

An Update on New and Emerging Therapies for Relapsing-Remitting Multiple Sclerosis

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In 1993, the US Food and Drug Administration (FDA) approved the first disease-modifying therapy (DMT), interferon (IFN) beta-1b, marking a major change in the management of multiple sclerosis (MS).¹ Prior to the development of DMTs, MS was considered an untreatable disease, and management strategies for MS were primarily focused on treating the acute attacks (relapses) that are characteristic of the disease course for the majority of MS patients¹ and on diminishing the associated neurological symptoms (symptomatic therapies).^{2,3} DMTs, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs,⁴ are used to slow the development of MS-related neurological damage and disability progression and to reduce the occurrence of relapses.^{1,5} By providing a more effective approach to MS treatment, DMTs may improve quality of life for individuals with MS.⁴

Following the first IFN product (subcutaneous [SC] IFN beta-1b [Betaseron, Bayer HealthCare Pharmaceuticals Inc; Extavia, Novartis Pharmaceuticals, Inc]), additional interferon products (IFN beta-1a intramuscular [IM], Avonex, Biogen Idec; and IFN beta-1a SC, Rebif, EMD Serono, Inc), glatiramer acetate (GA) (Copaxone, Teva Pharmaceutical Industries Ltd), natalizumab (Tysabri, Biogen Idec), fingolimod (Gilenya, Novartis Pharmaceuticals Corporation), and more recently, teriflunomide (Aubagio, Genzyme Corporation) and dimethyl fumarate (DMF; Tecfidera, Biogen Idec), have received FDA approval for the treatment of relapsing MS.^{1,4,6,7} Mitoxantrone is approved for the treatment of secondary-progressive MS (SPMS), progressive-relapsing MS, or worsening relapsing-remitting MS (RRMS).⁸ A stepwise approach was generally followed for MS DMTs used in the pre-oral era; therapy was usually initiated with IFN beta or GA, and patients who did not respond to these first-line agents were treated with natalizumab or, more rarely, mitoxantrone.^{9,10} First- and second-line DMTs have been shown to reduce the rate of MS relapses, slow the progression of disability, and reduce magnetic resonance imaging (MRI) measures of disease activity.^{1,5,11} Despite the demonstrated efficacy of DMTs, patient adherence to DMTs remains problematic.^{12,13} Poor patient adherence to therapy may result in reduced treatment efficacy in delaying MS progression and in poorer patient outcomes.¹⁴ There is some evidence

Abstract

Disease-modifying therapies (DMTs), known to actively reduce relapses and delay disability progression, have been used for the treatment of relapsing-remitting multiple sclerosis (RRMS) for over a decade. These well-known therapies include intramuscular (IM) interferon (IFN) beta-1a (Avonex), subcutaneous (SC) IFN beta-1a (Rebif), SC IFN beta-1b (Betaseron; Extavia), and SC glatiramer acetate (Copaxone). These first-line therapies have shown only partial benefits for controlling multiple sclerosis (MS) disease activity and are often associated with inadequate patient adherence. Low patient adherence to therapy may be related to the mode of administration or to the side effects associated with treatment. The intravenous DMT natalizumab (Tysabri; dosed monthly) provides high therapeutic efficacy and good compliance but is considered a second-line intervention because of the associated increased risk for progressive multifocal leukoencephalopathy. In 2010, fingolimod (Gilenya), the first oral DMT, was approved by the US Food and Drug Administration (FDA) for the treatment of MS. Recently, 2 new oral DMTs received FDA approval for the treatment of RRMS: teriflunomide (Aubagio) and dimethyl fumarate (Tecfidera). In addition, oral laquinimod, several monoclonal antibodies (eg, alemtuzumab, daclizumab, and ocrelizumab), and other agents have shown preliminary beneficial results in relapsing MS in phase 3 clinical trials. These new and emerging DMTs may provide a more efficacious individualized therapeutic approach, more favorable methods of administration (eg, oral administration), and/or a lower frequency of infusions (eg, annually, 3-5 daily infusions over a year for alemtuzumab) that may improve patient adherence and clinical outcomes.

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that poor patient adherence to DMT may be related to the fact that some of these agents are administered via SC or IM injection.^{10,14-16} In a study of 2648 patients receiving IFN beta or GA, the most common reasons for nonadherence to treatment were forgetting to administer the injection (50.2%) and other injection-related reasons (32.0%).¹⁵ To improve adherence to DMTs and outcomes associated with long-term DMT use, recent attention has focused on the development of DMTs with improved tolerability and efficacy and those that are orally administered or require less frequent administration.¹⁷⁻²² This review will briefly describe the efficacy and safety of established DMTs, including IFN beta, GA, natalizumab, and fingolimod; data from large phase 3 trials of the 2 DMTs that most recently received FDA approval (teriflunomide and DMF) are also described. Efficacy, quality of life, and tolerability data for new and emerging DMTs will also be discussed. Mitoxantrone, approved as treatment for SPMS and worsening RRMS, is not detailed further due to the relative infrequency of its use, mostly related to the side effects associated with its administration, including cardiotoxicity and leukemia, which developed even after administration of lower than the maximum recommended dose (ie, 140 mg/m²).²³

Established DMTs

IFN Beta

IFN beta, which has numerous immunomodulatory activities, was the first DMT approved for the management of MS and remains the foundation of many MS treatment algorithms.^{5,9,10} Three formulations of IFN beta are currently approved for the treatment of RRMS²⁴⁻²⁷: SC IFN beta-1b (administered every other day), SC IFN beta-1a (administered 3 times weekly), and IM IFN beta-1a (administered once weekly).^{5,28} In randomized, controlled, phase 3 studies, all formulations of IFN beta have been associated with an approximate 30% reduction in the annualized relapse rate compared with placebo, as well as significant decreases in MRI markers of disease activity compared with placebo ($P < .05$) in patients with RRMS (Table 1).²⁹⁻⁴¹ In addition, in short, controlled studies, significant delays in the time to sustained progression of disability have been observed with IFN beta-1a treatment compared with placebo ($P < .05$).^{29,30} The efficacy of different IFN beta formulations for decreasing the relapse rate and delaying disability progression in patients with MS is generally comparable; however, direct comparative studies have shown some differences in relapse outcomes, favoring the more frequent SC formulations over IM IFN beta-1a.⁴²⁻⁴⁵ In patients with a first demyelinating event (ie, patients with clinically isolated syndrome [CIS]), IFN beta-

1b treatment has been shown to significantly delay the time to development of clinically definite MS (CDMS) compared with placebo ($P < .0001$),³³ and IM IFN beta-1a has been associated with a significant decrease in the probability of developing CDMS compared with placebo ($P = .002$).³⁴ Flu-like symptoms and injection site reactions are 2 of the most common side effects associated with IFN beta therapy.^{29,31}

GA

Along with IFN beta, GA is considered to be a first-line DMT option for patients with MS.^{5,9,10} GA, a synthetic peptide with an amino acid composition similar to myelin basic protein, has widespread effects on the innate and adaptive immune systems, as well as potential (but unproven) direct neuroprotective and remyelinating effects.^{46,47} In a randomized, placebo-controlled, phase 3 study in patients with RRMS, GA treatment was associated with a 29% reduction in the 2-year relapse rate compared with placebo (Table 1).³⁵ GA treatment has also been associated with significant decreases in the overall number of gadolinium (Gd)-enhancing T1 lesions, number of new Gd-enhancing T1 lesions, and number of new T2 lesions compared with placebo in patients with RRMS ($P \leq .003$).³⁶ In patients with RRMS, no significant differences in relapse outcomes or disease progression have been observed in direct comparative studies of GA and SC IFN beta-1b or IFN beta-1a.⁴⁸⁻⁵⁰ In patients with CIS, treatment with GA has been shown to reduce the risk of progression to CDMS by 45%, delay the time to progression to CDMS by 115%, and significantly reduce the number of new T2 lesions over 2 years compared with placebo ($P < .0001$).³⁷ GA is generally well tolerated, but injection site reactions are relatively common in patients receiving GA treatment.^{35,37}

Natalizumab

Natalizumab is generally considered to be a second-line DMT for patients who have not responded to IFN beta or GA therapy.^{5,9,10,51} Recently, however, it was suggested as a first-line agent in patients who are anti-JC virus antibody negative (JC virus is the causal agent of progressive multifocal leukoencephalopathy [PML]) and present with very active disease or predictors for a worse course (ie, multiple, active Gd-enhancing brain MRI lesions, incomplete recovery from relapse, motor involvement, or African American race). Natalizumab, a humanized monoclonal antibody, is thought to act by reducing the migration of immune cells across the blood-brain barrier into the central nervous system.⁵² In a randomized, controlled, phase 3 study in patients with RRMS, natalizumab treatment was associated with a

■ **Table 1.** Established DMTs²⁹⁻⁴¹

DMT	Formulations/Administration	Efficacy in RRMS/CIS
IFN beta	<ul style="list-style-type: none"> • Subcutaneous IFN beta-1a • Intramuscular IFN beta-1a • Subcutaneous IFN beta-1b 	<ul style="list-style-type: none"> • Approximate 30% reduction on average in the annualized relapse rate compared with placebo in patients with RRMS²⁹⁻³² • Significant decreases in MRI markers of disease activity compared with placebo ($P < .05$) in patients with RRMS²⁹⁻³² • Significant delays in the time to sustained progression of disability (with IFN beta-1a) compared with placebo ($P < .05$) in patients with RRMS^{29,30} • Significant delays in the time to development of CDMS (with IFN beta-1b) compared with placebo ($P < .0001$) in patients with CIS³³ • Significant decrease in the probability of developing CDMS (with intramuscular IFN beta-1a) compared with placebo ($P = .002$) in patients with CIS³⁴
GA	<ul style="list-style-type: none"> • Subcutaneous 	<ul style="list-style-type: none"> • 29% reduction in the 2-year relapse rate compared with placebo in patients with RRMS³⁵ • Significant decreases in MRI markers of disease activity in patients with RRMS ($P \leq .003$)³⁶ • Significant 45% reduction in risk of progression to CDMS, significant 115% delay in the time progression to CDMS, and significant reduction in the number of new T2 lesions over 2 years compared with placebo ($P < .0001$) in patients with CIS³⁷
Natalizumab	<ul style="list-style-type: none"> • Intravenous infusion 	<ul style="list-style-type: none"> • Significant 68% reduction in the annualized relapse rate over 1 and 2 years of treatment compared with placebo ($P < .001$)³⁸ • Significant 42% reduction in the risk of sustained disability progression compared with placebo ($P < .001$)³⁸ • Significant reduction in MRI markers of disease activity compared with placebo ($P < .001$)³⁹ • Significant 54% reduction in the annualized relapse rate over 2 years and a significant 24% reduction in the risk of sustained disability progression at 2 years (in combination with subcutaneous IFN beta-1a) compared with IFN beta-1a alone ($P \leq .02$)⁴⁰
Fingolimod	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • Significant reduction in the annualized relapse rate compared with placebo ($>50\%$; $P \leq .01$)⁴¹ • Significant decrease in the number of Gd-enhancing lesions compared with placebo over 6 months ($P < .001$)⁴¹

CDMS indicates clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; GA, glatiramer acetate; Gd, gadolinium; IFN, interferon; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis.

significant 68% reduction in the annualized relapse rate over 1 and 2 years of treatment, and with a significant 42% reduction in the risk of sustained disability progression compared with placebo ($P < .001$; Table 1).³⁸ A separate, randomized, controlled study showed that combination therapy with natalizumab and SC IFN beta-1a was associated with a significant 54% reduction in the annualized relapse rate over 2 years and a significant 24% reduction in the risk of sustained disability progression at 2 years compared with IFN beta-1a therapy alone ($P \leq .02$).⁴⁰ Natalizumab treatment has also been shown to reduce the number of Gd-enhancing lesions by 92% and reduce the number of new or enlarging T2-hyperintense lesions by 83% compared with placebo ($P < .001$).³⁹ In addition, natalizumab treatment (both alone and in combination with SC IFN beta-1a) has been associated with significant improvements in measures of health-related quality of life, specifically the Short Form-36 (SF-36) health survey physical component summary score, over 1

and 2 years of treatment ($P < .05$).⁵³ In general, natalizumab has a favorable tolerability profile; however, natalizumab treatment has been associated with the rare but serious side effect of PML.⁴⁴ Certain patients are at an increased risk of developing PML, including patients who are anti-JC virus antibody positive, those who have previously used immunosuppressants, and those who have undergone longer (>2 years) durations of natalizumab treatment.^{54,55} Patients with all 3 risk factors have the highest risk of developing PML, with an estimated incidence of 11.1 cases per 1000 patients, while patients who are anti-JC virus antibody negative have the lowest risk for developing PML, with an estimated incidence of 0.09 cases or less per 1000 patients.⁵⁴ Identification of patients with risk factors that are associated with an increased likelihood of developing PML may aid patients and providers in making a more informed decision regarding the benefits and risks of natalizumab treatment.⁵⁵

■ **Table 2.** New and Emerging DMTs^{6,7,63-76}

DMT	Efficacy in RRMS
New oral DMTs	
Teriflunomide ⁶	<ul style="list-style-type: none"> • Significant reduction in the annualized relapse rate compared with placebo (31%; $P < .001$)⁶³ • Significant reductions in MRI markers of disease activity compared with placebo ($P < .001$)⁶³ • Significantly lower rate of confirmed disability progression over 2 years compared with placebo ($P = .03$)⁶³ • Significant reduction in MRI markers of disease activity as add-on to IFN beta or GA therapy compared with these therapeutics alone ($P \leq .05$)^{64,65}
DMF ⁷	<ul style="list-style-type: none"> • Significant reductions in the risk of relapse ($P \leq .002$) and the annualized relapse rate ($P < .001$) compared with placebo^{66,67} • Significant reductions in the risk of disability progression compared with placebo ($\geq 34\%$; $P \leq .01$)^{66,68} • Significant improvements in Short Form-36 health survey physical and mental component summary scores and global impression of well-being scores over 2 years of treatment ($P < .05$)^{66,68-70} • Significant increase in the percentage of patients with no clinical or MRI disease activity compared with placebo ($P < .05$)⁷⁰
Emerging monoclonal antibodies	
Alemtuzumab	<ul style="list-style-type: none"> • Significant reduction in the risk of relapse compared with subcutaneous IFN beta-1a (55%; $P < .0001$)⁷¹ • Significant decrease in MRI markers of disease activity compared with IFN beta-1a ($P \leq .04$)⁷¹ • Significant increase in the rate of sustained reduction in disability compared with IFN beta-1a ($P = .0002$)⁷² • Significant decrease in the risk of sustained accumulation of disability over 6 months compared with IFN beta-1a ($P = .0084$)⁷²
Daclizumab	<ul style="list-style-type: none"> • Significant reduction in the annualized relapse rate compared with placebo ($\geq 50\%$; $P \leq .0002$) and significant decrease in the percentage of patients who relapsed ($\geq 51\%$; $P \leq .0003$)⁷³ • Significant reduction in the rate of confirmed disability progression compared with placebo ($P \leq .021$)⁷³ • Significant improvements in the physical score on the Multiple Sclerosis Impact Scale compared with placebo ($P = .0007$)⁷³ • Significant improvements in MRI markers of disease activity compared with placebo ($P < .0001$)⁷³
Rituximab	<ul style="list-style-type: none"> • Significant reduction in the number of patients who experienced a relapse compared with placebo (20%; $P \geq .04$)⁷⁴ • Significant decrease in MRI markers of disease activity compared with placebo ($P < .001$)⁷⁴
Ocrelizumab	<ul style="list-style-type: none"> • Significant decrease in annualized relapse rate compared with placebo (~77%; $P \leq .0014$)⁷⁵ • Significant decrease in MRI markers of disease activity compared with placebo ($P < .0001$)⁷⁵
Emerging oral DMT	
Laquinimod	<ul style="list-style-type: none"> • Significant decrease in the annualized relapse rate compared with placebo (laquinimod, 0.30 ± 0.02; placebo, 0.39 ± 0.03; $P = .002$)⁷⁶ • Significant decrease in the risk of confirmed disability progression (laquinimod, 11.1%; placebo, 15.7%; $P = .01$)⁷⁶ • Significant decrease in MRI markers of disease activity compared with placebo ($P < .001$)⁷⁶

DMF indicates dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; IFN, interferon; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis.

Fingolimod

Fingolimod is the first FDA-approved oral DMT for the treatment of MS. It received approval in September 2010.⁴¹ Fingolimod is a sphingosine 1-phosphate receptor modulator that inhibits the egression of lymphocytes from lymph nodes, reducing the availability of activated lymphocytes and consequently impeding abnormal autoimmune processes.⁵² In a 2-year, randomized, placebo-controlled, phase 3 study

of fingolimod 0.5 or 1.25 mg per day, the annualized relapse rate was reduced by 54% to 60%, depending on the dose, compared with placebo ($P = .02$); these clinical improvements were supported by improvements in MRI measures of disease activity, including significant reductions in the number of new or enlarging T2-weighted lesions and Gd-enhancing lesions and a significantly smaller reduction in brain volume with both doses of fingolimod compared with placebo ($P < .001$).⁵⁶

In a 1-year direct comparative study in patients with RRMS, fingolimod treatment was associated with a significantly lower annualized relapse rate than IM IFN beta-1a ($P < .001$) in patients with RRMS; no significant difference was observed in the progression of disability between treatment groups.⁵⁷ Fingolimod is relatively safe and well tolerated; the most common adverse events (AEs) reported with fingolimod treatment include headache, influenza, nasopharyngitis, dyspnea, diarrhea, and nausea.⁴¹ Dose-dependent decreases in heart rate within an hour after dosing have also been observed in patients taking fingolimod and are associated with an increased incidence of bradycardia and atrioventricular block.^{41,57,58} There is, however, only 1 dose (0.5 mg) of fingolimod approved for the treatment of RRMS, and a 6-hour observation period following the first dose to monitor for symptoms of bradycardia is recommended.⁵⁸ Previous known exposure to varicella zoster virus and/or vaccination is required before initiating therapy.⁵⁹ This is based on 2 known cases of herpes infection resulting in death. Macular edema must be screened for prior to therapy and again at 4 months posttherapy.

New Oral DMTs

Teriflunomide

Teriflunomide received initial FDA approval in September 2012 for the treatment of RRMS.⁶ Teriflunomide inhibits the proliferation of stimulated T and B lymphocytes in the periphery that are thought to be responsible for the damaging inflammatory processes involved in MS and diminishes the number of activated T and B cells available to migrate into the central nervous system.⁶⁰⁻⁶² Teriflunomide also selectively and reversibly inhibits dihydroorotate dehydrogenase, a key enzyme in *de novo* pyrimidine synthesis required by rapidly dividing lymphocytes.⁶⁰⁻⁶² Treatment with teriflunomide has no effect on the pyrimidine salvage pathway, basic homeostatic cell functions of resting lymphocytes, or normal immune surveillance. Teriflunomide, which is given as a once-daily oral tablet, has demonstrated both preventive and therapeutic effects in preclinical models of MS.⁶⁰

In clinical studies, teriflunomide was associated with delayed disability progression and reductions in the annualized relapse in both DMT-naïve patients and patients who have previously taken a DMT, as well as with improvements in MRI markers of disease progression (Table 2).^{6,7,63-80} In a randomized, placebo-controlled, phase 2 trial of 2 doses of teriflunomide (7 or 14 mg/day) in patients with relapsing MS ($n = 179$) and a long-term, open-label extension ($n = 147$) of that phase 2 study (median treatment duration, 7.1 years), significant benefits were observed in MRI markers of disease progression over 36 weeks compared with

placebo ($P < .04$) and decreases were observed in the annualized relapse rate and rate of disability progression (based on Expanded Disability Status Scale [EDSS] scores).^{77,78} A 2-year, randomized, placebo-controlled, phase 3 study of teriflunomide (7 or 14 mg/day) in patients with relapsing MS ($n = 1088$) showed that the annualized relapse rate was reduced by approximately 31% for both doses of teriflunomide compared with placebo ($P < .001$) and the number of Gd-enhancing T1 lesions per scan and unique active lesions per scan were significantly lower in both teriflunomide groups than in the placebo group ($P < .001$; Table 2).⁶³ A significantly lower percentage of patients had confirmed disability progression over 2 years with teriflunomide 14 mg/day compared with placebo ($P = .03$).⁶³ In a study by Wolinsky and colleagues, teriflunomide 7 mg/day and 14 mg/day had significantly better outcomes for accumulated enhanced lesions ($P < .0001$ for both doses), and T1 ($P = .0161$ for 14 mg only) and T2 (7 mg, $P = .0404$; 14 mg, $P = .0004$) component lesion volumes compared with placebo.⁸⁰ These findings are complementary to previously published data from the same study, which showed significantly lower increases in total lesion volume with teriflunomide 7 mg ($P = .0317$) and 14 mg ($P = .0003$) compared with placebo.^{63,80}

Teriflunomide has also been evaluated as an add-on to IFN beta or GA therapy.^{64,65} In a 1-year, randomized, phase 2 study of teriflunomide (7 or 14 mg/day) in patients who were taking IFN beta for RRMS ($n = 116$), the number of Gd-enhancing T1 lesions was significantly reduced with both doses of teriflunomide added to IFN beta compared with IFN beta alone, with a relative risk reduction of more than 80% ($P \leq .0005$).⁶⁵ In another 1-year, randomized phase 2 study of teriflunomide (7 or 14 mg/day) in patients who were taking GA for relapsing MS ($n = 123$), the number of Gd-enhancing T1 lesions was significantly reduced with teriflunomide 7 mg/day added to GA compared with GA alone ($P = .031$).⁶⁴ In a randomized, controlled, phase 3 study directly comparing teriflunomide (7 or 14 mg/day) with SC IFN beta-1a, the percentage of patients who failed treatment (experienced a relapse or discontinued treatment) was similar for both doses of teriflunomide (7 mg/day, 48.6%; 14 mg/day, 37.8%) and for IFN beta-1a (42.3%).⁸¹ Lower percentages of patients in the teriflunomide groups (7 mg/day, 18.3%; 14 mg/day, 19.8%) discontinued treatment than in the IFN beta-1a group (28.8%), and satisfaction with treatment after 2 years was higher in both teriflunomide groups than in the IFN beta-1a group.⁸¹ Teriflunomide is generally safe and well tolerated.⁶³ In the previously described 2-year, randomized, placebo-controlled, phase 3 study of teriflunomide, the most common AEs that occurred more frequently in the terifluno-

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mide group than in the placebo group were diarrhea, nausea, hair thinning or decreased hair density, and elevated alanine aminotransferase levels (which were observed in 6.7% of patients in the placebo group, 12.0% of patients in the teriflunomide 7 mg/day group, and 14.2% of patients in the 14 mg/day group).⁶³ Monthly liver function monitoring for the first 6 months is recommended, as well as a baseline tuberculin skin test. Accelerated elimination of teriflunomide in cases of hepatotoxicity or pregnancy can be achieved (within 11 days) using cholestyramine or activated charcoal.

Dimethyl fumarate

DMF is a modified fumaric acid ester recently approved by the FDA for the treatment of RRMS.^{7,82} DMF is commonly used for the treatment of psoriasis⁸³ and is thought to have primarily immunomodulatory properties that are responsible for its activity in patients with MS.^{82,84,85} In a randomized, placebo-controlled, phase 2b study of DMF (120 mg once a day, 120 mg 3 times a day, or 240 mg 3 times a day) in patients with RRMS (n = 257), significant improvements were observed in MRI markers of disease activity over 122 weeks compared with placebo ($P \leq .014$), only with the higher dosage, and the annualized relapse rate was reduced by approximately 32% compared with placebo, although it did not reach significance.⁸⁶ A 2-year, randomized, placebo-controlled, phase 3 study investigated DMF 240 mg twice a day or 3 times a day in patients with RRMS (n = 1234). Compared with placebo, significant reductions were observed in the risk of relapse with both DMF twice a day and 3 times a day regimens (49% and 50%; $P < .001$), as well as reductions in the annualized relapse rate (53% and 48%; $P < .001$; Table 2).⁶⁶ Compared with placebo, the risk of disability progression was also significantly reduced with DMF 240 mg twice a day (38%; $P = .005$) and 3 times a day (34%; $P = .01$).⁶⁶ DMF was associated with significant improvements in measures of physical and mental function, health-related quality of life, and general well-being; SF-36 health survey physical and mental component summary scores and global impression of well-being scores improved significantly over 2 years of treatment ($P < .05$).^{66,69} An analysis of patients with MRI measures from that study (n = 469) showed that the percentage of patients with no clinical or MRI disease activity was significantly higher with both doses of DMF compared with placebo ($P < .05$).⁶⁶

In another 2-year, randomized, placebo- and active-controlled, phase 3 study of DMF (240 mg twice a day or 3 times a day), both doses of DMF were associated with significant reductions in the risk of relapse (twice a day, 34%; $P = .002$ and 3 times a day, 45%; $P = .001$) as well as the annualized

relapse rate (twice a day, 44% and 3 times a day, 51%; $P < .001$ for both doses) compared with placebo.⁶⁷ The study had an active comparator arm, GA. No significant differences in clinical and MRI outcomes were seen between the active treatment arms, although the study was not powered to evaluate head-to-head treatment superiority. However, all parameters were better in the DMF arms compared with the GA arm. These study results did not demonstrate a significant benefit in preventing sustained disability progression with DMF 240 mg twice a day (21%; $P = .25$) and 240 mg 3 times a day (24%; $P = .20$) compared with placebo at 2 years.⁶⁷ MRIs were performed in only 48% of enrolled patients (preplanned). The analysis showed that DMF 240 mg twice a day and 3 times a day reduce the number of new T1 lesions by 57% and 65% ($P = .001$ for both doses), respectively; the odds of developing more Gd-enhancing lesions were reduced by 74% and 65% ($P < .001$ for both doses), respectively.⁶⁷ DMF is generally safe and well tolerated; the most common AEs associated with DMF in phase 3 studies included flushing, gastrointestinal AEs (eg, diarrhea, nausea, vomiting), pruritus, and proteinuria.^{66,67} Recently, a few cases of PML were reported in patients receiving fumaric acid for psoriasis, either in a fixed-combination of DMF and 3 monoethyl hydrogen fumarate salts (Fumaderm, Biogen Idec) or a compounded fumaric acid ester product containing DMF and possibly other ingredients (eg, copper monoethyl fumaric acid; Psorinovo [compounding pharmacy, Mierlo-Hout]).⁸⁷⁻⁸⁹ These patients were lymphopenic for over 2 years while continuing on fumarate products. No cases of PML have been seen in patients with MS treated with DMF; however, patients who develop lymphopenia (a potential side effect of DMF), may need to be monitored more closely.^{87,89}

Emerging DMTs

Monoclonal Antibodies

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that targets the CD52 surface protein, which is found on all B and T cells in high concentration and, to a lesser degree, on other immune cells.^{22,90} Alemtuzumab has been associated with significant reductions in the relapse rate, disability progression, disability scores, and MRI measures of disease activity compared with SC IFN beta-1a.^{71,91-94}

In a 3-year, randomized, controlled phase 2 study of alemtuzumab (12 or 24 mg intravenously administered for 5 days at month 0, for 3 days at month 12, and [in approximately one-third of patients] for 3 days at month 24) in treatment-naïve patients with RRMS (n = 334), significant reductions in the annualized relapse rate and risk of sustained disability

were observed compared with SC IFN beta-1a ($P \leq .006$).⁹¹ Similar results were observed at 3 and 5 years.^{93,95} In a 2-year, randomized, controlled phase 3 study of alemtuzumab (12 mg intravenously for 5 days at month 0 and 3 days at month 12) in treatment-naïve patients with early RRMS ($n = 581$), alemtuzumab was associated with a significant 55% reduction in the risk of relapse at 2 years compared with SC IFN beta-1a ($P < .0001$; Table 2).⁷¹ The percentage of patients with Gd-enhancing lesions and new or enlarging T2-hyperintense lesions was significantly lower with alemtuzumab compared with IFN beta-1a ($P \leq .04$) and brain volume loss (as measured by brain parenchymal fraction) was reduced approximately 40% with alemtuzumab versus IFN beta-1a.⁷¹ In a separate, 2-year, randomized, controlled phase 3 study comparing alemtuzumab (12 or 24 mg intravenously on annual cycles) with SC IFN beta-1a in patients with RRMS ($n = 840$) not well controlled on previous DMTs (average of 1.5 to 1.7 relapses during the previous year with IFN beta or GA), the relapse rate was reduced by 49% compared with IFN beta-1a ($P < .0001$), and the percentage of relapse-free patients at 2 years was significantly higher with alemtuzumab (65%) than with IFN beta-1a (47%; $P < .0001$).⁷² In addition, the risk of sustained accumulation of disability was reduced by approximately 42% with alemtuzumab compared with IFN beta-1a over 2 years ($P = .0084$), and the percentage of patients with a sustained reduction in disability at 2 years was significantly higher in the alemtuzumab group (29%) than in the IFN beta-1a group (13%; $P = .0002$).⁷² Benefits in MRI measures of disease activity were also observed and were consistent with those observed in the previously described study.⁷²

Alemtuzumab treatment has been commonly associated with infusion reactions that are mostly mild to moderate and managed with premedication. Alemtuzumab has also been associated with an increase in infections (although few have been serious) and with potential delayed secondary autoimmune events⁹⁶⁻¹⁰¹; thyroid disorders have been observed in up to 30% of patients and immune thrombocytopenia purpura has been observed in up to 3% of patients who received alemtuzumab.^{95,102} There are rare cases of anti-glomerular basement membrane disease.

Daclizumab

Daclizumab is a recombinant humanized monoclonal anti-CD25 antibody that received FDA approval in 1997 for the prevention of renal allograft rejection.¹⁰³⁻¹⁰⁶ Daclizumab binds to and blocks the alpha subunit of the high-affinity interleukin-2 receptor (CD25), a transmembrane protein expressed on the surface of activated T cells; by blocking CD25, daclizumab inhibits T-cell expansion, resulting in

suppression of inflammation.^{103,106-108} Daclizumab treatment also causes the expansion of CD56 natural killer cells, which inhibit the survival of recently activated CD4+ T cells.^{107,109}

Daclizumab has been associated with improvements in MRI measures of disease activity, relapse rates, and disability progression.^{73,110-113} In a 6-month, open-label, phase 2 study in patients with MS who had not responded to IFN beta treatment ($n = 11$), daclizumab treatment (1 mg/kg intravenously 2 weeks apart in the first month, then 1 mg/kg every 4 weeks [7 total infusions]) was associated with a 78% reduction in new contrast-enhancing lesions and a significant improvement in the EDSS score and timed 25-foot walk ($P \leq .048$).¹¹⁰ These results were confirmed in a separate phase 2 study in patients with RRMS.¹¹² In a separate 1-year, randomized, double-blind, placebo-controlled, phase 2b study in 600 patients with RRMS, treatment with daclizumab high-yield process (150 or 300 mg SC every 4 weeks) resulted in significant ($\geq 50\%$) reductions in the annualized relapse rate compared with placebo ($P \leq .0002$), delays in disability progression, a significant improvement in the physical score of the Multiple Sclerosis Impact Scale (150-mg dose only), and significant benefit in MRI markers of disease progression ($P \leq .021$; Table 2).⁷³ Daclizumab treatment is generally well tolerated; mild infections, including upper respiratory infections, nasopharyngitis, and urinary tract infections, are among the most commonly reported side effects.^{73,110,111} In the large-scale, 1-year, phase 2b study, 1 patient who was recovering from a serious skin infection died from the complication of an undiagnosed abscess in a lower back muscle.^{73,114}

Rituximab

Rituximab is a mouse/human chimeric monoclonal antibody that targets the CD20 marker of B lymphocytes.¹⁸ In a randomized, controlled, phase 2 study in patients with RRMS ($n = 104$) who received 1 cycle of rituximab given as a 1000-mg dose at days 1 and 15, the number of patients who experienced a relapse over 24 and 48 weeks was significantly lower in the rituximab group (24 weeks, 14.5%; 48 weeks, 20.3%) than in the placebo group (24 weeks, 34.3%; 48 weeks, 40.0%; $P \leq .04$), and rituximab treatment was associated with a significant decrease in the number of Gd-enhancing lesions over 24 and 48 weeks compared with placebo ($P < .001$; Table 2).⁷⁴ Infusion-related AEs were reported by a higher percentage of patients in the rituximab group than in the placebo group after the first infusion; the most common drug-related AEs in the rituximab group included chills, headache, nausea, pruritus, pyrexia, fatigue, throat irritation, and pharyngolaryngeal pain.⁷⁴

Reports

Ocrelizumab

Ocrelizumab is a humanized immunoglobulin G1 anti-CD20 antibody that targets mature B lymphocytes and is currently being evaluated for the management of relapsing MS.¹¹⁵ In a 48-week, randomized, placebo- and active-controlled, phase 2 study of ocrelizumab (600 or 2000 mg intravenously on days 1 and 15 of 2 cycles approximately 6 months apart) in patients with RRMS (n = 220), the mean total number of Gd-enhancing lesions over weeks 12, 16, 20, and 24 was significantly lower in the ocrelizumab 600 mg (0.6 lesions) and 2000 mg (0.2 lesions) groups than in the placebo group (5.5 lesions; $P < .0001$).⁷⁵ The annualized relapse rate was also significantly lower in both the ocrelizumab 600 mg group (0.13) and 2000 mg group (0.17) than in the placebo group (0.64) at 24 weeks of treatment ($P \leq .0014$; Table 2).⁷⁵ Ocrelizumab was well tolerated with similar rates of AEs and serious AEs compared with placebo; infusion-related reactions were reported by a higher percentage of patients in the ocrelizumab group than in the placebo group following the first infusion.⁷⁵ Studies of ocrelizumab in patients with systemic lupus erythematosus and rheumatoid arthritis were discontinued because of serious infectious AEs.¹¹⁵

Oral DMT

Laquinimod

Laquinimod is a quinolone-carboxamide that acts by modulating pro-inflammatory immune responses and interfering with cell trafficking; it may have possible neuroprotective effects.¹¹⁶⁻¹¹⁹ In clinical studies, laquinimod was associated with reductions in disease activity based on clinical (annualized relapse rate and risk of disability progression) and MRI measures.^{76,120-122} In a 24-week, randomized, placebo-controlled, phase 2 study of laquinimod (0.1 or 0.3 mg/day) in patients with RRMS (n = 209), laquinimod 0.3 mg per day reduced the mean cumulative number of active lesions by 44% compared with placebo ($P = .0498$).¹²⁰ In a separate 36-week, randomized, placebo-controlled, phase 2 study in patients with RRMS (n = 306), laquinimod 0.6 mg per day was associated with a significant reduction of approximately 40% in the mean cumulative number of Gd-enhancing lesions per scan compared with placebo ($P = .0048$)¹²¹; continued suppression of disease activity was observed in a 36-week extension study (n = 257).¹²² In a 2-year, randomized, placebo-controlled, phase 3 study in patients with RRMS (n = 1106), laquinimod 0.6 mg per day was associated with a significant reduction in the mean annualized relapse rate compared with placebo (0.30 ± 0.02 vs 0.39 ± 0.03 ; $P = .002$) and with a significant reduction in the risk of confirmed disability progression (11.1% vs 15.7%; $P = .01$;

Table 2).⁷⁶ The mean cumulative number of Gd-enhancing lesions (laquinimod, 1.33 ± 0.14 ; placebo, 2.12 ± 0.22) and the numbers of new or enlarging T2-weighted lesions (laquinimod, 5.03 ± 0.08 ; placebo, 7.14 ± 0.07) were significantly lower with laquinimod compared with placebo ($P < .001$).⁷⁶ The most common AEs associated with laquinimod include elevated liver enzyme levels, elevated fibrinogen levels, respiratory tract infections, headache, asthenic conditions, insomnia, nausea and vomiting, dizziness, arthralgia, diarrhea, cough, and musculoskeletal pain.¹¹⁹ An ongoing large phase 3 trial evaluating the benefit of a higher dose of laquinimod in RRMS patients is in progress.

Other Emerging Agents for MS

All of the previously described therapeutics have shown benefit in the treatment of patients with only relapsing forms of MS. Additional therapeutics are being explored for the treatment of MS, including antigen- and antigen-receptor-based therapies, vaccinations, cellular therapies, agents that promote neuroprotection or neural repair, and agents that are currently available for other indications.¹²³ Clinical efficacy and safety data for antigen-specific therapies, such as dirucotide, is lacking, but studies of these innovative therapeutics are ongoing and promising new agents are emerging.¹²³ The application of antigen-specific therapies may also be hindered by a lack of biomarkers, which prevents the development of individualized treatment, and by the heterogeneity of targets in MS.¹²³ While cellular therapies (eg, bone marrow transplants, mesenchymal stem cells) offer many potential benefits, the risk of side effects associated with these treatments necessitates careful analysis of their efficacy and safety.¹²³

Conclusion

Currently available DMTs have been shown to reduce the occurrence of relapses and slow the development of MS-related neurological damage and disability progression (mostly due to relapses and inflammatory injury), resulting in improved patient quality of life.^{4,5} Despite the proven efficacy of these DMTs, a need remains for DMTs with increased efficacy (primarily related to the progressive state of the disease) and improved safety and tolerability. In part, because the majority of currently available DMTs require IM or SC parenteral administration, their use may be associated with poor compliance.¹⁰ Newly emerging DMTs, including the approved oral therapeutics (fingolimod, teriflunomide, and DMF) or therapeutics that are administered less frequently (eg, alemtuzumab), may be associated with improved patient compliance with therapy,¹⁰ as well as improved patient outcomes, particularly for patients who show a lack of efficacy and/or tolerability

for currently available DMTs. As further efficacy and safety data for these therapies become available, their role in the treatment of MS will become more firmly established and their use may improve disease status and patients' quality of life.

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