidence-based efficacy and safety data to guide treatment deci-

sions. Guidelines, more head-to-head studies, and thorough cost-effectiveness evaluations are needed to fully determine the role of newer DMDs in current therapeutic strategies.

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**Funding source:** This activity is supported by educational grants from EMD Serono, Inc, and Teva Pharmaceuticals, Ltd.

**Author disclosure:** Dr Tullman reports consultancy/advisory board membership with Acorda Therapeutics, Allergan, Biogen Idec, Genzyme, Novartis, and Teva Pharmaceuticals. He also reports grant support from Acorda Therapeutics and honoraria from Acorda Therapeutics, Biogen Idec, EMD Serono, Novartis, Pfizer, and Teva Pharmaceuticals.

**Authorship information:** Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision.

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