

Current Strategies in the Treatment of Multiple Sclerosis

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation, demyelination, and axonal degeneration.¹⁻⁵ Although descriptions date back as far as the Middle Ages, MS was first recognized as a distinct disease in 1868 when Jean-Martin Charcot, professor of Neurology at the University of Paris, referred to the condition as *sclérose en plaques*.⁶⁻⁸ MS affects roughly 400,000 people in the United States and 2.5 million people worldwide.^{2,4} MS is associated with a heterogeneous array of signs and symptoms because of involvement of the motor, sensory, visual, and autonomic systems.^{1,3,5,9,10}

Twenty-five years ago, the first disease-modifying treatment (DMT), interferon beta-1b, was approved by the US FDA for the treatment of MS.¹¹ Since that time, and especially over the last 5 years, an increasing number of novel DMTs have been approved for the treatment of MS.^{3,12} These agents decrease but do not completely eliminate disease progression and/or disability in patients with MS.^{1,5,12,13}

Overview of MS

MS is among the most common causes of neurological disability in young adults.^{4,15,16} The known prevalence of MS is increasing, which is most likely due to greater awareness and improved imaging techniques.^{17,18} The clinical presentation of MS is extremely variable and is largely unpredictable.^{10,18}

Approximately half of all patients with MS require walking assistance within 15 years of disease onset.¹⁹ MS does not usually diminish life expectancy; however, the development of complications (eg, pneumonia, urosepsis) can lead to a shorter than average life expectancy.^{10,15} Suicide rates for patients diagnosed with MS are up to 7.5 times higher than those rates observed in the general population.¹⁶

Regarding pathogenesis of MS, both genetic and environmental factors are thought to play a role.^{3,6,9,10,15} Several causative factors appear to affect risk of developing MS, such as previous viral infections; distance from the equator prior to age 15 (ie, above the 37th parallel); family history (primarily first-degree relatives); cigarette smoking; and decreased sunlight exposure/vitamin D levels.^{3,9,10} Multiple studies of sunlight exposure and vitamin D levels suggest that increased vitamin D consumption in early life may decrease likelihood of MS.⁹

Although the disease can affect any ethnic group, individuals of Northern European descent are more likely to be affected than other ethnicities.^{3,10} MS typically presents in adults 20 to 45 years of age, but occasionally it presents in childhood or in later middle age.^{10,18,19} Women are more frequently diagnosed with MS compared with men by at least a 2:1 ratio and as high as 3:1.^{6,10,18,19}

MS is characterized by destruction of the myelin on neurons (demyelination) and subsequent damage to the underlying axon.²⁰ The demyelinating plaque, the main pathologic hallmark of MS, contains a

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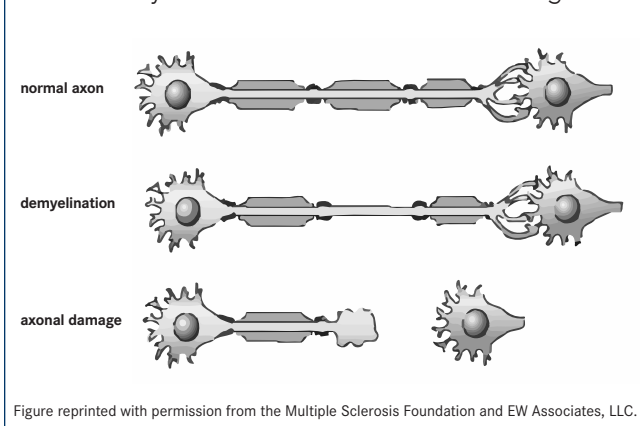
FIGURE. Myelin Destruction and Axonal Damage

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prominent immunologic response dominated by CD8+ and CD4+ T cells. When activated, these T cells (primarily TH1 cells) cross the blood–brain barrier into the CNS and attack the myelin sheath on the axons (see **Figure**). The resulting inflammation deteriorates the myelin, which slows or interrupts the conduction of nerve impulses along the axons.^{1,9}

Demyelination leads to axonal damage, which can affect both white and gray matter. Recent data have highlighted the involvement of gray matter, which may be especially relevant to the irreversible disability that occurs in MS.¹⁸ Over time, demyelination can leave the underlying axon exposed and susceptible to damage.^{9,18,20} Axon loss is believed to be the major cause of permanent disability in patients with MS. B cells and their products also contribute to the pathogenesis of MS. B cells produce proinflammatory and anti-inflammatory cytokines, where proinflammatory cytokines activate T cells for T cell mediated demyelination.^{9,18,20}

Diagnosing Multiple Sclerosis

MS is a diagnosis of exclusion.¹⁰ The diagnosis is based on clinical expertise and involves obtaining evidence from a clinical examination, medical history, laboratory tests, and magnetic resonance imaging (MRI) scans of the brain and spinal cord.²¹ These tests are intended to gather data consistent with MS, while ruling out other possible causes not consistent with the disease.¹⁰

Despite the lack of a diagnostic test for MS, MRI scans are increasingly recognized as essential noninvasive tools for initial investigation of suspected disease.²² MRI scans show high sensitivity for detection of focal white matter lesions in the CNS and specifically for lesions disseminated in time and space. Dissemination in space is fulfilled by the presence of 1 or more lesions in 2 of 4 characteristic anatomic locations, while dissemination in time is demonstrated by simultaneous presence of gadolinium (Gd) enhancing and Gd non-enhancing lesions at follow-up MRI examination.²² Gray matter lesions are

associated with cognitive impairment and are present in the brains of patients with MS. MRI sensitivity is much lower in detecting gray matter lesions compared with detecting white matter lesions.²² There is currently a lack of standardized image acquisition and analysis for gray matter lesions.

The McDonald criteria are the most widely accepted diagnostic criteria for MS.²³ A diagnosis of MS requires that lesions are disseminated in time and space, referring to the occurrence of at least 2 episodes of neurological dysfunction reflecting distinct sites of CNS damage that cannot be explained by any other mechanisms.^{10,19} The goal of the McDonald criteria is to diagnose MS as soon as possible by allowing MRI-detected brain lesions, cerebrospinal fluid abnormalities, and visual-evoked potentials (VEPs) to substitute for clinical lesions in defining “separated by time and space.” The original criteria were released in 2001,²³ updated in 2005²⁴ and 2010,²⁵ and revisions to the McDonald criteria in 2017 have further simplified the diagnosis of MS.²⁶

Types of Multiple Sclerosis

Approximately 80% of MS cases present initially as clinically isolated syndrome (CIS),³ which refers to an acute clinical attack affecting 1 or more sites in the CNS, and can convert to clinically defined MS (CDMS).³ The rate of conversion to CDMS varies based on initial presentation. At baseline, 82% of patients with more than 1 clinically silent white matter MRI lesion eventually develop CDMS, as compared with only 21% of patients with normal MRIs who go on to develop CDMS.³ A majority of CDMS falls under the category of relapsing-remitting MS (RRMS), but other types include secondary progressive MS, primary progressive MS, and progressive relapsing MS.⁹

Less commonly, patients also present with radiologically isolated syndrome (RIS).¹⁰ In cases of RIS, individuals have clinical scenarios not typical of MS, yet obtain MRI scans for other reasons (eg, headache) and have radiological scans suggestive of MS. See **Table 1** for additional information on types of MS.

Treating Multiple Sclerosis

The clinical management of MS should be considered as 3 distinct parallel pathways^{3,10}:

1. Relapses (acute exacerbations) should be treated with appropriate therapies.
2. Symptomatic problems associated with MS should be managed with additional medications to prevent and/or treat complications and to preserve quality of life (QoL).
3. Disease-modifying therapies should be used to decrease the number and severity of relapses, to

decrease progression, and to prevent/minimize neuronal damage.

Treating Acute Exacerbations

Corticosteroids are considered the mainstay of treatment for acute exacerbations.^{10,28,29} Treatment with corticosteroids is associated with immunomodulation, anti-inflammatory effects, restoration of the blood–brain barrier, and reduction of edema.²⁹ Numerous controlled clinical trials have found that corticosteroid therapy hastens recovery time from acute attacks, and that high-dose corticosteroids are significantly more effective than moderate-dose regimens.²⁹ However, it is important to note that although high-dose corticosteroids have proven to shorten the duration of acute attacks, they have *not* demonstrated the ability to alter the progression of the disease.³ The American Academy of Neurology recommends intravenous methylprednisolone (500 to 1000 mg/day for 3 to 10 days) for the treatment of acute exacerbations.³⁰ Some evidence suggests that equivalent doses of high-dose oral corticosteroids are comparable

pharmacokinetically to intravenous methylprednisolone; definitive studies are lacking.¹⁰ Alternatives to corticosteroids, such as plasma exchange and intravenous immunoglobulin, should be considered for patients who do not respond or who are not considered viable candidates for corticosteroid therapy.^{3,10} See **Table 2** for additional information on dosing and indications.

Symptom Management

The localization and severity of MS lesions within the brain and spinal cord are unpredictable and, therefore, a wide range of body systems can be adversely affected to varying degrees. Consequently, MS is associated with a host of symptoms and comorbidities that can negatively impact activities of daily living and QoL (see **Table 3**).³¹

Common symptomatic problems associated with MS include bladder dysfunction (various subtypes), bowel dysfunction (various subtypes), cognitive dysfunction, sexual dysfunction, depression, fatigue, gait disturbances, pain (various subtypes), and spasticity.^{3,7,10,31} Because no 2 patients with MS are alike, symptomatic problems

TABLE 1. Types of Multiple Sclerosis^{3,9,10,19,27}

Categories	Description
Benign MS	<ul style="list-style-type: none"> • Challenging concept and diagnosis • Characterized by very minimal disease activity (eg, few exacerbations that are often sensory) and minimal disability accruing over time • Diagnosis typically made in hindsight
Relapsing-Remitting MS (RRMS)	<ul style="list-style-type: none"> • Most common type of MS; accounts for 85% of cases at diagnosis • Characterized by a worsening of pre-existing symptoms or the onset of new symptoms for periods exceeding 24 hours without concomitant fever • Correlation exists between new brain MRI lesions and clinical attacks (exacerbations), but typically there are many more new MRI lesions than new clinical symptoms • Exacerbations tend to decrease over time
Progressive Disease	
Secondary-Progressive MS (SPMS)	<ul style="list-style-type: none"> • RRMS can progress to SPMS • Characterized by axonal injury and atrophy in both white and gray matter, with a likely underlying neurodegenerative pathogenesis, but less inflammation • Without treatment with disease-modifying therapies (DMTs), approximately 50% of patients with RRMS will develop SPMS after 10 to 15 years • Adherence to DMTs decreases conversion of RRMS to SPMS
Primary-Progressive MS (PPMS)	<ul style="list-style-type: none"> • Less than 15% of patients develop PPMS at baseline • Characterized by symptoms that worsen from onset of disease without relapses or remissions • Differs from RRMS: later age at onset (~40 years), associated with spinal cord disease, and a slight male predominance • PPMS accounts for <5% of cases
Progressive-Remitting MS (PRMS)	<ul style="list-style-type: none"> • Some clinicians do not recognize PRMS as subtype of MS • Characterized by progressive disease from the start, with intermittent flare-ups along the way • There are no periods of remission • PRMS accounts for <5% of cases

MRI indicates magnetic resonance imaging; MS, multiple sclerosis.

TABLE 2. Dosing and Indications for FDA-Approved Disease-Modifying Therapies^{11,14,32-43}

Generic Name (Brand name)	Recommended Dose	Indication
First-Generation Injectable Products		
Interferon beta-1b (Betaseron)	250 mcg SC every other day	Relapsing forms of MS (including CIS)
Interferon beta-1a (Avonex)	30 mcg IM once weekly	Relapsing forms of MS (including CIS)
Interferon beta-1a (Rebif)	22-44 mcg SC TIW	Relapsing forms of MS
Interferon beta-1b (Extavia)	250 mcg SC every other day	Relapsing forms of MS (including CIS)
PegINF beta-1b (Plegridy)	125 mcg SC every other day	Relapsing forms of MS
Glatiramer acetate (Copaxone; Glatopa)	20 mg SC once daily ^{35,36} 40 mg SC TIW ³⁵	Relapsing forms of MS
Orally Administered Products		
Fingolimod (Gilenya)	0.5 mg once	Relapsing forms of MS
Dimethyl fumarate (Tecfidera)	120 mg BID for 1 week; then 240 mg BID	Relapsing forms of MS
Teriflunomide (Aubagio)	7 mg or 14 mg once daily	Relapsing forms of MS
Postmillennial Injectable Products		
Natalizumab (Tysabri)	300 mg IV infusion every 4 weeks	Relapsing forms of MS
Alemtuzumab (Lemtrada)	<u>Year 1:</u> 12 mg IV infusion on 5 consecutive days <u>Year 2:</u> 12 mg IV infusion for 3 consecutive days	Relapsing forms of MS in patients who have had an inadequate response to ≥2 previous DMTs
Ocrelizumab (Ocrevus)	<u>Start dose:</u> 300 mg IV infusion, followed by a second 300 mg IV infusion 2 weeks later <u>Subsequent dose:</u> 600 mg IV infusion every 6 months	Relapsing or primary progressive MS
Daclizumab (Zinbryta)*	150 mg SC once monthly	Relapsing forms of MS in patients who have had an inadequate response to ≥2 previous DMTs

*In March 2018, daclizumab (Zinbryta) was withdrawn worldwide following reports of inflammatory encephalitis and meningoencephalitis.

BID indicates twice daily; CIS, clinically-isolated syndrome; DMT, disease-modifying therapy; IM, intramuscular; IV, intravenous; MS, multiple sclerosis; SC, subcutaneous; TIW, three times weekly.

tend to vary tremendously. Generally, symptomatic issues may be less severe or averted when patients are adherent to DMTs.

Disease-Modifying Therapies

Current FDA-approved, first-generation, injectable DMTs include 4 interferon beta formulations (5 branded products)^{11,14,32-34} and glatiramer acetate (2 branded products).^{35,36} In addition to these products, 3 oral agents (fingolimod,³⁷ dimethyl fumarate,³⁸ and teriflunomide³⁹), and 4 injectable products (natalizumab,⁴⁰ alemtuzumab,⁴¹ ocrelizumab,⁴² and daclizumab^{*43}) are indicated for the treatment of MS. Mitoxantrone is also approved for worsening MS⁴⁴; however, it is rarely used in clinical practice due to potential cardiac toxicity and risk of secondary leukemias.^{10,18}

Treatment with DMTs has been shown to reduce relapse rates and slow progression of changes, progression of disability, and cognitive decline, but efficacy varies among products.¹⁰

As with efficacy, safety considerations also vary greatly between products. The interferon beta products and glatiramer acetate are generally associated with fewer adverse events, in terms of number and severity,¹² whereas products such as natalizumab, daclizumab*, and alemtuzumab, which have Risk Evaluation and Mitigation Strategies (REMS), are associated with higher frequency and severity of adverse events.^{12,40,41,43}

Interferon Beta Products. The interferon beta products appear to exhibit potent activity at the blood–brain barrier and impair trafficking of inflammatory cells into the CNS, thereby decreasing inflammation.^{4,10,18} They decrease T cell production of interferon gamma (a pro-inflammatory cytokine), decrease the production of pro-inflammatory T-helper 1 lymphocytes and increase the production of T-helper 2 anti-inflammatory lymphocytes, and decrease T-lymphocytes trafficking into the CNS.^{4,10,18} By suppressing T-cell proliferation, these products may decrease permeability of the blood–brain barrier by decreasing matrix

metalloproteinases.¹⁰ These effects appear to be exerted in the periphery and at the blood–brain barrier level.

In pivotal trials, the interferon beta products decreased relapses in patients with RRMS by approximately one-third compared with placebo.^{45–47} Data also suggested that these products decreased the number of lesions, reduced disease burden on MRI, and delayed progression of physical disability.

Influenza-like symptoms, such as fever, chills, tiredness, malaise, and muscle aches, are the most common adverse events (AEs), occurring in approximately 60% of patients.^{11,14,32,34} Over time, influenza-like symptoms tend to decrease.¹⁰ Treatment with antipyretics such as ibuprofen or acetaminophen and/or low-dose oral corticosteroids may decrease these symptoms. Injection site reactions, increased spasticity, mild anemia, thrombocytopenia, and menstrual irregularities have also been reported with these products.^{11,14,32,34} Although depression is a common symptomatic problem in patients with MS, all of the interferon beta products can produce depressive symptoms.¹⁰ Treatment with any of these products can result in the development of neutralizing antibodies.^{4,10,12,19} These antibodies can decrease the effectiveness of the interferon beta product.

Glatiramer Acetate. Glatiramer acetate is a synthetic mixture of polypeptides produced by the random combinations of 4 amino acids that are frequently found in myelin basic protein.^{10,48,49} While the exact mechanism of glatiramer acetate is not known, it appears that immunomodulatory effects can be attributed to its ability to alter T-cell differentiation. Treatment is thought to promote the development of Th2 cells, which have anti-inflammatory properties. These cells suppress the immune attack on myelin within the CNS. Evidence also suggests that glatiramer acetate has neuroprotective properties.⁵⁰ Glatiramer acetate slows brain atrophy and stimulates CD4 T cells to produce brain-derived neurotrophic factor, which helps to protect the brain from axonal damage.¹² In addition, glatiramer acetate reduces the formation of chronic black holes.

The 20-mg formulation of glatiramer acetate produces similar decreases in annualized relapse rates compared with the interferon beta products.^{10,12,49} Multicenter trials with the 20-mg formulation have demonstrated significant reductions in mean annual relapse rate; other trials have suggested that glatiramer acetate slows progression of disability and delays the appearance of T1 holes on brain MRIs.¹⁰ Data suggest that the 40-mg three-times-per-week formulation has similar efficacy to the 20-mg formulation.^{10,49}

Glatiramer acetate is generally well tolerated, with injection site reactions (such as mild pain and itching) the most commonly reported events.⁴ Approximately

10% to 15% of patients who receive glatiramer acetate experience a transient reaction, known as postinjection reaction, consisting of chest pain, palpitations, and/or trouble breathing within minutes of administering a dose.^{9,12} This reaction usually only happens once and typically resolves within 30 minutes without residual adverse consequences. Lipoatrophy has also been reported with glatiramer acetate.^{9,35}

Fingolimod. The mechanism underlying the therapeutic effect of fingolimod in MS is not known, but it may involve the reduction of lymphocyte migration into the CNS.^{19,49} Fingolimod, a sphingosine-1-phosphate (S1P) receptor agonist, binds to the S1P receptor. The immunosuppressant properties of fingolimod enable the product to sequester circulating lymphocytes into secondary lymphoid organs.^{10,49} Nodal trapping of lymphocytes renders them unavailable for entering into the CNS and attacking myelin.¹⁸ Data suggest that fingolimod may also have neuroprotective properties.¹⁰

Efficacy of fingolimod was established in three phase 3 pivotal trials.^{51,52} These trials were conducted in patients with RRMS. TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) was a double-blinded, placebo-controlled trial. When compared with placebo, fingolimod 0.5 mg significantly reduced annualized relapse rates by 54%.⁵² Risk of disability progression was also reduced, as were the number of new or enlarged lesions and loss of brain volume compared with placebo. FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) was a double-blind, double-dummy trial. In this trial, fingolimod 0.5 mg significantly decreased annualized relapse rates when compared with intramuscular (IM) interferon beta-1a.⁵² Relapses, lesion activity, and brain loss were also significantly improved with fingolimod.

Common AEs associated with fingolimod include headache, influenza, diarrhea, back pain, liver enzyme elevations, and cough.³⁷ More serious safety concerns include increased risk of malignancies, bradycardia/atrioventricular block (first dose only), increased risk of opportunistic infections, first-dose bradycardia, hypertension, shortness of breath, and macular edema. The FDA-approved labeling of fingolimod requires first-dose monitoring (including re-initiation after discontinuation for greater than 14 days) for at least 6 hours. The first-dose monitoring, which requires electrocardiograms prior to dosing and at the end of the observation period, evaluates for bradycardia. As of September 2015, progressive multifocal leukoencephalopathy (PML) had been reported in 3 patients after each reached 3 years of exposure (see **Table 4**).¹⁰

Dimethyl Fumarate. Dimethyl fumarate is an in vitro nicotinic acid receptor agonist and an in vitro activator

TABLE 3. Pharmacological Interventions for Symptom Management^{3,7,10,31}

Symptomatic Problem	Pharmacological Interventions ^a
Detrusor overactivity	<u>First-line</u> : anticholinergic medications (eg, terazosin, tamsulosin, alfuzosin, silodosin) <u>Second-line</u> (either alone or in combination with baclofen): imipramine <u>Refractory</u> : botulinum toxin
Detrusor sphincter dyssynergia	<ul style="list-style-type: none"> • Alpha-antagonist medications (eg, alfuzosin, doxazosin, terazosin, silodosin)
Constipation	<u>First-line</u> : bulking agents (eg, psyllium, methylcellulose, calcium polycarbophil) <u>Second-line</u> : osmotic agents (eg, magnesium sulfate, magnesium citrate, polyethylene glycol), stimulant laxatives (eg, bisacodyl, senna, cascara, castor oil), and stool softeners (eg, docusate sodium, docusate calcium)
Fecal incontinence	<ul style="list-style-type: none"> • Bulking agents (eg, methylcellulose) • Loperamide (an antidiarrheal product)
Cognitive dysfunction	<ul style="list-style-type: none"> • Cholinesterase inhibitors (eg, donepezil) • NMDA receptor antagonists (eg, memantine) • Stimulating or activating products (eg, amantadine, methylphenidate)
Depression	<ul style="list-style-type: none"> • Selective serotonin reuptake inhibitors • Selective norepinephrine reuptake inhibitors • Tricyclic antidepressants • Bupropion • Mirtazapine
Fatigue	<ul style="list-style-type: none"> • Modafinil/armodafinil • Selective serotonin reuptake inhibitors (eg, fluoxetine) • Amantadine
Gait disturbances	<ul style="list-style-type: none"> • Dalfampridine
Trigeminal neuralgia	<u>First-line</u> : carbamazepine and oxcarbazepine <u>Second-line</u> : baclofen, lamotrigine, and misoprostol
Lhermitte's sign	<ul style="list-style-type: none"> • Gabapentin • Pregabalin • Carbamazepine
Neurogenic pain	<ul style="list-style-type: none"> • Carbamazepine • Tricyclic antidepressants • Gabapentin • Pregabalin • Duloxetine • Topiramate
Spasticity	<u>First-line</u> : baclofen <u>Second-line</u> (either alone in combination with baclofen): tizanidine, diazepam, clonazepam, dantrolene, or clonidine <u>Refractory</u> : botulinum toxin or intrathecal baclofen

^aWith the exception of dalfampridine, none of the symptomatic treatments above are FDA-approved specifically for multiple sclerosis.

of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway.¹⁰ Within the CNS, dimethyl fumarate decreases inflammation.⁴⁸ The pharmacological effect is due to the active metabolite monomethyl fumarate.⁴

The efficacy of dimethyl fumarate in patients with RRMS was established in two phase 3 pivotal trials.^{54,55} The DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS) trial was a randomized, placebo-controlled, double-blind study.⁵⁴ When compared with placebo, relapses over 2 years were significantly improved

with 240 mg BID (twice daily) dimethyl fumarate (27% vs 46%, respectively). There was also a reduction in annualized relapse rate of 53%, reduction in confirmed progression of disability of 38%, and a reduction in the number of new or enlarging T2 lesions and Gd-enhancing lesions.

CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis) was a randomized, placebo-controlled, double-blind trial.⁵⁶ Glatiramer acetate was a reference comparator; however, the study was not powered to directly compare dimethyl fumarate with

glatiramer acetate. When compared with placebo, relative risk reduction was significantly decreased with dimethyl fumarate 240 mg BID (44%) and with glatiramer acetate (29%). In addition, the number of new or enlarging T2 lesions was also significantly decreased with both dimethyl fumarate and glatiramer acetate.

Gastrointestinal events (including nausea, vomiting, diarrhea, abdominal pain) and flushing (including warmth, redness, or itching of the face or upper body) are the most common adverse reactions with dimethyl fumarate.¹⁰ Over time, these events appear to dissipate. Lymphocytopenia and increased liver- function enzymes have also been reported. Two cases of PML were reported as of September 2015.

Teriflunomide. Teriflunomide, which appears to have anti-inflammatory and antiproliferative properties, is an immunomodulatory agent.^{10,12} It inhibits dihydroorotate dehydrogenase, which is the rate-limiting enzyme in the *de novo* synthesis of pyrimidine, leading to an indication of proliferation of autoreactive B and T cells. Replication of hematopoietic and memory cells is preserved through the salvage pathway based on the existing pyrimidine pool. Teriflunomide also appears to have immunomodulatory properties with induction of a shift to an anti-inflammatory cytokine profile, a class switching of immunoglobulins, and a reduction of interleukin (IL-2) production and IL-2 receptor expression.

The efficacy of teriflunomide in patients with RRMS was established in two phase 3 pivotal trials.^{56,57} In the TEMSO (Teriflunomide Multiple Sclerosis Oral) and TOWER (Teriflunomide Oral in People with Relapsing-Remitting Multiple Sclerosis) trials, treatment with teriflunomide 14 mg significantly decreased annualized relapse rates by 32% and 36%, respectively, compared with placebo. Additionally, the risk of disability progression was also significantly decreased in both trials.

Teriflunomide is generally well tolerated; common AEs include gastrointestinal symptoms, hair thinning, skin rashes, weight loss, infections, and increased liver function.¹² Teriflunomide requires a black box warning because of the risk of hepatotoxicity and teratogenicity (based on animal data).³⁹ Monitoring of liver function and avoidance in pregnancy are therefore essential. Women of child-bearing potential must use reliable contraception while receiving teriflunomide and for 2 years after the last dose. Since teriflunomide is present in semen, the same contraceptive precautions apply to men.³⁹

Natalizumab. Natalizumab is a humanized monoclonal antibody that antagonizes the alpha-4 integrin of the adhesion molecule very late in the activating antigen (VLA)-4 on leukocytes.^{10,12} Inhibition of VLA-4 is responsible for blockade of T cells across the blood-brain barrier.

The efficacy of natalizumab in patients with RRMS was

TABLE 4. What is Progressive Multifocal Leukoencephalopathy (PML)?^{12,53}

PML is a rare event caused by the John Cunningham (JC) virus, which is ubiquitous throughout the world. It presents as an asymptomatic infection in 50% to 60% of cases. PML likely results from convergence of multiple factors including virus mutation, host factors, and effects of drugs that reduce central nervous system surveillance. In general, PML has a mortality rate of 30% to 50% in the first few months following diagnosis, but outcome depends on the severity of the underlying disease and treatment received. Those who survive PML can be left with severe neurological disabilities.

established in 2 phase 3 pivotal trials.^{58,59} In the 2-year AFFIRM (A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis), annual relapse rates were significantly decreased by >60%, Gd-enhancing lesions were significantly decreased by >90%, and progression of disability was significantly decreased with natalizumab versus placebo.⁵⁸ In the 2-year SENTINEL (The Safety and Efficacy of Natalizumab in Combination with Interferon beta-1a in Patients with Relapsing-Remitting Multiple Sclerosis) trial, patients receiving natalizumab plus interferon beta-1a IM had relapse rate decreases of >50% and Gd-enhancing lesion decreases of 84% compared with interferon beta-1a IM monotherapy.⁵⁹

Infusion reactions have been reported in some patients. Serious hypersensitivity reactions have been reported in 1.3% of patients and are often associated with neutralizing antibodies. Other adverse events including mild lymphocytosis and increased liver function have also been reported. Several months after the FDA approval of natalizumab, the product was withdrawn from the market because of 2 cases of PML. The product was later allowed back on the market in the United States, with the requirement that all patients and prescribers register with a mandatory REMS program (**Table 5**).

Alemtuzumab. Alemtuzumab, a humanized monoclonal antibody, binds to the cell surface of CD52 on T and B lymphocytes, natural killer cells, monocytes, and macrophages.⁴¹ Within minutes of administration, alemtuzumab leads to depletion of CD52-positive cells through antibody-dependent, cell-mediated cytolysis and complement depletion.

The efficacy of alemtuzumab was established in 2 phase 3 pivotal trials of alemtuzumab versus interferon beta 1-a, known as CARE-MS.^{61,62} These trials were conducted in patients with RRMS. In these trials, alemtuzumab significantly decreased annualized relapses when compared with subcutaneous (SC) interferon beta-1a (CARE-MS-I, 54.9%⁶¹; CARE-MS-II, 49.4%⁶²). A significant reduction in

6-month accumulation was only observed in CARE-MS-II. MRI measures also proved superior with alemtuzumab versus interferon beta-1a SQ, as there were significantly fewer Gd-enhancing lesions, fewer new or enlarging T2 lesions, and less brain atrophy.^{61,62}

The most common adverse events include infusion-related symptoms and infections.⁴ Infusion-associated reactions, which are reported in 90% of patients, are typically mild to moderate in intensity; they consist of headache, rash, pyrexia, and nausea. Respiratory tract and urinary tract infections are the most common reported infections.¹⁰ Opportunistic infections such as cytomegalovirus and pulmonary nocardiosis have also been reported.⁴ The accumulation of herpes infections during the CARE-MS clinical trial program led to the implementation of prophylactic acyclovir treatment for the first 4 weeks after the infusions. Secondary autoimmune disease (primarily thyroid disease) affects approximately 30% to 40% of patients. There is also a small but serious risk of developing immune thrombocytopenia.

Ocrelizumab. Ocrelizumab is a humanized monoclonal antibody.^{63,64} It binds to CD20, a cell surface antigen that is present on pre-B and mature B lymphocytes, resulting in B-cell depletion. Ocrelizumab is structurally similar to rituximab, a product commonly used off-label for the treatment of MS.

The approval of ocrelizumab was supported by data from two phase 3 trials, OPERA I and OPERA II, which evaluated the use of ocrelizumab in patients with RRMS.^{63,64} In these studies, ocrelizumab decreased relapses by approximately 50%, slowed the worsening of disability, and reduced the number of Gd-enhancing lesions compared with interferon beta-1a SC. The ORATORIO study evaluated the use of ocrelizumab in patients with PPMS.^{63,64} After 3 years, treatment with ocrelizumab has been associated with decreased progression of disability and decreased signs of disease activity in the brain (MRI lesions) compared with placebo.

The most common adverse events with ocrelizumab are infusion reactions and upper respiratory tract infections, which are generally mild to moderate in severity.^{63,64} Other adverse events (specifically infections and malignancies) have also been reported with ocrelizumab. Treatment with ocrelizumab also increases the risk of upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. Because of the increased risk of infection, ocrelizumab is contraindicated in patients who are experiencing active hepatitis B infections and should be avoided in patients with active infections until the infection has resolved. There also appears to be an

increased risk of breast cancer with ocrelizumab, based on the phase 3 clinical trials. PML and suicide have been reported in 1 patient each.

Daclizumab*. Daclizumab is a humanized monoclonal antibody that targets CD25, a subunit of the human high-affinity IL-2 receptor.^{9,12} It inhibits CD25-IL-2 complex formation, which is typically abnormal in MS patients. Targeting CD25 causes several immunological effects, including expansion of immunoregulatory CD56^{bright} natural killer cells, inhibition of T-cell activation by dendritic cells, and reduction in lymphoid tissue inducer cells.

The approval of daclizumab was supported by data from two phase 3 clinical trials.^{65,66} These trials were conducted in patients with RRMS. In the DECIDE trial, daclizumab significantly decreased the annualized relapse rate by 45% compared with interferon beta-1a IM.⁶⁶ At 96 weeks, 73% of patients treated with daclizumab were relapse-free compared with 59% of interferon beta-1a IM-treated patients. Daclizumab also significantly decreased the number of new or newly enlarging T2-hyperintense lesions at week 96, with a 54% reduction relative to interferon beta-1a IM. In the SELECT trial, annualized relapse rates were decreased by 54% with daclizumab 150 mg versus placebo.^{65,66} New Gd-enhancing lesions, number of new or newly enlarging T2-hyperintense lesions, and proportion of patients who relapsed were also decreased. Sustained disability progression at year 1 was reduced by 57%.

Among the most common adverse events with daclizumab are nasopharyngitis, upper respiratory tract infections, rash, influenza, dermatitis, oropharyngeal pain,

TABLE 5. Natalizumab REMS Program⁶⁰

Restricted access program that serves to educate healthcare providers and patients about the use and risks of natalizumab

Mandates in the natalizumab REMS program:

Natalizumab is used only as monotherapy in patients with RRMS who have not responded adequately to or who cannot tolerate first-line DMTs.

Natalizumab is administered only through infusion centers registered with the REMS program.

Before initiating therapy, patients must receive brain MRI. Patients must be evaluated at 3 and 6 months after the first infusion and every 6 months thereafter.

Estimated risk for developing PML while receiving treatment with natalizumab is low; the following factors appear to impact the overall risk:

- Duration of treatment \geq 24 months
- History of JCV infection
- Prior immunosuppressant use

JCV indicates John Cunningham virus; REMS, risk evaluation and mitigation strategies.

bronchitis, eczema, and elevated liver function.^{65,66} Serious infections and serious cutaneous adverse events have also been reported.

Conclusions

Since 1992, the field of multiple sclerosis has been characterized by significant advances. Fourteen branded products, of varying levels of safety and efficacy, have been approved and are now routinely prescribed. Although these agents decrease progression and/or disability in patients with MS, it is important to note that none of them completely eliminates disease progression and disability.^{1,5,13}

*** In March 2018, Biogen withdrew daclizumab (Zinbryta) worldwide following reports of inflammatory encephalitis and meningoencephalitis.**

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