

# Multiple Sclerosis Review

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS).<sup>1,2</sup> MS attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees.<sup>3,4</sup>

The course of MS is highly varied and unpredictable. In most patients, the disease is characterized initially by episodes of reversible neurological deficits, which is often followed by progressive neurological deterioration over time.

From 250,000 to 350,000 patients in the U.S. have MS,<sup>5</sup> and 50% of patients will need help walking within 15 years after the onset of the disease.<sup>6</sup>

Twice as many women are affected as men, and persons of Northern European descent appear to be at highest risk for MS.<sup>2,7</sup> The disease is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid (CSF). MS typically presents in adults 20 to 45 years of age; occasionally, it presents in childhood or late middle age.<sup>7</sup>

The cause is unknown, but it appears to involve a combination of genetic susceptibility and a nongenetic trigger, such as a virus, metabolism, or environmental factors, that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS.<sup>7</sup>

Neurologists agree that patients may be grouped into four major categories based on the course of disease:<sup>2</sup>

1. *Relapsing-remitting MS*: the most common form, affecting about 85% of MS patients. It is marked by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission, when symptoms improve or disappear.
2. *Secondary progressive MS*: may develop in some patients with relapsing-remitting disease. For many patients, treatment with disease-modifying agents helps delay such progression. The disease course continues to worsen with or without periods of remission or leveling off of symptom severity (plateaus).
3. *Primary progressive MS*: affects approximately 10% of MS patients. Symptoms continue to worsen gradually from the beginning. There are no relapses or remissions, but there may be occasional plateaus. This form of MS is more resistant to the drugs typically used to treat the disease.
4. *Progressive-relapsing MS*: a rare form, affecting fewer than 5% of patients. It is progressive from the start, with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission.



## DISEASE OVERVIEW

There is no single diagnostic test for MS.<sup>2</sup> The diagnosis is based on evidence of (1) at least two different lesions (plaques or scars) in the white matter of the CNS (the space dissemination criterion); (2) at least two different episodes in the disease course (the time dissemination criterion); and (3) chronic inflammation of the CNS, as determined by analysis of the CSF (the inflammatory criterion).

The presence of one or more of these criteria allows a general diagnosis of MS, which may be refined according to the subsequent course of the disease. An international panel on the diagnosis of MS suggested that the time dissemination criterion should be confirmed by clinical signs on MRI at least 3 months after the previous clinical episode or on a previous MRI. The panel also suggested that the inflammatory criterion could replace the space dissemination criterion when the latter is missing at the clinical and paraclinical levels.<sup>8</sup>

To make a diagnosis of MS, the physician must:<sup>2</sup>

- find evidence of damage in at least two separate areas of the CNS, which includes the brain, spinal cord, and optic nerves.
- determine that the damaged areas developed at least 1 month apart.
- exclude all other possible diagnoses.
- observe that the symptoms last for more than 24 hours and occur as distinct episodes separated by 1 month or more.
- perform an MRI (the most sensitive imaging test for MS)
- perform a spinal tap and examination for oligoclonal bands.



At autopsy, multiple, discrete pink or gray areas that have a hard, rubbery texture are identified within the white matter. The lesions are composed of areas of myelin and oligodendrocyte loss along with infiltrates of inflammatory cells, including lymphocytes and macrophages.<sup>2</sup> The relative preservation of axons and neurons within these lesions helps to differentiate MS from other destructive pathological processes that are accompanied by focal inflammation.<sup>2</sup>

More than 30% of MS patients have moderate-to-severe spasticity, mostly in the legs. Initial clinical findings in MS patients are often sensory disturbances, the most common of which are paresthesias (numbness and tingling), dysesthesias (burning and "pins and needles"), diplopia, ataxia, vertigo, and bladder (urinary sphincter) disturbances. A common manifestation of MS is unilateral numbness affecting one leg that spreads to involve the other leg and rises to the pelvis, abdomen, or thorax. Sensory disturbances usually resolve but sometimes evolve into chronic neuropathic pain. Trigeminal neuralgia also occurs. Another

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common presenting sign of MS is optic neuritis, highlighted by complete or partial loss of vision.<sup>2</sup>

Bladder dysfunction occurs in more than 90% of MS patients and results in weekly or more frequent episodes of incontinence in one-third of patients.<sup>2</sup> At least 30% of patients experience constipation. Fatigue occurs in 90% of patients and is the most common work-related disability associated with MS.<sup>2</sup> Sexual problems are often experienced as well.<sup>7</sup>

## DISEASE-MODIFYING THERAPIES

The goals of therapy with disease-modifying agents in patients with MS include shortening the duration of acute exacerbations, decreasing their frequency, and providing symptomatic relief.<sup>7</sup> No curative, FDA-approved therapies for MS are currently available.

Symptomatic treatments are aimed at maintaining function and improving quality of life.<sup>9</sup> It is common practice to treat acute relapses of MS with a short course (typically 3 to 5 days) of a corticosteroid that has a rapid onset of action and that produces few adverse drug effects (AEs), such as intravenous (IV) methylprednisolone or dexamethasone.<sup>7,9-11</sup> Brief courses of corticosteroids (e.g., oral prednisone 60 to 100 mg once daily, tapered over a period of 2 to 3 weeks, or IV methylprednisolone 500 to 1,000 mg once daily for 3 to 5 days) are also used to treat acute exacerbations and to shorten the duration of MS attacks.<sup>2,12</sup>

Although there is no cure for MS, eight FDA-approved therapeutic agents can reduce disease activity and progression in patients with relapsing forms of MS, including patients with secondary progressive MS who continue to have relapses (Table 1).

### Beta Interferons (Avonex, Betaseron, Rebif, Extavia)

The four beta interferon drugs—Avonex (Biogen Idec), Rebif (Pfizer), Betaseron (Bayer), and Extavia (Novartis)—are naturally occurring cytokines secreted by immune cells. These agents inhibit viral replication via a variety of immunomodulating and antiviral activities.<sup>7,13</sup>

Although the mechanisms of action of interferons beta-1a and beta-1b in MS are unknown, these cytokines perform regulatory functions in the immune system, and their anti-

inflammatory properties are thought to be beneficial.<sup>7</sup> The beta interferons have been shown to reduce the incidence of relapses by approximately one-third and are recommended for patients with relapsing-remitting MS who have intolerance to glatiramer acetate.<sup>14,15</sup> In randomized, double-blind, placebo-controlled trials, the use of beta interferons in patients with MS reduced inflammatory lesions by 50% to 80%, as shown on brain MRI scans.<sup>16-18</sup> Moreover, there is evidence that these drugs improve quality of life and cognitive function.<sup>18-20</sup>

Patients treated with any of the interferon beta agents are at risk for liver function abnormalities, leukopenia, thyroid disease, and depression.<sup>7</sup> It is necessary to monitor liver enzymes (alanine amino transferase [ALT] and aspartate amino transferase [AST]) and the white blood cell (WBC) count with differential upon the initiation of treatment and periodically thereafter.<sup>7</sup>

Flu-like symptoms (e.g., fever, chills, malaise, muscle aches, and fatigue) occur in approximately 60% of patients who receive interferon beta-1a or beta-1b.<sup>2</sup> Other common AEs associated with beta interferons include injection-site reactions and worsening of pre-existing spasticity.<sup>2</sup>

Treatment with any of the beta interferons can result in the development of neutralizing antibodies, although the long-term importance of these antibodies is unknown.<sup>21</sup> Peripheral neuropathy was reported as a side effect of treatment with interferon alfa but not with interferon beta.<sup>22</sup> The neuropathy dissipated after discontinuation of interferon alfa.

### Glatiramer Acetate (Copaxone)

Glatiramer acetate (Copaxone, Teva) is a synthesized copolymer polypeptide mixture consisting of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine. The drug was originally designed to mimic and compete with myelin basic protein.<sup>7</sup> Subcutaneous (SQ) glatiramer acetate (20 mg/day) has been shown to reduce the rate of attacks in patients with relapsing-remitting MS.<sup>7</sup>

The U.S. Glatiramer Acetate Study evaluated 15 years of treatment with this drug as the sole disease-modifying therapy for relapsing-remitting MS.<sup>23</sup> A total of 223 patients received at least one dose of glatiramer acetate at the study's initiation in 1991. At year 15, more than 80% of patients were still walk-

**Table 1 FDA-Approved Disease-Modifying Agents for the Treatment of Multiple Sclerosis**

Drug	Brand (Manufacturer)	Recommended Dose	Dosing Frequency	Route
Interferon beta-1a	Avonex (Biogen Idec)	30 mcg	Once weekly	IM
Interferon beta-1a	Rebif (Pfizer)	22 or 44 mcg	Three times weekly	SQ
Interferon beta-1b	Betaseron (Bayer)	0.25 mg	Every other day	SQ
Interferon beta-1b	Extavia (Novartis)	0.25 mg	Every other day	SQ
Glatiramer acetate	Copaxone (Teva)	20 mg	Once daily	SQ
Mitoxantrone	Novantrone (EMD Serono)	5 to 12 mg/m <sup>2</sup>	Short infusion (about 5 to 15 minutes) every 3 months	IV
Natalizumab	Tysabri (Biogen Idec)	300 mg	1-hour infusion every 4 weeks	IV
Fingolimod	Gilenya (Novartis)	0.5 mg	Once daily	PO

IM = intramuscular; IV = intravenous; PO = per os (by mouth); SQ = subcutaneous.

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ing without assistance despite having had MS for a duration of 22 years. Annual relapse rates showed a continuous decline, from 1.12 at baseline to 0.25 per year, and 65% of patients did not advance to secondary progressive MS. In all of the glatiramer acetate-treated patients, annual relapse rates declined from 1.18 to 0.43, and secondary progressive MS developed in only 25%. There were no long-term safety problems.

The drug's mechanism of action is distinct from that of the beta interferons; therefore, patients may respond differently to this agent. Although the precise mechanism of action is unknown, animal studies and *in vitro* observations suggest that upon administration, glatiramer acetate–specific suppressor T cells are induced and activated in the periphery.<sup>24</sup> This medication is recommended as a first-line treatment in patients with relapsing–remitting MS and in patients who cannot tolerate beta interferons.<sup>25</sup> In MRI evaluations of patients with relapsing–remitting MS, glatiramer acetate reduced inflammatory activity by one-third.<sup>26,27</sup>

Unlike the interferon betas, glatiramer acetate does not cause liver function abnormalities, leukopenia, or thyroid disease, and it is not associated with depression or a flu-like reaction.<sup>7</sup>

In a poll of more than 2,100 MS patients treated with glatiramer acetate, 44% reported experiencing AEs (4% were significant).<sup>28</sup> Common AEs were injection-site reactions (35%), itch or rash (11%), flu-like symptoms (8%), chest pain (4%), hot flashes (4%), and headache (4%). Transient reactions included flushing and chest tightness or pain immediately after the injection.<sup>24</sup>

### Mitoxantrone (Novantrone)

Prior to its approval for use in MS, mitoxantrone (Novantrone, EMD Serono) was used to treat certain forms of cancer. Mitoxantrone suppresses the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath. As a synthetic antineoplastic anthracenedione, it intercalates into DNA and interferes with RNA. This medication is a potent inhibitor of topoisomerase II, an enzyme responsible for repairing damaged DNA.<sup>29</sup> *In vitro* studies have shown that mitoxantrone inhibits B-cell, T-cell, and macrophage proliferation and impairs antigen presentation as well as the secretion of interferon gamma, tumor necrosis factor (TNF)-alpha, and interleukin-2 (IL-2).<sup>29</sup>

In a double-blind, randomized trial, patients with relapsing–remitting MS who received mitoxantrone (8 mg/m<sup>2</sup> monthly) showed significantly reduced relapse rates at 1 year compared with patients given placebo ( $P = 0.014$ ).<sup>30</sup> In another double-blind study, patients with relapsing secondary progressive MS received mitoxantrone (12 mg/m<sup>2</sup> monthly) for 3 months, followed by 12 mg/m<sup>2</sup> every 3 months for up to 32 months.<sup>31</sup> These patients showed significant positive improvements in disability scores, as measured by the Expanded Disability Status Scale (EDSS).

In five randomized, blinded, controlled trials and an open-label safety study conducted in patients with worsening MS, the most common AEs associated with mitoxantrone included nausea and vomiting (18%–85%), alopecia (33%–61%), amenorrhea (8%–53%), urinary tract infections (6%–32%), and upper respiratory tract infections (4%–53%).<sup>30</sup> Leukopenia occurred in 10% to 19% of patients. The use of mitoxantrone can lead to

serious AEs, particularly cardiotoxicity; myelosuppression; and, rarely, leukemia. Limited cardiotoxicity was reported in these clinical studies.<sup>30</sup>

Mitoxantrone provides effective treatment for worsening relapsing–remitting MS or secondary progressive MS. When mitoxantrone is used as recommended, the risk of substantial myelosuppressive and cardiotoxic effects can be reduced by careful patient selection, drug administration, and monitoring. The lifetime cumulative dose should be strictly limited to 140 mg/m<sup>2</sup> or 2 to 3 years of therapy.

### Natalizumab (Tysabri)

Natalizumab (Tysabri, Biogen Idec/Elan) is a recombinant humanized immunoglobulin (IgG<sub>4</sub>) monoclonal antibody. Like the beta interferons and glatiramer acetate, its precise mechanism of action in patients with MS has not been fully defined. Natalizumab binds to the alpha 4-subunit of alpha 4β1 and alpha 4β7 integrins expressed on the surface of leukocytes (except neutrophils), and it inhibits the alpha 4-mediated adhesion of leukocytes to their counterreceptors.<sup>32</sup>

Administered intravenously once a month, natalizumab is directed against an adhesion molecule called very late activating antigen 4 (VLA-4). Natalizumab markedly reduces the attack rate in patients with MS and significantly improves all measures of severity.<sup>33</sup>

The FDA's approval of natalizumab for the treatment of MS was based on two randomized, double-blind, placebo-controlled trials involving more than 2,000 patients. In both studies, neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRIs were evaluated annually.<sup>32</sup>

In study 1, 942 patients had not received a beta interferon or glatiramer acetate for at least the previous 6 months. The patients received a 300-mg IV infusion of natalizumab or placebo every 4 weeks for up to 28 months. Patients receiving natalizumab had an annualized relapse rate of 0.22, compared with a relapse rate of 0.67 for patients taking placebo, representing a relative reduction of 67% with the study drug. Of the natalizumab group, 76% remained relapse-free compared with 41% of the placebo group.<sup>32</sup>

In study 2, 1,171 MS patients had experienced one or more relapses while receiving intramuscular (IM) interferon beta-1a (30 mcg once weekly) during the year before enrollment into the study. They received a 300-mg IV infusion of natalizumab or placebo every 4 weeks for up to 28 months. All of the patients continued taking interferon beta-1a once weekly. The natalizumab-treated patients had an annualized relapse rate of 0.33, compared with 0.75 for patients taking placebo, representing a 56% reduction with natalizumab. Of the natalizumab-treated patients, 54% remained relapse-free, compared with 46% of the placebo patients.<sup>32</sup>

The safety of natalizumab is an important consideration. In the drug's prescribing information, a boxed warning indicates a potential increase in the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.<sup>32,33</sup> The risk of PML increases the longer the patient takes the drug. Natalizumab should not be used in patients with a compromised immune system. MRI scanning is required before treatment is initiated, and an analysis of the CSF for John

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Cunningham virus (JC) DNA is recommended. Anaphylaxis and serious infections have also occurred.<sup>34</sup>

One report suggested that screening for JCV in the CSF of natalizumab-treated patients might be able to identify patients with an increased risk of developing PML and that discontinuing treatment in these patients might prevent clinical illness.<sup>34</sup>

On January 20, 2012, the FDA approved a product label change for natalizumab to identify anti-JCV antibody status as a risk factor for PML. The parallel approval of the Stratify JCV test will enable neurologists to determine the JC virus infection status of patients to aid in treatment decisions. The assay will be offered through Quest's Focus Diagnostics laboratory in the U.S.

### Fingolimod (Gilenya)

Fingolimod (Gilenya, Novartis) is the first orally administered, disease-modifying drug approved by the FDA to reduce relapses and to delay the progression of disability in patients with relapsing forms of MS.<sup>35</sup> Fingolimod is a sphingosine-1-phosphate receptor modulator that is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate, which in turn blocks the migration of lymphocytes from lymph nodes, thereby reducing the number of lymphocytes in peripheral blood. The mechanism underlying the therapeutic effect of fingolimod in MS is unknown, but it might involve the reduction of lymphocyte migration into the CNS.<sup>36</sup>

Two pivotal studies of fingolimod were conducted in patients with relapsing-remitting MS. A 12-month study, TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis), compared fingolimod (0.5 mg and 1.25 mg) with interferon beta-1a,<sup>36-38</sup> and the 24-month FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) trial compared fingolimod (0.5 mg and 1.25 mg) with placebo.<sup>36,39</sup> TRANSFORMS included 1,153 evaluable patients with relapsing-remitting MS. Annualized relapse rates were significantly lower in both fingolimod treatment groups—0.16 for 0.5 mg and 0.20 for 1.25 mg—compared with the interferon group (0.33;  $P < 0.001$  for both comparisons).<sup>36,37</sup>

In a 24-month extension of this study, patients receiving continuous fingolimod showed persistent improvements in the annualized relapse rate. With fingolimod 0.5 mg, relapse rates were 0.12 in months 0 to 12 and 0.11 in months 13 to 24. Corresponding relapse rates with fingolimod 1.25 mg were 0.15 and 0.11, respectively. In patients who initially received interferon beta-1a, the annualized relapse rate was lower after they were switched to fingolimod, compared with the previous 12 months.<sup>38</sup> Thus, in both the initial 12-month study and the 24-month extension, the 1.25-mg dose of fingolimod resulted in no additional benefit over the 0.5-mg dose.<sup>36-38</sup>

FREEDOMS involved 1,033 evaluable patients with relapsing-remitting MS. Annualized relapse rates were 0.16 with fingolimod 1.25 mg, 0.18 with fingolimod 0.5 mg, and 0.40 with placebo ( $P < 0.001$  for either dose vs. placebo). Fingolimod therapy significantly reduced the risk of disability progression over the 24-month treatment period compared with placebo ( $P = 0.02$ ).<sup>36,39</sup> As in TRANSFORMS, the 1.25-mg dose of fingolimod provided no additional benefit over the 0.5-mg dose.<sup>36</sup>

A total of 1,703 patients receiving fingolimod (0.5 or 1.25 mg) constituted the safety population in the two pivotal studies of patients with relapsing-remitting MS. The most common AEs associated with fingolimod 0.5 mg included headache, elevated ALT and AST levels, influenza viral infections, diarrhea, back pain, and cough.<sup>36</sup> Serum transaminase elevations were the only AEs that led to interruption of treatment in more than 1% of those receiving fingolimod 0.5 mg; treatment was interrupted in 3.8% of patients.<sup>40</sup>

Patients should be observed for 6 hours after the first dose of fingolimod to monitor for signs and symptoms of bradycardia. Fingolimod may increase the risk of infection, and macular edema can occur with or without visual symptoms. Liver transaminase levels may also be increased.<sup>36</sup>

Two patients receiving fingolimod (1.25 mg) died in the TRANSFORMS study. One death was caused by disseminated primary varicella zoster infection; the other death was attributed to herpes simplex encephalitis.<sup>37</sup>

### SYMPTOMATIC TREATMENT

#### Dalfampridine (Ampyra)

Dalfampridine (Ampyra, Acorda) is the first drug approved by the FDA that has been found to improve walking in patients with any type of MS.<sup>41</sup> In clinical studies, approximately one-third of dalfampridine-treated patients had faster walking speeds compared with placebo-treated patients. The average walking speed was approximately 25% above baseline.<sup>42</sup>

Dalfampridine tablets contain a sustained-release formulation of 4-aminopyridine, which blocks potassium channels on the surface of nerve fibers.<sup>43</sup> This blocking ability may improve the conduction of nerve signals in nerve fibers whose insulating myelin coating has been damaged by MS. Before the introduction of dalfampridine, no pharmacological treatment had been available for MS-related walking difficulty.

The maximum recommended dosage is one 10-mg tablet twice daily, taken with or without food. This dosage should not be exceeded. The tablets should be taken approximately 12 hours apart, and patients should not take double or extra doses if a dose is missed.<sup>43</sup>

When given at a dosage greater than that recommended in the product labeling, dalfampridine can cause seizures. Common AEs associated with dalfampridine include urinary tract infections, insomnia, dizziness, headache, nausea, weakness, back pain, balance disorders, swelling in the nose or throat, constipation, diarrhea, indigestion, throat pain, and burning, tingling, or itching of the skin.<sup>43</sup>

### OFF-LABEL TREATMENT OPTIONS

The following therapeutic agents have not been approved by the FDA for the treatment of MS, but physicians often use them off label for this purpose.

#### Azathioprine (Imuran)

Azathioprine (Imuran, Prometheus), an orally administered immunosuppressant agent, is administered at a dosage of 2 to 3 mg/kg per day to treat secondary progressive MS. In a meta-analysis of several small studies, azathioprine reduced relapse rates in both relapsing-remitting and secondary progressive MS.<sup>2</sup>

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Methotrexate (e.g., Rheumatrex, DAVA), an oral immunosuppressant, was originally developed (and continues to be used) for chemotherapy, either alone or in combination with other agents. Methotrexate is effective in a variety of cancers. It is also used to treat severe psoriasis and rheumatoid arthritis. In one study, methotrexate slowed the progression of upper-extremity dysfunction in patients with secondary progressive MS.<sup>7</sup> More studies are needed to establish the efficacy and safety of methotrexate in MS. Patients treated with methotrexate should be monitored for hepatotoxicity.

## Cyclophosphamide

Cyclophosphamide (e.g., Cytoxan, Bristol-Myers Squibb), a cytotoxic alkylating agent, was found to be beneficial in reducing the number of relapses in patients with relapsing-remitting MS when they were given with interferon beta-1a.<sup>44</sup> Cyclophosphamide binds to DNA and interferes with mitosis and cell replication.<sup>45</sup>

The disease-modifying agents that are currently approved for use in MS have only limited or no bioavailability in the brain and spinal cord. In contrast, cyclophosphamide readily penetrates the blood-brain barrier and the CNS parenchyma. It has been used to treat patients with MS in clinical trials and in clinical practice (in an off-label fashion) for more than 30 years. However, efficacy data for this drug have been contradictory.<sup>45</sup>

## Mycophenolate Mofetil (CellCept)

The immunosuppressive agent mycophenolate mofetil (MMF; CellCept, Genentech) is relatively selective for activated lymphocytes. It is administered orally at dosages of 500 or 1,000 mg twice daily, alone or in combination with an interferon beta, for patients with relapsing-remitting and secondary progressive MS. However, its efficacy in MS is controversial.<sup>7</sup> In a preliminary study, the combination of MMF

and interferon beta-1a was well tolerated in 13 patients with relapsing-remitting MS, but efficacy results after 12 months of therapy were not statistically significant compared with placebo.<sup>46</sup> MMF deserves further investigation in MS, with a larger sample size and a longer follow-up period.

## Cladribine

Oral cladribine (Merck KGaA, Germany) is an adenosine deaminase-resistant purine nucleoside that is relatively selective for lymphocytes.<sup>7</sup> It does not alter attack rates or the progression of MS, but it does reduce lesions in the brain.<sup>7</sup> In July 2010, the FDA accepted a New Drug Application (NDA) for cladribine tablets from Merck KGaA; however, in June 2011, the company discontinued developing the drug for the treatment of MS because of a cancer risk. This discontinuation may give a boost to the oral usage of fingolimod. Merck/Serono has decided to not to pursue approval by the FDA. The drug will no longer be sold in Russia and Australia, where it had been available as Movectro. Used in the injectable form as Leustatin (Janssen), cladribine has been used to treat cancer.

## DRUGS IN DEVELOPMENT

Several agents aimed at treating MS are currently in the research pipeline (Table 2).

### Laquinimod

Laquinimod (Active Biotech/Teva) is a synthetic, orally active, small-molecule, anti-inflammatory agent that affects the immune system.<sup>47,48</sup> Laquinimod alters T-cell populations to promote a regulatory T-helper (Th2) response instead of the attack-focused Th1 response, and it appears to increase the synthesis of neuroprotective molecules.<sup>49</sup>

In the recently completed phase 3 ALLEGRO trial, a total of 1,106 patients with relapsing-remitting MS received laquinimod (0.6 mg) or placebo for 24 months.<sup>50</sup> Patients treated with

**Table 2 Potential Medications for Multiple Sclerosis**

Drug Name	Company	Description	Therapeutic Dosage
Laquinimod	Active Biotech/ Teva	Synthetic small-molecule, anti-inflammatory agent	0.6 mg once daily PO
Teriflunomide	Sanofi/Genzyme	Immune modulator; active metabolite of leflunomide	7 mg or 14 mg once daily PO
BG-12 (dimethyl fumarate)	Biogen Idec	Immune modulator	240 mg twice or three times daily PO
Daclizumab (Zenapax)	Roche	CD25-targeted humanized monoclonal antibody	1.0 mg/kg IV <sup>a</sup>
Alemtuzumab (Campath)	Genzyme	CD52-targeted humanized monoclonal antibody	30 mg/day three times per week for 12 weeks IV <sup>b</sup>
Rituximab (Rituxan)	Genentech	CD20-targeted chimeric murine/human monoclonal antibody	375 mg/m <sup>2</sup> IV <sup>c</sup>
Ocrelizumab	Roche/Biogen Idec	CD20-targeted humanized monoclonal antibody	600 mg or 2,000 mg in two doses (on days 1 and 15) <sup>d</sup>

IV = intravenous; PO = *per os* (by mouth).

<sup>a</sup> For prophylaxis of acute organ rejection in patients receiving renal transplants.

<sup>b</sup> For treatment of B-cell chronic lymphocytic leukemia.

<sup>c</sup> For treatment of non-Hodgkin's lymphoma.

<sup>d</sup> Dosages used in phase 2 clinical trial in MS.

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laquinimod experienced a statistically significant reduction of 23% in annualized relapse rates compared with patients given placebo ( $P = 0.0024$ ). The drug also reduced the risk of disability progression by 36% ( $P = 0.0122$ ) and brain atrophy by 33% ( $P < 0.0001$ ).

In the 24-month, phase 3 BRAVO trial (Blinded Reference Arm of Interferon Beta-1a [Avonex]), also recently completed, laquinimod (0.6 mg) resulted in a significant 21% reduction in the annualized relapse rate ( $P = 0.026$ ), a 34% reduction in the risk of disability progression ( $P = 0.044$ ), and a 28% reduction in brain volume loss ( $P < 0.0001$ ), compared with placebo, in patients with relapsing-remitting MS.<sup>51</sup> These results were achieved, however, after adjusting for dissimilarities in two baseline MRI characteristics between the two treatment groups. Without this adjustment, laquinimod failed to statistically achieve the study's primary endpoint of reducing the annualized relapse rate when compared with placebo ( $P = 0.075$ ). Additional analyses of the BRAVO study data are ongoing.

### Teriflunomide (Aubagio)

Teriflunomide (Aubagio, Sanofi/Genzyme), the active metabolite of leflunomide (Arava, Sanofi), is an immune-modulating drug that reversibly inhibits the *de novo* synthesis of pyrimidine by blocking the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH). By inhibiting DHODH and reducing DNA synthesis, teriflunomide exerts a cytostatic effect on proliferating B and T cells.<sup>52,53</sup> Teriflunomide has been used to treat rheumatoid arthritis since 1998.<sup>52</sup>

In the recent phase 3 Teriflunomide Multiple Sclerosis Oral (TEMSO) trial, teriflunomide (7 mg or 14 mg) was compared with placebo in 1,088 patients with relapsing forms of MS. After 2 years, both doses of teriflunomide significantly reduced the annualized relapse rate versus placebo (37% vs. 54%, respectively;  $P < 0.001$ ). Confirmed disability progression occurred in 27.3% of placebo-treated patients, compared with 21.7% of the patients receiving teriflunomide (7 mg) ( $P = 0.08$ ) and 20.2% of those given teriflunomide (14 mg) ( $P = 0.03$ ).<sup>54</sup>

In another recent phase 3 study, the TENERE trial, teriflunomide (7 mg and 14 mg) was compared with interferon beta-1a (Rebif) in 324 patients with relapsing MS.<sup>55</sup> In this study, teriflunomide failed to show statistically significant superiority over interferon in reducing the risk of treatment failure (the study's primary composite endpoint). Teriflunomide, however, was non-inferior and numerically superior to interferon. At the higher teriflunomide dose (14 mg), 37.8% of patients had confirmed relapse or permanent treatment discontinuation over a period of 2 years compared with 42.3% of the interferon-treated patients. The numerical superiority of teriflunomide may have been helped by the higher dropout rate in the interferon arm (21.8% interferon vs. 10.9% teriflunomide 14 mg). A long-term extension of the TENERE trial is ongoing.

Teriflunomide is being investigated in several other multinational phase 3 studies involving patients with MS. TOWER, a phase 3 trial, for example, is comparing teriflunomide (7 mg and 14 mg) with placebo in 1,110 patients with relapsing MS.<sup>56</sup> The primary outcome measure is the annualized relapse rate. The anticipated completion date is February 2013.

In the phase 3 TERACLES trial, teriflunomide is being compared with placebo in 1,455 patients previously treated with

interferon beta.<sup>57</sup> This is the first phase 3 study of an oral drug as an add-on to standard therapy in relapsing MS. The trial is expected to finish in April 2014.<sup>58</sup>

Another ongoing phase 3 trial, TOPIC, is comparing teriflunomide (7 mg or 14 mg) with placebo in 780 patients who presented with their first clinical symptom of MS.<sup>59</sup> The primary objective is to see whether teriflunomide can prevent or delay conversion to clinically definite MS. The trial's estimated completion date is November 2015. In October 2011, Sanofi SA and its subsidiary Genzyme announced that the FDA had accepted for review the company's NDA for oral teriflunomide as a potential therapy for relapsing MS.

### BG-12 (Dimethyl Fumarate)

BG-12 (Biogen Idec) is an investigational, orally administered immune modulator currently in phase 3 clinical development as monotherapy for relapsing-remitting MS.<sup>60</sup> In 2008, BG-12 received a fast-track designation in MS from the FDA.

DEFINE (Determination of the Efficacy and safety of oral Fumarate IN rElapsing-remitting MS) was the first phase 3 study to evaluate BG-12 in patients with MS. In this 2-year, randomized, double-blind, placebo-controlled trial, BG-12 (240 mg twice or three times daily) was compared with placebo in 1,200 patients with relapsing-remitting disease. Preliminary results, released in April 2011, showed that both the twice-daily and three-times-daily doses provided a statistically significant reduction ( $P < 0.0001$ ) in the proportion of patients with relapsing-remitting MS who relapsed at 2 years compared with placebo.<sup>61</sup>

BG-12 is also being evaluated in patients with relapsing-remitting MS in the ongoing CONFIRM (Comparator and an oral Fumarate in Relapsing-remitting MS) trial. In this 2-year randomized, placebo-controlled, double-blind study, patients are being treated with either oral BG-12 (240 mg twice or three times daily) or SQ glatiramer acetate (Copaxone).<sup>62</sup>

### Daclizumab (Zenapax)

Daclizumab (Zenapax, Roche) is an FDA-approved immunosuppressive, humanized IgG<sub>1</sub> monoclonal antibody that binds specifically to the CD25 alpha subunit of the high-affinity IL-2 receptor on the surface of activated lymphocytes.<sup>63</sup> The medication is thought to work by selectively binding to and inhibiting the IL-2 receptor on activated T cells without causing T-cell depletion. Daclizumab is approved as part of an immunosuppressive regimen for the prevention of acute organ rejection after kidney transplantation.

In the phase 2 CHOICE trial, SQ daclizumab (2 mg/kg every 2 weeks), in combination with interferon beta, provided a 72% reduction in the number of new or enlarged MS lesions, compared with interferon beta alone, in patients with active, relapsing MS.<sup>64</sup> In a pharmacodynamic subanalysis, daclizumab was associated with an increase in the CD56(bright) subset of natural killer cells, which help regulate the immune system. This increase was linked to the significant reduction in the formation of MS lesions.

Preliminary results from the phase 2b SELECT trial were announced in August 2011.<sup>65</sup> SELECT was designed to compare SQ daclizumab (150 or 300 mg once every 4 weeks) for 12 months with placebo in 600 patients with relapsing-remit-

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ting MS. Daclizumab significantly reduced the annualized relapse rate by 54% in the 150-mg arm ( $P < 0.0001$ ) and by 50% in the 300-mg arm ( $P = 0.0002$ ) compared with placebo. Daclizumab also reduced the proportion of patients who relapsed by 55% (150 mg) and 51% (300 mg) and decreased the risk of sustained disability progression by 57% (150 mg) and 43% (300 mg). Additional analyses are ongoing.

In a retrospective evaluation of 12 patients with relapsing-remitting MS, long-term treatment with daclizumab (24 to 60 months; average, 42.1 months) was generally well tolerated.<sup>66</sup> Rash and lymphadenopathy were the most common AEs in four and two patients, respectively. One of the cases of lymphadenopathy was associated with Epstein-Barr virus infection.

### Alemtuzumab (Campath/Lemtrada)

Alemtuzumab (Campath/Lemtrada, Genzyme/Sanofi) is a humanized monoclonal antibody targeting CD52, a broadly expressed cell-surface molecule on immune cells. The drug causes a rapid, long-lasting removal of lymphocyte populations from the circulation and may confer neuroprotective effects.<sup>67,68</sup> Under the trade name Campath, it is indicated as monotherapy for B-cell chronic lymphocytic leukemia (B-CLL).<sup>67</sup> Campath is currently undergoing further development as Lemtrada and is expected to be submitted for FDA and European approval, possibly in early 2012.

In a phase 2, randomized, double-blind study (CAMMS223), 334 patients with early, relapsing-remitting MS received annual IV cycles of alemtuzumab (12 or 24 mg/day) or SQ interferon beta-1a (44 mcg three times per week) for 36 months.<sup>69</sup> Alemtuzumab significantly reduced the annualized relapse rate compared with the beta interferon (0.10 vs. 0.36, respectively;  $P < 0.001$ ) and also reduced the rate of sustained accumulation of disability (9.0% vs. 26.2%, respectively;  $P < 0.001$ ).

Further analysis, together with parallel experimental studies, suggested that alemtuzumab not only reduced disease activity as a result of its immune-cell-depleting effect; it also conferred neuroprotective effects, presumably by inducing the production of neurotrophic factors in autoreactive T cells. However, compared with the interferon beta-1a group, the alemtuzumab-treated patients experienced increased rates of autoimmunity, including thyroid disorders (23% vs. 3%, respectively) and immune thrombocytopenic purpura (3% vs. 1%), respectively, demonstrating that alemtuzumab-mediated skewing of the immune-cell compartment has a broad influence on immune functions. The alemtuzumab patients also had more infections than the beta interferon group (3% vs. 1%).<sup>69</sup>

CAMMS223 included an extended phase for the collection of long-term efficacy and safety data. Preliminary 5-year data were reported in April 2011.<sup>70</sup> Alemtuzumab reduced the risk of experiencing sustained accumulation of disability through year 5 by 72% compared with interferon beta-1a ( $P < 0.0001$ ). Moreover, at year 5, 86% of alemtuzumab-treated patients were free of disability compared with 62% of patients who received interferon beta-1a. Alemtuzumab also reduced the risk of relapse by 65% compared with the beta interferon ( $P < 0.0001$ ). Approximately 72% of alemtuzumab-treated patients were relapse-free at year 5 compared with 41% of patients receiving interferon beta-1a.

Following the phase 2 CAMMS223 study, alemtuzumab was

evaluated in two pivotal phase 3 trials in patients with MS. The Comparison of Alemtuzumab and Rebif Efficacy in MS, Study One (CARE-MS I) compared alemtuzumab with high-dose interferon beta-1a (Rebif) in patients with early, active remitting-relapsing MS who had not received previous treatment for MS, except steroids.<sup>71</sup> CARE-MS II compared alemtuzumab with interferon beta-1a in patients with relapsing-remitting MS who had relapsed while receiving approved MS therapies.<sup>72</sup>

In CARE-MS I, alemtuzumab (12 mg/day IV for 5 days, with a second 3-day IV administration 1 year later) was compared with interferon beta-1a (44 mcg SQ three times per week) in 581 treatment-naïve patients.<sup>71</sup> Alemtuzumab provided a 55% reduction in the relapse rate compared with interferon beta-1a over 2 years of treatment ( $P < 0.0001$ ). Moreover, fewer alemtuzumab-treated patients (8%) experienced a sustained increase or worsening in disability, as measured by the Expanded Disability Status Scale (EDSS), compared with interferon-treated patients (8% vs. 11%, respectively;  $P = 0.22$ ).

Common AEs associated with alemtuzumab included infusion-related reactions, which were generally mild to moderate in severity. In addition, the incidence of infections was increased. The most common infections involved the upper respiratory and urinary tracts along with oral herpes. These infections were mainly mild to moderate, and none was life-threatening or fatal. The incidence of serious AEs was similar for alemtuzumab and interferon beta-1a (18.4% vs. 14.4%, respectively). Eighteen percent of alemtuzumab-treated patients experienced an autoimmune, thyroid-related AE, and 0.8% developed immune thrombocytopenia.<sup>71</sup>

In CARE-MS II, 840 patients who had experienced a relapse after receiving other MS therapies were given alemtuzumab (12 mg IV once daily for 5 days, then again once daily for 3 days 1 year later) or interferon beta-1a (44 mcg SQ three times per week) over the 2-year study period.<sup>72</sup> A 49% reduction in the relapse rate was observed for alemtuzumab compared with interferon beta-1a ( $P < 0.0001$ ). There was also a 42% reduction in the risk of sustained worsening of disability after treatment with alemtuzumab, as measured by the EDSS ( $P = 0.0084$ ).

The most common AEs associated with alemtuzumab were infusion-related reactions (headache, rash, nausea, hives, fever, itching, insomnia, and fatigue). Both groups experienced infections, with a higher incidence in the alemtuzumab group (i.e., upper respiratory and urinary tract infections, sinusitis, and herpes simplex infections). Treatment-related infections were generally mild to moderate in severity; none was life-threatening or fatal. During the 2-year study period, 16% of alemtuzumab patients experienced an autoimmune, thyroid-related AE, and 1% developed immune thrombocytopenia.<sup>72</sup>

Despite the efficacy rates reported in CARE-MS I and CARE-MS II, safety concerns (potentially fatal thrombocytopenic purpura) may place alemtuzumab as a last-line therapy for MS.

### Rituximab (Rituxan)

Rituximab (Rituxan, Genentech) is a genetically engineered chimeric murine/human monoclonal IgG<sub>1</sub> kappa antibody directed against the CD20 antigen, a hydrophobic transmembrane protein located on pre-B and mature B lymphocytes. CD20 regulates early steps in the activation process for cell-cycle initiation and differentiation. The Fab domain of

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rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune–effector functions to mediate B-cell lysis *in vitro*.<sup>73</sup>

In an open-label, phase 1 study, patients with relapsing–remitting MS received two courses of rituximab 6 months apart and were observed for 72 weeks.<sup>74</sup> Mild-to-moderate infusion-related effects were reported. Infections were also mild or moderate in severity, and none led to discontinuation of therapy. An apparent reduction in relapses was noted over the 72-week follow-up period compared with the year before treatment.

The effects of B-cell depletion with rituximab in MS patients were investigated in a double-blind, phase 2 clinical study.<sup>75</sup> A total of 104 patients with relapsing–remitting MS were randomly assigned to receive two courses of rituximab (1,000 mg IV) or placebo and were observed for 48 weeks. The primary efficacy endpoint was the total count of gadolinium-enhancing (GdE) lesions detected on MRI brain scans at weeks 12, 16, 20, and 24. Clinical outcomes included the proportion of patients who experienced relapse. Rituximab-treated patients had significantly reduced counts of GdE brain lesions at each evaluation time point compared with the placebo-treated patients ( $P < 0.001$ ), as well as a significant reduction in the total number of new GdE lesions ( $P < 0.001$ ). Fewer rituximab patients experienced relapse at week 24 (14.5% vs. 34.3% receiving placebo;  $P = 0.02$ ) and at week 48 (20.3% vs. 40.0% receiving placebo;  $P = 0.04$ ).<sup>75</sup>

In a small phase 2 clinical study, based on blinded radiological endpoints, Naismith et al. found that rituximab add-on therapy was effective for MS.<sup>76</sup> Thirty patients who had experienced relapse within the previous 18 months, despite the use of an injectable disease-modifying agent, and who had at least one GdE lesion on any of three pretreatment MRIs received rituximab (375 mg/m<sup>2</sup>) weekly for four doses. Three monthly post-treatment brain MRI scans were obtained, beginning 12 weeks after the first infusion. Multiple Sclerosis Functional Composite (MSFC) and EDSS scores were obtained at baseline and throughout the post-treatment follow-up period.

After rituximab treatment, 74% of MRI scans showed no GdE activity compared with 26% of scans at baseline ( $P < 0.0001$ ). The mean number of lesions was reduced from 2.81 per month to 0.33 per month after treatment, representing an 88% reduction. MSFC scores showed significant improvement ( $P = 0.02$ ), and EDSS scores remained stable. Rituximab was well tolerated, with no serious AEs reported.<sup>77</sup> This phase 2 study indicated that add-on rituximab reduced brain lesions in patients with MS. B-cell–modulating therapy remains a potential option for patients with relapsing MS who have shown an inadequate response to standard injectable therapies.

In a phase 3 study, Fleischmann reported a case of PML in association with rituximab in a patient with rheumatoid arthritis and Sjögren's syndrome.<sup>77</sup> This finding has caused some concern. PML was diagnosed approximately 18 months after the last course of rituximab, and the patient died 1 month later. More study is needed on the risk of PML with rituximab.

### Ocrelizumab

Ocrelizumab (Roche/Biogen Idec) is a humanized anti-CD20 monoclonal antibody that targets mature B lymphocytes.<sup>78,79</sup> It was developed specifically for use in autoimmune

diseases, such as MS, rheumatoid arthritis, and lupus erythematosus.<sup>79</sup> However, in March 2010, Roche suspended the development of ocrelizumab for the treatment of rheumatoid arthritis and lupus, citing the occurrence of serious infections, some fatal, in clinical trials.<sup>80,81</sup> Research continued in MS.

Results from a phase 2 trial of ocrelizumab in patients with relapsing–remitting MS were published in 2011.<sup>78</sup> In this randomized, double-blind, placebo-controlled study, 218 adults, 18 to 55 years of age, received low-dose ocrelizumab (600 mg) or high-dose ocrelizumab (2,000 mg), both given in two doses 2 weeks apart, or with intramuscular, once-weekly interferon beta-1a (30 mcg). At week 24, the number of GdE-enhancing brain lesions was 89% lower with ocrelizumab 600 mg than with placebo ( $P < 0.0001$ ) and 96% lower with ocrelizumab 2,000 mg ( $P < 0.001$ ). Both doses were more effective than interferon beta-1a in reducing the number of brain lesions. Annualized relapse rates were 80% lower with ocrelizumab 600 mg than with placebo and 73% lower with ocrelizumab 2,000 mg.

### Ibudilast

Medici Nova Inc. of San Diego has received U.S. patent and trademark approval for oral ibudilast (MN-166), either alone or in combination with other drugs, for treating progressive forms of MS and/or neuropathic pain.<sup>82</sup> A few clinical trials have shown favorable effects on measures of disability progression in MS patients. The drug's mechanism of action includes the inhibition of leukotriene activity, phosphodiesterases, and nitric oxide synthase.

### COST CONSIDERATIONS

The 2012 price of glatiramer acetate (Copaxone) is about \$42,300 per year, a 39% jump since January 2010. Novartis' pricing for fingolimod (Gilenya) is higher, at \$48,000 per year, in part because it's the first drug in tablet form, whereas the other MS treatments must be injected or infused. As of 2012, Biogen's natalizumab (Tysabri) costs about \$3,566 per month, or \$42,788 per year. The price of Avonex is \$37,544 per year, according to Biogen Idec.

### CONCLUSION

The FDA has approved eight medications for relapsing–remitting MS. All have been shown to reduce the number of relapses (attacks or exacerbations) and the number of new lesions (plaques or scars) on MRI brain scans. Five injectables—four beta interferons (Avonex, Betaseron, Extavia, and Rebif) and the copolymer polypeptide mixture glatiramer acetate—are generally viewed as first-line treatments for MS. Most experts recommend that treatment begin with one of these drugs as soon as the diagnosis of relapsing–remitting MS has been confirmed. Second-line therapies include natalizumab and mitoxantrone (Novantrone).

MS is a progressive disease with no cure so far. Although treatments are available to manage the disease course, they are only partially effective. Therefore, MS worsens in some patients despite everything they and their physicians do to prevent it. Patients with relapsing–remitting MS, the most common form of MS, experience attacks of worsening neurological functioning, followed by periods of remission characterized by partial or complete recovery.

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A combination of drugs and physical, speech, and occupational therapies; exercise; rest; and healthful nutrition may relieve symptoms and promote a satisfactory quality of life.

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