Present and Emerging Therapies for Multiple Sclerosis

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ABSTRACT

Purpose of Review: The treatment of multiple sclerosis (MS) is evolving beyond the current parenteral immunomodulators and early oral alternatives, offering physicians considerable choice of therapies. Although all agents are tested in similarly designed clinical studies, comparison of their outcomes is not possible except in carefully controlled head-to-head comparator studies. In this review, the current, recent, and most imminent therapies are discussed and an overall summary is presented along with a discussion of how they are perceived relative to the older or other recent agents.

Recent Findings: The list of potentially effective agents for the treatment of MS may be exhaustive, but several have now completed their phase 3 trials and have received or imminently expect government approval. This review discusses these new agents in terms of their perceived mechanisms of action and their respective results, and attempts to position them among the currently approved and utilized agents for MS.

Summary: Although it is not yet possible to predict which treatment is best suited to a given patient, it is nevertheless important to have a perspective of the possible agents and their efficacy and safety, and a plan regarding how to use them in order to maximize benefit and minimize harm in controlling relapsing MS.

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INTRODUCTION

The 1990s brought the first treatments that were intended to alter the natural history of multiple sclerosis (MS) by reducing relapses and stalling the buildup of disability. Now, after nearly 3 decades of treatment with the disease-modifying therapies (DMT) interferon-β (IFN-β) and glatiramer acetate (GA), many new agents are entering or poised to enter the world of current therapy for relapsing MS. The website *www.ClinicalTrials.gov* lists more than 800 ongoing trials for MS, with many new agents in development or in phase 1 and 2 testing. With three oral therapies now available, several more emerging, and a number of specialized monoclonal antibody treatments available or soon to be, the treatment of MS is becoming more complex. Treatment choices now depend on a full understanding of a patient's clinical condition and what might be the ideal choice of medication based on a perceived understanding of what may be transpiring in an individual and what is hoped to be gained—a more "personalized" approach.

A concept of MS immunopathogenesis[1] forms the basis for understanding why many of the therapies have been developed and where and how in the disease process they might

make a difference (**Figure 4-1**).[2] In some cases, agents have emerged from experience in treatment of non-CNS autoimmune diseases such as psoriasis or rheumatoid arthritis. Fingolimod, for example, came to MS from the world of organ transplantation, despite having failed to reduce the need for stronger immunosuppression in the prevention of organ rejection. Teriflunomide is a descendant of the currently approved treatment leflunomide for rheumatoid arthritis. Dimethyl fumarate (DMF) and other fumaric acid esters have been used for years to treat psoriasis. More monoclonal antibodies (all named with the suffix –mab) and the chimeric receptor–targeted molecules (those with the suffix –cept) are also emerging from trials and showing some promise for the treatment of MS. Most recently, the direction has expanded to include the B-cell component of the immune cascade, which might be more involved in progressive disease.

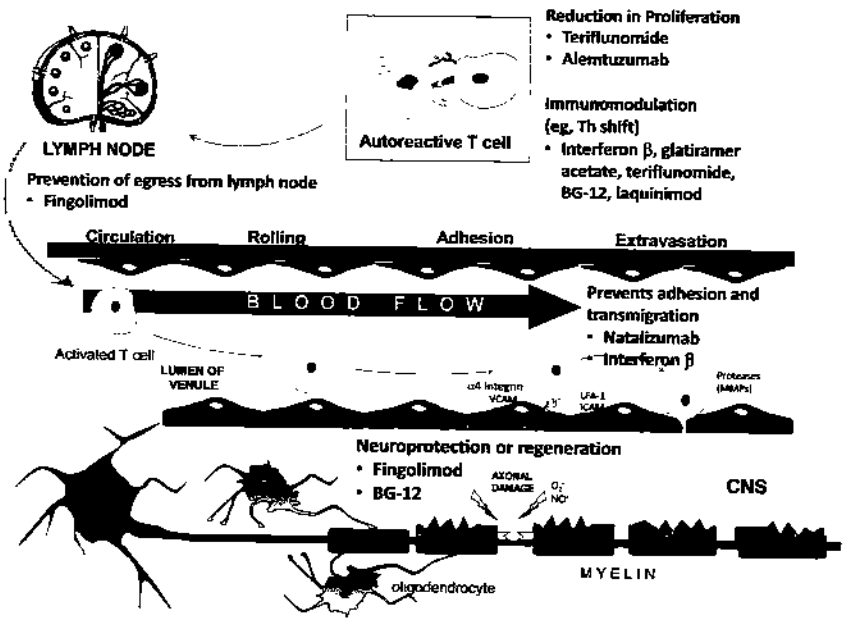

FIGURE 4-1 A simplified overview of the postulated mechanism of action of standard injectables and new oral therapies. Fingolimod reduces available circulating lymphocytes by blocking lymphocyte egress from lymph nodes. Teriflunomide does so by depleting the de novo pyrimidine pools often used by the most activated and proliferating lymphocytes, sparing the slowly proliferating ones (eg, memory T cells) that utilize mostly the salvage pyrimidine pools. Alemtuzumab removes the offending autoreactive cells by cytotoxicity and depletion, whereas natalizumab simply blocks their access to the CNS by blocking adhesion and preventing transmigration across the blood-brain barrier. The newer oral therapies, such as laquinimod, dimethyl fumarate (of which BG-12 is a formulation manufactured as an enteric-coated microtablet to improve gastrointestinal tolerability), and probably teriflunomide, may act like interferon-β and glatiramer acetate to modulate cytokines and lymphocyte activation. Fingolimod and dimethyl fumarate hypothetically can cross into the CNS and may act locally to stimulate repair or regeneration or prevent damage (eg, as antioxidants).

Th = T helper; VCAM = vascular cell adhesion molecule; LFA-1 = leukocyte function associated antigen 1; ICAM = intercellular adhesion molecule; MMPs = matrix metalloproteases; O_2 = oxygen; NO = nitric oxide; CNS = central nervous system.

KEY POINT

■ Experience with interferon-β and glatiramer acetate over several decades has assured us of their relative safety in the general public of unselected patients with multiple sclerosis. The same cannot be said of all of the newer agents.

As each new treatment becomes available, it will have to be positioned in the current management scheme, which is not always easy given that most of the trials that lead to their approval are against placebo arms. Several questions arise:

1. How will these treatments compare to IFN-β or GA? Some of the newer trials now include a comparator arm to help address this question.
2. Can the new treatments be used in combination with GA or IFN-β to improve outcomes? Combination trials have been slow to emerge after the first combination of IFN-β and natalizumab[3] raised concerns that it was the combination that led to progressive multifocal leukoencephalopathy (PML).
3. Will they be used in escalation only when patients fail first-line treatment? Because of higher toxicities compared with IFN-β or GA, some treatments are considered "second-line" or greater, while others may be clear alternatives to the traditional first-line agents.
4. Will there be a way to determine who might respond to one drug over another? Biomarkers are starting to shed some light on this important area.
5. Will newer agents be used as "pulse" therapy or "rescue" therapy in tandem or in combination with first-line therapy? Some agents clearly cannot be used lifelong because of cumulative toxicities (eg, alemtuzumab).
6. If escalation or initiation is performed using second-line or higher agents, does this need to be permanent, or can it be only temporary (eg, 6 months to a year)? Could a treating physician reduce ongoing disease activity with a temporary escalation to a more toxic second-line or higher drug, then return to a safer first-line treatment that might maintain that response?

Many questions will be left unanswered for now but are posed to be addressed in upcoming studies. What is clear, however, is that newer therapies with better tolerability and same or better efficacy compared to IFN-β or GA are needed, given that adherence to these first-line agents can be poor, with discontinuation rates of approximately 25% after 1 to 2 years of therapy.[4]

There has been a flurry of activity concerning MS therapies, and a number of the important trials have now been published or presented, with results summarized in Table 4-1. All of these address relapsing MS, although ongoing trials are targeting both primary or secondary progressive MS.

PRESENT INJECTABLE THERAPIES FOR DISEASE MODIFICATION IN MULTIPLE SCLEROSIS

Beginning in 1993, a series of injectable therapies was released for disease modification in MS. These are well known to the clinical neurologist and have undergone extensive evaluation both during pivotal phase 3 trials and in after-marketing studies. Efficacy, tolerability, and safety are well characterized for these medications. This review will briefly summarize their characteristics but focus on newer oral agents (fingolimod, teriflunomide, and dimethyl fumarate) as well as emerging medications.

INTERFERON-β

Since 1993, four IFN-β preparations have received regulatory approval to treat MS. There are two preparations of subcutaneous IFN-β-1b, one of IM

TABLE 4-1 Summary of Study Results Comparing All Recent Therapies Against Placebo

Study Agent	Natalizumab	Fingolimod	Teriflunomide	Laquinimod	BG-12
Relapse rate reduction	68%	54%	31%	23%	53%
Annualized relapse rate	0.23	0.18	0.37	0.28	0.17
Absolute relapse rate reduction	0.50	0.22	0.17	0.09	0.19
Number needed to treat (2-year relapse)	2	5	6	11	5
Relative reduction in new T2 and gadolinium-positive (Gd+) MRI activity	83% in T2 92% in Gd+	74% in T2 82% in Gd+	67% in T2 80% in Gd+	30% in T2 37% in Gd+	85% in T2 90% in Gd+
Relative reduction in Expanded Disability Status Scale progression	42%	30%	30%	36%	38%
Absolute reduction in proportion progressing	0.120	0.064	0.071	0.036	0.110
Number needed to treat (2-year progression)	8	14	14	28	9

IFN-β-1a, and one of subcutaneous IFN-β-1a. IFN-β modulates T-cell and B-cell function, decreases expression of matrix metalloproteinases, reverses blood-brain barrier disruption, and alters expression of a number of cytokines.[5] A series of phase 3 studies in relapsing MS support the benefit of IFN-β in reducing relapses (by approximately 30%), disability progression, and MRI lesion activity and accrual.[6–10]

These agents are generally well tolerated, and the risk profile has been well characterized. The most common side effects include flulike symptoms (eg, fever, chills, malaise, myalgia) after injection, sometimes with concomitant worsening of preexisting neurologic symptoms. These symptoms usually last from several to 24 hours after injection and are worse with the initiation of therapy. In most cases they attenuate over time. Other side effects include injection-site reactions with subcutaneous forms of the medications, rare skin necrosis, depression, leukopenia, liver abnormalities, and thyroid disorders. Patients with preexisting headache syndromes or spasticity may experience a worsening of these symptoms with IFN-β therapy. All of these medicines can now be given with an autoinjector. A subset of patients on IFN-β therapy will develop neutralizing antibodies, which appear to reduce the efficacy of these medications. Testing for these antibodies appears most useful when patients develop relapses while on interferons to assess whether recurrent disease activity may be due to the development of antibodies.[11]

Presently, all of these agents are approved by the US Food and Drug Administration (FDA) as first-line therapy for relapsing MS, and many are available in multiple countries around the world.

Glatiramer Acetate

GA is a complex mixture of random synthetic polypeptides. It probably

functions as an altered peptide ligand for the major histocompatibility complex (MHC) class II molecules—instead of being a myelin antigen that can stimulate adverse T-cell autoreactivity, it stimulates regulatory T cells that resemble myelin-reactive T cells in having a propensity for CNS migration.[5] GA may also stimulate neuroprotective or repair mechanisms. Two phase 3 studies demonstrated that GA 20 mg/d administered by subcutaneous injection reduced annualized relapse rate (ARR) in relapsing MS[12,13] with a reduction of approximately 30% in the second study. A separate randomized controlled trial demonstrated a benefit in terms of MRI measures, including gadolinium-enhancing lesions, new T2 lesions, and the proportion of lesions evolving into T1-hypointense "black holes."[14,15] GA is currently approved in the United States, European Union, and many other countries for relapsing MS, at a recommended daily dose of 20 mg subcutaneously. The Glatiramer Acetate Low-Frequency Administration (GALA) study assessed a lower-frequency dosing regimen of GA (40 mg administered 3 times a week) compared with placebo in patients with relapsing MS. This study yielded positive results on primary end points but awaits final publication.[16] GA is not indicated for the treatment of progressive forms of MS.

GA is generally well tolerated, with the most common side effects being injection-site tenderness, pruritus, erythema, or induration. Lipoatrophy (loss of subcutaneous fat with scarring) sometimes occurs with prolonged treatment, may be permanent, and can be a significant cosmetic issue. GA occasionally causes a postinjection systemic reaction comprising various combinations of flushing, diaphoresis, chest tightness, dyspnea, palpitations, and anxiety, beginning within minutes of injection and resolving spontaneously in 1 to 30 minutes. This reaction typically occurs once or at most a few times in a given patient and does not recur with continued dosing. Its etiology remains uncertain, but it does not appear to represent a hypersensitivity reaction, bronchospasm, or cardiac compromise. Patients should be advised of this potential reaction. In contrast to IFN-β, GA is not associated with constitutional side effects, depression, liver enzyme abnormalities, low blood counts, worsening headaches and spasticity, or neutralizing antibodies.

Natalizumab

Natalizumab is a humanized monoclonal antibody that binds α4-integrin and blocks interaction of α4β1-integrin on leukocytes with vascular cell adhesion molecules and connecting segment-1 (CS-1) on fibronectin sites on vascular endothelial cells.[17] As a result, migration of leukocytes from the blood into the CNS is inhibited. A phase 3 trial in relapsing MS showed that monthly IV infusions of 300 mg natalizumab reduced ARR by 68% over 2 years, disability progression by 42%, and MRI gadolinium-enhancing lesion number by 92%, relative to the study placebo group.[18,19] A second phase 3 study supported these results, showing that natalizumab combined with IFN-β-1a IM was more effective than IFN-β-1a IM plus placebo infusions.[3]

Natalizumab is generally well tolerated. In pivotal trials, side effects significantly associated with natalizumab included anxiety, fatigue, pharyngitis, sinus congestion, peripheral edema, and infusion-related symptoms (headache, flushing, erythema, nausea, fatigue, and dizziness). Allergic hypersensitivity reactions, including anaphylaxis, urticaria, pruritus, and anaphylactoid syndromes, occurred in 4% of natalizumab-treated patients and were serious in 1%. Approximately 6% of patients develop

persistent antinatalizumab-neutralizing antibodies.[20] In addition to reducing the efficacy of natalizumab, the presence of neutralizing antibodies increases the risk for hypersensitivity reactions. Rare hepatotoxicity has been reported, usually at the initiation of therapy.

The key safety concern with natalizumab is an increased risk for PML, a concern that did not surface during the course of the original trials. This is a serious, often fatal opportunistic infection of oligodendrocytes caused by reactivation of latent John Cunningham (JC) polyomavirus. Formal guidelines are provided in the United States by the Tysabri Outreach: Unified Commitment to Health (TOUCH) risk management program, which requires direct questioning of the patient at each infusion for symptoms suggestive of PML. MRI is performed before treatment and intermittently during natalizumab therapy. Manifestations that suggest PML include subacutely worsening visual, motor, or cognitive changes and/or gradually enlarging T2 hyperintensities with minimal or no gadolinium enhancement. If PML is suspected, natalizumab treatment should be suspended, MRI obtained, and CSF examination performed, including PCR for JC virus. Repeat CSF examination may be required if a high level of suspicion remains after initial negative testing. Brain biopsy is necessary in some patients—for example, where the diagnosis cannot be confirmed by MRI and CSF testing. At present, immune reconstitution is the main therapy for PML. Pharmacokinetic studies have shown that plasma exchange accelerates removal of natalizumab from the blood.[21] The recommended protocol is five exchanges every other day. For additional information on risk stratification while using natalizumab, see "Multiple Sclerosis Treatment: Risk Mitigation" by Drs Ontaneda and Fox in this issue of CONTINUUM.

Natalizumab is generally considered for patients who have relapsing MS and continued disease activity despite use of one or more of the standard disease therapies or who are intolerant of the standard agents.[22] It also can be considered for patients with disease characteristics that suggest high risk of disability and for whom a more potent although potentially more risky agent is felt to be appropriate (Case 4-1).

PRESENT AND EMERGING ORAL AGENTS

Fingolimod

Fingolimod is the first oral drug to receive North American and European regulatory approval to reduce relapses in patients with relapsing MS. Fingolimod is a sphingosine-1-phosphate receptor (S1P1) modulator and has immunoregulatory features.[23] Fingolimod inhibits the migration of T cells from lymphoid tissue into the peripheral circulation and target organs, including the CNS. Two phase 3 studies (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis [FREEDOMS], a placebo-controlled 24-month trial, and Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis [TRANSFORMS], a 12-month head-to-head trial with comparator IFN-β-1a IM) demonstrated that orally administered fingolimod (0.5 mg/d) was effective and superior to IFN-β-1a IM at reducing ARR and MRI activity in patients with relapsing MS[24,25] (see Case 4-1). Although fingolimod is generally well tolerated, specific safety issues have been identified (eg, first-dose bradycardia, the possible risk of herpes virus dissemination, macular edema, long-term consequences of elevated blood pressure),

KEY POINT

- Safety in a carefully selected study set of patients cannot predict how a disease-modifying drug will do when given more generally to unselected patients.

KEY POINT

- Although all agents are tested primarily for their ability to reduce relapses, in populations with low relapse rates, supportive effects are also sought from efficacy on other metrics such as MRI and Expanded Disability Status Scale progression.

Case 4-1

A 39-year-old physical education teacher had relapsing multiple sclerosis (MS) for nearly 10 years. He started out taking glatiramer acetate (GA), but after three moderate attacks over 2 years, the last of which left him with mild leg weakness, he switched to interferon-β-1a (IFN-β-1a) subcutaneously 3 times a week and had few to no relapses for 6 years with only a modest change on his MRI (a few new T2 lesions over the same period). Within the past year, however, he experienced two moderately severe attacks: the first in his brainstem with internuclear ophthalmoplegia and ataxia that partially recovered after steroid treatment, leaving some mild residual gait ataxia, and the second a transverse myelitis that produced weakness and bladder disturbance. His recent MRI showed several new T2 lesions and at least half a dozen enhancing lesions. He is JC virus antibody–positive and concerned about progressive multifocal leukoencephalopathy (PML).

Comment. The long course of disease, the age and sex of the patient, the accumulating disability with residual deficits following attacks, the MRI load with activity, and failure to control the disease with a first-line disease-modifying drug all point to a much higher risk of imminent disease progression. Clearly, this patient warrants an escalation in treatment with a drug that has a potentially greater potency than either GA or IFN-β and preferably has a rapid onset of activity. Fingolimod, natalizumab, or alemtuzumab might be considered, since all have demonstrated that they are capable of disease control in patients who break through first-line treatments. Because of this patient's concerns about the risk of PML with natalizumab, remaining possibilities would be to switch to fingolimod and maintain it or use alemtuzumab for 2 years, then fall back to IFN-β-1a subcutaneously 3 times a week, with which he was familiar and comfortable. The patient agreed to adhere to a monitoring program for the long-term risks of alemtuzumab, given to this patient as part of an investigational trial.

and these potential risks should be carefully considered. Further long-term data are needed to assess the safety profile of fingolimod. Of clinical concern is a patient started on fingolimod who died on the second day of treatment. Further analysis of this and other cases led to a more stringent set of criteria for fingolimod therapy and more careful first-dose observation. A specific risk management program has been instituted for this medication (see "Multiple Sclerosis Treatment: Risk Mitigation" by Drs Ontaneda and Fox in this issue of CONTINUUM).

Teriflunomide

Derived directly from leflunomide, teriflunomide is an antimetabolite that interferes with the de novo synthesis of pyrimidines, sparing the salvage pathway, by inhibiting the mitochondrial enzyme dihydro-orotate dehydrogenase. This has the effect of blocking cell replication in rapidly dividing cells, but the exact mechanism by which this translates into efficacy for MS is unknown. Typically, the cells that are more involved in mediating autoimmune processes will be more susceptible to the antimetabolite effects of teriflunomide.

A phase 3 study (the Teriflunomide Multiple Sclerosis Oral [TEMSO] trial)[26,27] showed a significant effect on the primary outcome of relapse rate, with secondary outcomes on MRI and disability (Expanded Disability Status

Scale [EDSS] progression) also reaching statistical significance over placebo. TEMSO was a 2-year randomized placebo-controlled trial in 1088 patients with active relapsing MS. Both 7-mg and 14-mg doses reduced the primary end point of ARR relative to placebo by 31.2% (7 mg) (P=.0002) and 31.5% (14 mg) (P=.0005). Both doses were effective at reducing various MRI outcomes, but a dose response was seen as well, often favoring the higher 14-mg dose. Reduction in new enhancing or T2 lesion formation was nearly twice as great in the higher-dosed group (67% versus 39%). There was a 29.8% reduction in the 3-month sustained progression of disability with 14 mg of teriflunomide compared to placebo (P=.029). Of the patients on placebo, 27.3% met the definition of EDSS progression compared with 21.7% (7 mg) and 20.2% (14 mg) of the patients treated with teriflunomide. The beneficial effect observed for both doses of teriflunomide in TEMSO on ARR and risk of disability progression was consistent regardless of gender, age, geographic region, baseline EDSS score, relapse rate, various MRI parameters, or the prior use of other DMT.[27] The severity of relapses was also examined, and compared with placebo, teriflunomide reduced annualized rates of relapses that resulted in sustained EDSS score changes by 37% (P=.0002) and 39% (P=.0002); relapses leading to hospitalization by 36% (P=.015) and 59% (P<.0001); and relapses requiring corticosteroid treatments by 29% (P=.001) and 34% (P=.0003) for the 7-mg and 14-mg doses, respectively. In this study, with clinical assessments every 3 months and MRI scans every 6 months, 52 (14.3%) patients on placebo, 67 (18.4%) on the 7-mg dose, and 82 (22.9%) on the 14-mg dose remained completely free of disease activity over the 2 years of the study.

A second phase 3 study was completed and presented but has not yet been published. The Teriflunomide Oral in People with Relapsing-Remitting Multiple Sclerosis (TOWER) study,[28] like TEMSO, focused on relapsing MS, with ARR being the primary end point, and time to disease progression the key secondary end point; no MRI studies were performed. Follow-up continued in all study subjects until the last patient recruited reached 48 weeks of treatment, so there was variable data from patients completing up to 2 years of treatment. 1169 patients were randomized to placebo or to 7 mg or 14 mg teriflunomide, and there was a 22.3% (7 mg) and 36.3% (14 mg) reduction in ARR relative to placebo (P=.0183 and .0001, respectively). Only teriflunomide 14 mg showed a significant reduction in 12-week confirmed EDSS progression relative to placebo (31.5%, P=.0442). However, progression rates were lower than in TEMSO, with only 16.8% of placebo patients meeting the definition of EDSS progression versus 11.9% of the 14-mg teriflunomide group.

A Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon-β-1a in Patients with Relapsing Multiple Sclerosis (TENERE)[29] was a 2-year, rater-blinded comparator study that included 324 people with relapsing MS with an EDSS score of 5.5 or lower, randomizing patients to receive teriflunomide 7 mg/d or 14 mg/d, or interferon-β-1a (44 μg 3 times a week). The primary end point was (1) risk of failure as defined by the first occurrence of relapse or (2) permanent study treatment discontinuation for any cause, whichever came first. No statistical superiority was observed between the interferon-β1a and teriflunomide arms (either 7 mg or 14 mg) on risk of treatment failure, the primary composite

end point of the study, where 48.6% (n = 109) and 37.8% (n = 111) of patients receiving 7 mg or 14 mg, respectively, of teriflunomide reached the primary end point, versus 42.3% (n = 104) of patients taking interferon-β1a.

Safety. The safety profile of teriflunomide appears reasonable based on the clinical trial experience. Hair thinning or gastrointestinal upset was noted in a subgroup of patients. The potential for teratogenicity has come from preclinical studies, which is of particular concern in women of childbearing potential. A specific washout program using cholestyramine or activated charcoal can be used to remove teriflunomide from the system; however, without this washout, teriflunomide may remain in the system for months after the last dose. Careful counseling is therefore recommended in women of childbearing age contemplating teriflunomide.

Discussion. Teriflunomide appears to be a relatively safe and well-tolerated oral medicine with efficacy on reducing MS relapses, progression, and MRI activity not dissimilar from IFN-β or GA and managed to demonstrate significant effects on all clinical measures in both registry trials. It appears to be a reasonable alternative to these other first-line injectable agents (Case 4-2).

Dimethyl Fumarate

DMF is a fumaric acid ester that can be taken orally and is immediately hydrolyzed by esterases to its metabolite monomethyl fumarate (MMF). DMF is better tolerated than MMF, as it is associated with lower gastrointestinal side effects. MMF is eliminated mainly through breathing, while only small amounts of intact MMF are excreted through urine or feces. BG-12 is a formulation of DMF manufactured as

Case 4-2

A 22-year-old, unmarried law student who had a busy lifestyle in addition to her studies experienced a bout of optic neuritis about 6 months ago with full recovery. Her MRI at the time showed only a couple of small lesions, and she elected to forego therapy because she was not interested in injectable agents. She presented after a clear but mild episode of transverse myelitis that left her only with dysesthesia in her feet, but observations from her examination were normal and her Expanded Disability Status Scale (EDSS) score was 0. She made it clear that she would not take anything that was "too intrusive," involved cumbersome pretesting or ongoing monitoring, or had any significant side effects, although they may all occur during the initiation period. She had no intention of becoming pregnant for several years.

Comment. Choice of therapy here must address not only what is thought of as the best option for the patient, but also the realities of the situation. Still "early" in her disease course, she showed a low risk of imminent disease progression, so any of the first-line treatments could be considered. Because of her dislike of injections, injectable agents are not a good option. Orally available options and their risks and benefits should be discussed in this case, as well as the need to actively remove teriflunomide from the patient's system if she decided to become pregnant sometime in the future. She opted to begin teriflunomide and agreed to strict contraception to prevent pregnancy.

an enteric-coated microtablet to improve gastrointestinal tolerability. The exact mechanism by which it exerts its positive anti-inflammatory effects is unknown. It may act on the major transcription factor known as nuclear factor erythroid 2–related factor 2 (Nrf-2), which is released from binding to kelch-like ECH-associated protein 1 (Keap-1) via the activity of DMF. In turn, Nrf-2 upregulates an array of antioxidative pathways, such as increased glutathione levels. Nrf-2 pathway activation also leads to an inhibition of the translocation of nuclear factor-κB into the nucleus, which would normally turn on the expression of a cascade of inflammatory cytokines, chemokines, and adhesion molecules.[30]

Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (DEFINE)[31] was one of two large phase 3 studies comparing two doses of BG-12 to placebo; 1234 patients with relapsing MS and EDSS scores of 5.0 or lower were randomized to receive placebo (n = 408) or 240 mg of BG-12 twice a day (n = 410) or 3 times a day (n = 416), and clinic visits were every 12 weeks. MRI studies were performed at baseline, 24, 48, and 96 weeks in a subgroup of patients (n = 540). The primary outcome was the proportion of patients relapsing at 2 years, whereas the difference in ARR and the risk for disability progression (measured by EDSS scores) were considered secondary outcome measures in this study. Both doses of BG-12 reduced the proportion of patients relapsing by nearly 50% ($P<.001$).[10] Whereas 46% of placebo patients relapsed, only 27% of the patients dosed with BG-12 twice a day and 26% of those dosed 3 times a day had at least one relapse by 2 years ($P<.001$ for both comparisons). BG-12 twice a day reduced the ARR relative to the placebo population by 53% and BG-12 3 times a day by 48% ($P<.001$ for both comparisons). EDSS progression confirmed at 12 weeks was also reduced by both dosing regimens: whereas 27% of patients treated with placebo progressed, only 16% of those treated twice a day with BG-12 and 18% of those treated 3 times a day with BG-12 did so, a relative reduction of 38% and 34%, respectively. New or newly enlarging MRI lesions were also substantially reduced by both doses: 85% and 74% for BG-12 twice a day and 3 times a day, respectively, versus placebo ($P<.001$ for both comparisons).

The second study, called Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (CONFIRM),[32] tested the same two doses of BG-12 against an active comparator (GA 20 mg/d subcutaneously) in 1430 patients randomized to all three treatment arms and placebo. The trial was powered to compare the two doses of BG-12 against placebo but was neither designed nor powered for the comparison for GA. The primary end point was the difference in ARR over a period of 2 years. At 2 years, the ARR compared with placebo was 44% lower with BG-12 twice a day ($P<.01$), 51% lower with BG-12 3 times a day ($P<.001$), and 29% lower with GA ($P=.01$). No significant reduction in EDSS progression occurred with either dose of BG-12 or GA versus placebo (21%, 24%, and 7%, respectively, but none were statistically significant). On MRI, BG-12 twice a day, BG-12 3 times a day, and GA all significantly reduced the numbers of new or enlarging T2-weighted hyperintense lesions (all $P<.001$) and new T1-weighted hypointense lesions ($P<.001$, $P<.001$, and $P=.002$, respectively).

Safety. The most frequently reported adverse events of concern are shown in **Table 4-2**. These events

were more common with BG-12 than with placebo, with the highest incidence in the first 30 days of treatment and decreasing thereafter. Roughly 30% of patients discontinued the study drug in both studies. Flushing and diarrhea were most common, followed by nausea and abdominal pain. No other major side effects emerged from phase 3 studies or subsequent open-label studies to date.

Discussion. BG-12 appears to be another promising candidate agent for first-line treatment of relapsing MS and is now approved by the FDA. Potential negative aspects include the twice a day dosing and initial gastrointestinal and flushing symptoms, but short-term safety and efficacy appear to be overall good. Fumaderm or its generic equivalent, a combination of fumaric acid esters, has been available in Germany and Europe but only recently was associated with a few cases of PML in patients treated mainly for psoriasis.[33] Whether BG-12 will turn out to have similar problems remains to be determined.

Laquinimod

Laquinimod was derived from roquinimex, an immunomodulatory drug that was first developed in the early 1980s. Phase 3 studies of linomide were halted in the 1990s because of the occurrence of two cardiovascular-related deaths and at least eight nonfatal myocardial infarctions. Modifications were made that were thought to reduce the side effects without compromising on the potential beneficial immunomodulatory properties. The exact mechanism of action is unknown, but many properties have been demonstrated in at least in vitro and animal studies. Of great interest is that laquinimod appears to be able to cross into the CNS, achieving concentrations 7% to 8% that of peripheral blood,[34] an amount that might double in the presence of some blood-brain barrier permeability as might be seen in experimental autoimmune encephalomyelitis (EAE) or MS. Laquinimod was effective in EAE experiments, possibly because of a reduction of leukocyte trafficking into the CNS or the modulation of inflammatory cytokine production. Other properties include the possible "protection" of axonal integrity, possibly via the production of brain-derived neurotropic factor.

The first phase 3 study, Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis

TABLE 4-2 Frequently Reported Adverse Events With BG-12 as Compared to Placebo

Adverse Event	BG-12[a] (%)	BG-12[b] (%)	Placebo[c] (%)
Flushing	38	31	5/4
Diarrhea	15	13	13/8
Nausea	13	11	9/8
Upper abdominal pain	10	10	7/5
Abdominal pain	11	<1	5/0

[a] Adverse events reported in the Determining the Efficacy and Tolerability of Cholesteryl Ester Transfer Protein Inhibition with Anacetrapib (DEFINE) study, which used twice-daily dosing.
[b] Adverse events reported in the Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (CONFIRM) study, which used twice-daily dosing.
[c] Adverse events reported with placebo in the DEFINE study/adverse events reported with placebo in the CONFIRM study.

(ALLEGRO),[35] compared laquinimod 0.6 mg/d to placebo in 1106 patients with relapsing MS. Mean EDSS score at baseline was 2.6 in both groups. Disease duration before the study was 8.7 and 8.6 years, respectively. One or more gadolinium-positive lesions were present in 45.7% of placebo and 40.4% of the laquinimod arm. The primary end point was the number of confirmed relapses (and the difference in ARR); secondary end points included the cumulative number of gadolinium-positive and new or newly enlarging T2 lesions, as well as disability (measured by EDSS scores) and the Multiple Sclerosis Functional Composite at 24 months. Some dropout of patients occurred in this study, with 79% of laquinimod and 77% of placebo-treated patients completing the follow-up. The main reasons for discontinuation were adverse events and the resulting perception of patients that their disease was not under control.

Laquinimod produced a modest yet statistically significant 23% reduction in ARR compared with placebo (Table 4-3). Treatment was also associated with a 36% reduction in EDSS progression versus placebo for 3-month confirmed progression (P=.0122) (but amounting to only a roughly 5% absolute change in the percent progressing compared to placebo). This reduction in progression increased to a 48% reduction if one used a 6-month confirmed progression (P=.0023).

Both the mean cumulative number of gadolinium-positive lesions and new T2 lesions were significantly lower in the patients treated with laquinimod. Cumulative gadolinium-positive lesions were reduced by 37% (P=.0003) and new T2 lesions by 30% (P=.0002). Similarly, new T1-hypointense lesions, which are thought to reflect more severe tissue damage, were reduced by 27% during the 2 years of the study. Additional exploratory analyses showed that laquinimod reduced severe relapses (requiring hospitalization) by 38% and the requirement for steroids by 27%.

Serious adverse events occurred in 22.2% of patients on laquinimod versus 16.2% of those on placebo. In particular, no cardiovascular or pulmonary problems occurred. The most common adverse event occurring more often with treatment was elevation in liver function tests (alanine aminotransferase) in 6.9% of the laquinimod group and 2.7% of the placebo group. Most elevations were more than 3 times the upper limit of normal (4.9% in the laquinimod group and 2.0% of those taking placebo). Some excess of abdominal pain (5.3% on laquinimod versus 2.9% on placebo) and back pain (16% on laquinimod versus 9% on placebo) was reported.

TABLE 4-3 Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis (ALLEGRO) Study Primary End Point

End Point	Placebo	Laquinimod	Relative Risk (95% Confidence Interval)	P =
Annualized relapse rate	0.395	0.304	0.770 (0.650–0.911)	.0024
Expanded Disability Status Scale progression	11.1%	15.7%	0.641 (0.452–0.908)	.0122

The second phase 3 study, called Laquinimod Double-Blind Placebo-Controlled Study in Relapsing-Remitting Multiple Sclerosis Patients with a Rater-Blinded Reference Arm of Interferon-β-1a (BRAVO),[36] was also a 2-year, multicenter, randomized, double-blind, parallel-group, placebo-controlled study comparing the safety, efficacy, and tolerability of a once-daily, oral, 0.6-mg dose of laquinimod with placebo along with a single blinded group of patients receiving IFN-β-1a as an active comparator. Patients were required to have had at least one relapse in the prior year or two relapses in the prior 2 years, or one relapse within 2 years and a gadolinium-positive lesion in the prior 2 years. An eligible 1331 patients were randomly assigned in a 1:1:1 manner to receive laquinimod (n = 434), placebo (n = 450), or 30 μg once weekly of IFN-β-1a (n = 447). The primary end point was the efficacy of 0.6 mg/d laquinimod, measured by ARR versus placebo. Secondary outcome measures included effect on the accumulation of disability (measured by EDSS score) and brain atrophy. Gadolinium-positive lesions were found at baseline in 39.6% of the laquinimod group, 33.4% of the placebo group, and 38.1% of the IFN-β-1a group. The mean EDSS score was similar among the three groups at approximately 2.6, and disease duration from first onset of symptoms was 6.6, 6.9, and 7.0 years for the laquinimod, placebo, and IFN-β-1a IM groups, respectively. The three groups overall appeared similar to the patients recruited to the ALLEGRO study.

At 24 months in the unadjusted primary analysis, the ARR for laquinimod versus placebo did not reach statistical significance but showed an 18% trend in reduction compared with the 25% statistically significant reduction achieved using IFN-β-1a versus placebo (Table 4-4). However, after a predefined adjustment was made using covariates accounting for differences in baseline MRI activity between laquinimod and placebo, the laquinimod comparison with placebo did reach statistical significance: still a modest 21% reduction in ARR compared with the 29% corrected value for IFN-β-1a.

MRI outcomes were also more modest with laquinimod compared with IFN-β-1a, with only a 22% relative reduction (P=.062) in gadolinium-positive lesions (versus 60% with IFN-β-1a) and a 19% reduction in new T2 lesions (P=.037) (versus 52% with IFN-β-1a) against placebo. A reduction in brain atrophy by 32.8% was noted at 24 months (P<.0001), although the significance of this finding in relapsing MS is still controversial (ie, should brain volume decrease as inflammation is

TABLE 4-4 Laquinimod Double-Blind Placebo-Controlled Study in Relapsing-Remitting Multiple Sclerosis Patients With a Rater-Blinded Reference Arm of Interferon-ß-1a (BRAVO): Primary End Point in Unadjusted and Adjusted Analyses

End Point	Placebo	Laquinimod	P =	Interferon-ß-1a	P =
Annualized relapse rate (unadjusted analysis)	0.34	0.28	.075	0.26	.007
Annualized relapse rate (adjusted analysis)	0.37	0.29	.026	0.27	.002

brought into check, or should it increase to reflect regeneration or repair?).

Overall, 9.7% of patients on laquinimod, 13.3% of those on placebo, and 10.5% of those on IFN-β-1a met the definition of sustained 3-month confirmed EDSS progression, yielding a 33.5% reduction relative to placebo for laquinimod ($P=.04$) and a 28.7% reduction ($P=.09$) with IFN-β-1a, in post hoc corrected analyses.

Safety. Adverse events were infrequent and balanced through the groups. Two malignant neoplasms occurred in each of the laquinimod and IFN-β-1a groups, with one case of thyroid cancer in each group, one case of skin squamous cell carcinoma in the laquinimod group, and one case of colon cancer in the IFN-β-1a group. Back pain was seen again in this study, although it generally resolved on treatment. An increase in liver function tests on laquinimod was also noted, with elevations that were for the most part mild (ie, less than 5 times the upper limits of normal (ULN). Of patients receiving laquinimod, 28.9% had increased liver function tests between 1 and 3 times ULN, and 4.2% had increases of greater than 3 times ULN. A similar proportion of patients receiving IFN-β-1a showed liver enzyme elevations in this same range.

Discussion. Based on the results of these two large studies with laquinimod and its modest effects on relapses and MRI, and seemingly more robust effect on brain volume changes and perhaps on EDSS progression, it is unlikely that this agent will offer a competitive benefit over either teriflunomide or BG-12. However, studies are examining whether higher doses of laquinimod might offer greater benefit while maintaining a satisfactory safety and tolerability profile. At the present time, FDA regulatory approval is not being sought.

EMERGING THERAPIES OF INTEREST

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that targets CD52, found on lymphocytes and monocytes. It is quite effective at achieving a rapid and sustained lymphocyte depletion, which benefits patients with chronic lymphocytic leukemia. A single 5-day pulse of alemtuzumab depletes circulating lymphocytes and monocytes, which then recover at variable rates, with CD4-positive T lymphocytes being the slowest.

Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, study I (CARE-MS I)[37] was a phase 3, global, randomized clinical trial comparing treatment with alemtuzumab (12 mg/d over a 5-day IV administration, with a second 3-day IV administration 1 year later) to IFN-β-1a subcutaneously 3 times a week in 581 patients with relapsing MS previously naive to any DMT, randomized 2:1 alemtuzumab to IFN-β-1a. This study declared two co-primary efficacy end points: (1) reduction in relapse rate and (2) 6-month sustained accumulation of disability based on the EDSS score. A success was only declared if both co-primary end points were met ($P\leq.05$) or if one co-primary end point is met against using a more stringent statistical threshold ($P\leq.025$). Patients were not blinded to their treatment, but all raters were masked and the quality of this masking was assessed at each EDSS evaluation. Mean time from onset of first symptoms was about 2 years in each group; 51% of IFN-β-1a and 46% of alemtuzumab patients had at least one gadolinium-positive lesion at screening. To prevent herpes infections, the protocol was amended halfway through the trial, such that 6% of all alemtuzumab patients took oral acyclovir during their first infusion times and 66% took it during the second treatment.

KEY POINT

- Alemtuzumab is the only potential new therapy that demonstrated all of its efficacy against an active comparator (subcutaneous IFN-β-1a) and showed treatment effects that were the same or greater than all of the other agents were able to demonstrate against placebo. It might also be a therapy that requires only one or two treatments, with follow-up treatments only for patients who continue to have disease activity.

Results showed that treatment with alemtuzumab reduced ARR by 55% compared to IFN-β-1a over 2 years ($P<.0001$; ARR 0.39 for IFN-β-1a and 0.18 for alemtuzumab). On a secondary outcome measure, 58.7% of IFN-β-1a patients and 77.6% of alemtuzumab-treated patients remained relapse free for 2 years ($P<.0001$). At 2 years, fewer alemtuzumab (8%) than IFN-β-1a patients (11.1%) had experienced a 6-month sustained increase in EDSS scores, but this difference was not statistically significant ($P=.22$).

Some MRI outcomes favored alemtuzumab over IFN-β-1a, such as the reduced percentage of patients with new and enlarging T2 lesions (48 versus 58, $P=.035$); with new gadolinium-positive lesions (15 versus 27, $P=.0006$) or persisting gadolinium-positive lesions at 24 months (7 versus 19, $P<.0001$); and with new T1-hypointense lesions (24 versus 31, $P=.05$). Alemtuzumab led to a nonsignificant reduction in the T2-burden of disease of -9.3% compared to IFN-β-1a at -6.5% (median change at year 2) ($P=.31$). Alemtuzumab-treated patients had slower progression of brain atrophy compared to IFN-β-1a (-0.87 versus -1.49 median percent change in brain parenchymal fraction from baseline, $P<.0001$). More alemtuzumab-treared patients (39%) remained free of disease activity both clinically and on MRI (ie, disease-activity free) compared to IFN-β-1a (27%) (odds ratio = 1.75, $P=.006$).

CARE-MS II[38] was a second phase 3 randomized trial, which included 840 patients who were previously treated with disease-modifying agents but continued to have relapses. Similar to CARE-MS I, patients were randomized to high-dose alemtuzumab, low-dose alemtuzumab, and placebo in a 2:2:1 ratio, but this time with patients treated with either alemtuzumab 12 mg or 24 mg compared with those treated with IFN-β-1a subcutaneously 3 times a week, who were unblinded to their therapy, although all raters were blinded. All patients receiving alemtuzumab also took oral acyclovir during their infusions and for 28 days afterward to reduce the frequency of herpetic infections. A similar co-primary outcome to CARE-MS I was determined based on relapse rate and sustained accumulation of disability. Nearly two-thirds of the patients had been on IFN-β preparations and about one-third on GA before entry; only 3% of each group had been exposed to natalizumab.

Annualized relapse rate was significantly reduced by alemtuzumab (0.26), 49.4% relative to IFN-β-1a (0.52) over the 2-year study ($P<.0001$). A statistically significant 42% reduction in the risk for sustained accumulation of disability ($P=.0084$) was also observed in favor of alemtuzumab (12.7%) versus IFN-β-1a (21.1%). In fact, significantly more alemtuzumab-treated patients had sustained improvements in their EDSS scores (28.8%) than IFN-β-1a–treated patients (12.93%) ($P=.0002$). Although there was no significant change in the T2 burden of disease in favor of alemtuzumab, significantly fewer patients had new or enlarging T2 lesions (46% versus 68%, $P<.0001$) and new gadolinium-positive lesions over 24 months (9% versus 23%, $P<.0001$). There was also less reduction in mean brain parenchymal fraction (-0.615% versus -0.81%, $P=.01$). Of interest were the more twice as many patients treated with alemtuzumab (32%) who remained completely free of disease activity (no relapse, progression, or MRI activity) compared to IFN-β-1a (14%) ($P<.0001$). Positive outcomes for alemtuzumab seemed independent of the previous treatment. No advantage of the 24 mg over 12 mg alemtuzumab was evident, although the

24 mg treatment displayed a tendency toward more frequent side effects.

Safety. There were common adverse events associated with alemtuzumab, such as mild-moderate infusion-related reactions (90%), but only 3% were considered serious. The incidence of infections was higher, the most common being upper respiratory tract infection and urinary tract infection as well as oral herpes. The incidence of serious adverse events was similar between the two treatment arms (18.4% for alemtuzumab versus 14.4% for IFN-β-1a). The most worrisome adverse events concern the development of secondary autoimmune disorders after treatment with alemtuzumab. In this study, 18.1% of alemtuzumab-treated patients developed an autoimmune thyroid-related problem (which included thyrotoxicosis in some) and 0.8% developed immune thrombocytopenia (ITP) during the study period. No cases of Goodpasture syndrome occurred during the study; however, a patient in the extension study developed glomerulonephritis with a slightly elevated antiglomerular basement membrane antibody level after a third treatment with alemtuzumab. Two cases of thyroid papillary carcinoma were noted in the alemtuzumab-treated patients. Rare autoimmune pancytopenia was noted in the CARE-MS I trial.

Discussion. Exactly where alemtuzumab will ultimately fit into the treatment regimen is not clear. To some, the attraction of a yearly treatment over 3 to 5 days that sustains benefits for years to come in the absence of more regular medication is very appealing; however, there is a risk of significant secondary autoimmune disease that could occur quite some time from the actual treatment and will require several years of ongoing monitoring of blood and probably urine. CARE-MS II indicates that alemtuzumab might be a "go-to" agent once patients break through first-line therapy (see **Case 4-2**). Recently, this idea was supported by an open-label study of patients who experienced more than two attacks while taking IFN-β and were considered refractory.[39] Although alemtuzumab consistently shows efficacy in head-to-head studies, its safety risk relegates it to a second or higher tier of treatment.

KEY POINT

- Given how few head-to-head trials have been conducted, comparing efficacy among disease-modifying drugs is difficult, so the indication (first- or second-line) comes from the risk profile, with riskier agents relegated to a higher tier.

Daclizumab

Daclizumab is a humanized monoclonal antibody against the α-chain of the high-affinity interleukin-2 (IL-2) receptor CD25. CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, which enhances high-affinity IL-2 signal transduction. Because CD25 antagonism selectively inhibits activated T cells, daclizumab treatment was postulated to be useful in patients with autoimmune conditions characterized by abnormal T-cell responses, such as MS. CD25 antagonism causes expansion of a regulatory subset of natural killer (NK) cells known as $CD56^{bright}$ NKs (**Figure 4-2**). This expansion was associated with a reduction in MS disease activity, presumably through the $CD56^{bright}$ NK cell–mediated lysis of autologous activated T cells that would be responsible for attacking the CNS in MS.[40]

The earliest large study with daclizumab was known as Daclizumab in Active Relapsing Multiple Sclerosis (CHOICE)[41] and was an "add-on" to IFN-β. That study did show that the combination was effective at reducing gadolinium-positive lesions. Since then, the molecule has undergone a refinement in production and changed company hands.

Safety and Efficacy Study of Daclizumab High-Yield Process to Treat

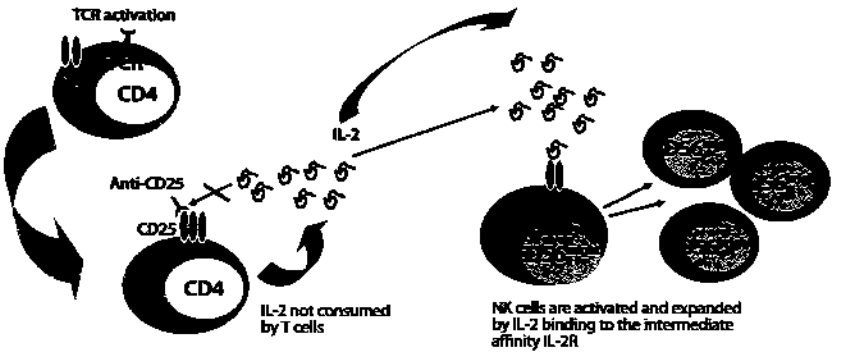

FIGURE 4-2 Daclizumab treatment reduces activated T cells and increases $CD56^{bright}$ natural killer cell proliferation via intermediate affinity interleukin-2 signalling, offering a potential biomarker for efficacy.

TCR = T-cell receptor; CD4 = cluster of differentiation 4; CD25 = cluster of differentiation 25; IL-2 = interleukin-2; NK = natural killer.

Relapsing-Remitting Multiple Sclerosis (SELECT)[42] studied daclizumab high-yield process in a 52-week study of once-monthly subcutaneous treatment of 150 mg or 300 mg daclizumab in a randomized, double-blind, placebo-controlled trial of monotherapy in 600 patients with relapsing MS. Patients had at least one relapse in the 12 months before randomization or one new gadolinium-positive lesion in the prior 6 weeks. The agent was well tolerated, with over 90% of entered patients completing the study.

The primary end point was ARR (Table 4-5). A smaller MRI substudy included 309 of the overall patients. The study resulted in a 50% to 54% reduction in ARR relative to placebo. Additionally, more than 80% of daclizumab-treated patients were relapse free at 52 weeks compared with 64% of placebo patients. Daclizumab showed a trend toward an effect on confirmed 3-month EDSS progression, a 57% reduction in the 150-mg group ($P=.021$), and a 43% reduction with the 300-mg dose that did not reach statistical significance ($P=.09$).

Results of the MRI substudy in 309 patients showed that, compared with placebo, there was a 69% to 78% reduction in new or enlarging gadolinium-positive lesions between weeks 8 and

TABLE 4-5 Safety and Efficacy Study of Daclizumab High-Yield Process to Treat Relapsing-Remitting Multiple Sclerosis (SELECT): Primary End Point for Daclizumab Versus Placebo

End Point	Placebo	Daclizumab 150 mg	*P*	Daclizumab 300 mg	*P*
Annualized relapse rate	0.46	0.21	<.001	0.23	.0002

TABLE 4-6 **Safety and Efficacy Study of Daclizumab High-Yield Process to Treat Relapsing-Remitting Multiple Sclerosis (SELECT): Reduction in New or Enlarging T2 Lesions for Daclizumab Versus Placebo at Week 52**

End Point	Placebo	Daclizumab 150 mg	P	Daclizumab 300 mg	P
New or newly enlarging T2 lesions	8.1	2.4	<.0001	1.7	<.0001

24 (Table 4-6). Looking at this outcome in the overall population of 600 patients, there was a 79% to 86% reduction in new gadolinium-positive lesions at week 52 versus placebo. Similarly, new or enlarging T2 lesions were affected, with a reduction of 70% to 79% in the whole cohort at week 52.

Safety. Adverse events and serious adverse events were similar in all three groups (Table 4-7). One death occurred in the trial in a patient with a psoas abscess that was not diagnosed before death.

The most common adverse events were nasopharyngitis, upper respiratory tract infection, and headache. Serious infections occurred in 1% and 3% of the daclizumab groups. Four malignancies occurred: one in each of the placebo and 150-mg groups, and two in the 300-mg group. Raised liver function tests were also noted, with levels greater than 5 times ULN in 4% of daclizumab-treated patients. Interestingly, these increases generally occurred later in treatment, with a median of 308 days; all of the increases resolved spontaneously.

Discussion. Daclizumab is now being studied in a phase 3 registration clinical trial called Efficacy and Safety of Daclizumab High-Yield Process versus Interferon-β-1a in Patients with Relapsing-Remitting Multiple Sclerosis (DECIDE). DECIDE is designed to evaluate the efficacy and safety of once-monthly subcutaneous administration as a monotherapy compared with IFN-β1-a.

Ocrelizumab

Ocrelizumab is a recombinant monoclonal antibody structurally similar to rituximab (nearly 89% homology),

TABLE 4-7 **Safety and Efficacy Study of Daclizumab High-Yield Process to Treat Relapsing-Remitting Multiple Sclerosis (SELECT): Adverse Events**

Event	Placebo (%)	Daclizumab 150 mg (%)	Daclizumab 300 mg (%)
Any adverse event	78	72	76
Any serious adverse event	27	16	18
Any serious adverse event excluding MS relapse	6	7	9
Death (n)	0	1	0

MS = multiple sclerosis.

KEY POINT

- Multiple sclerosis trials have evolved over the past few decades, but so have the populations studied. Changes in diagnostic criteria have led to selection overall of patients with earlier and milder disease compared with older studies.

which is more humanized rather than chimeric and binds to CD20 on B cells. A small study in 104 patients randomized 2:1 to receive rituximab showed a 91% reduction in the number of gadolinium-positive lesions compared to placebo, despite a greater number of gadolinium-positive lesions at baseline (mean 0.5 versus 5.5 lesions at 24 weeks, $P<.001$), which was sustained out to 48 weeks ($P<.001$). There was also a significant reduction in ARR at week 24 compared to placebo (14.5% versus 34.3%, $P=.02$) and sustained out to week 48 (20.3% versus 40.0%, $P=.04$).[43]

In the only phase 2 study thus far of ocrelizumab in MS, 218 relapsing MS patients were randomized to placebo, low-dose (600 mg) or high-dose (2000 mg) IV ocrelizumab given on days 1 and 15, or IFN-β-1a IM (30 μg weekly) and followed for 24 weeks.[44] Only the IFN-β-1a group was unblinded to therapy. At week 24, all patients were then moved to the 600-mg ocrelizumab treatment, except for the 2000-mg group, which had their dose reduced to 1000 mg; these dosages were then repeated for a total of three cycles at weeks 24, 48, and 96. The primary end point was the total number of gadolinium-positive lesions counted at 4 weekly intervals starting from weeks 12 to 24.

There were significant differences in the primary end point of total number of gadolinium-positive lesions at weeks 12 to 24 ($P<.0001$) in both ocrelizumab groups compared to placebo and IFN-β-1a (corresponding to relative risk reductions of 89% for the 600-mg group and 96% in the 2000-mg group). More patients were free of gadolinium-positive lesions in the first 24 weeks in both ocrelizumab groups (77% at 600 mg and 82% at 2000 mg) compared to either the placebo or IFN-β-1a (35% and 48%). Compared to placebo, ARR was 80% lower in the 600-mg ocrelizumab group ($P=.0005$) and 73% lower in the 2000-mg ocrelizumab group ($P=.0014$). Only the 600-mg ocrelizumab group had a significantly lower ARR versus IFN-β-1a (0.36, $P=.03$).

Safety. Although overall rates of adverse events were similar between the treatment arms, one unusual death occurred in the higher-dose 2000-mg group, described as a severe inflammatory response syndrome, which likely followed from sepsis, although no particular pathogen was found. Infusion-related events were more frequent with the first cycle with ocrelizumab (35% with 600 mg and 44% with 2000 mg), but no significant differences between groups were evident after the second part of that treatment infusion given at day 15.

Discussion. Ocrelizumab, albeit in phase 2 testing, produced strong suppression of disease activity characterized by MRI and relapse in relapsing MS, but the true safety has not yet been established. Three large phase 3 trials are underway—one in primary progressive MS (called A Study of Ocrelizumab in Patients with Primary Progressive Multiple Sclerosis [ORATORIO]), and the other two in relapsing MS (A Study to Evaluate the Efficacy and Safety Of Ocrelizumab in Comparison to Interferon-β-1a in Patients with Relapsing Multiple Sclerosis [OPERA] I and II).

Reconciling the New Treatments

Comparing across clinical trials is very difficult given the changing scenario of patients (see **Table 4-1**), newer diagnostic criteria for MS, and, most importantly, the ever-changing behavior of the placebo groups in terms of their risk for events. Indeed, even between the now-required two registry phase 3 trials for each of the new therapies, the

groups, recruited around the same time, behaved differently.

Calculating the NNT could offer some degree of comparison by looking at absolute differences among agents, assuming that although the behavior of placebo groups changes, the overall magnitude of an effect should be consistent. However, when event rates become very low, the NNT will not only reflect the magnitude of the treatment effect but also factor in the rarity of the event in question. All of the studies had to choose a primary end point and were powered to allow a determination of a treatment effect, if there was one. All primary outcomes were relapse related, although powering for relapse usually overpowers for MRI, which is a much more frequent event, but underpowers for clinical disability progression—a much rarer event. It is therefore not surprising that all of the successful studies were able to show an effect on relapse, but not all on progression. Even with the older agents such as IFN-β or GA, ARR has consistently decreased over the years (**Figure 4-3A**, **Figure 4-3B**). The lowest ARR attained is still in the range of 0.3 relapses per year, whereas only the newer oral agents seem capable of reducing ARR below 0.2. Still, the overall reduction in ARR is somewhat difficult to appreciate in terms of benefit, since 0.2 translates into about one attack every 5 years. Factoring in the cost of preventing only one attack every 5 years, it is important to have both secondary outcomes and patient-related outcomes to appreciate the overall benefit that patients will receive from treatment. The NNT, a measure thought to allow for comparison of efficacy across different studies, has limited application in populations with very low frequency of events. In a population with high relapse rates, a low NNT is achievable and reflects efficacy, but in populations with low relapse rates, a higher NNT is seen, owing to the infrequency of attacks. For example, in older studies, a reduction of 0.5 ARR (placebo ARR 1.0 and treatment arm 0.5, or a 50% relative rate reduction) yields a NNT of 2 (ie, two patients need to be treated with the disease-modifying drug for 2 years so that one patient is spared an attack). In a more contemporary study where placebo ARR is closer to 0.5 and treatment ARR is 0.25, the same relative rate reduction of 50% now yields double the NNT at 4, which reflects the efficacy but also the lesser frequency of the event.

Other problems arise when one compares across clinical studies—not just because of different patient groups but also different inclusion or exclusion criteria, definitions of relapse, blinding of evaluators for relapse or progression or even in the way MRI studies are performed and analyzed, their frequency, and the metrics used. Natalizumab, the oldest of the newer medications, still looks good, especially given the NNT for relapse or progression (see **Table 4-1**), but we must keep in mind that the NNT for even IFN-β and GA in recent trials are also in the same range.[45]

In the CARE-MS trials or TENERE, patients were randomized to the active comparator (IFN-β-1a subcutaneously), with planned statistical analysis of the comparison, allowing one to be truly capable of making a direct, head-to-head comparison. Similarly, the TRANSFORMS study[25] was set up as a true comparator of fingolimod to IFN-β-1a IM, going to the extreme of having a "double dummy" control to try to ensure double blinding, which differs from the CARE-MS or TENERE trials which made no attempt to conceal the treatment allocation from

KEY POINTS

- Registration studies look at highly informative (those at high risk for relapse) and carefully selected (those who are otherwise healthy and unlikely to have side effects) patients to demonstrate efficacy over a short period of 1 to 2 years, which does not necessarily indicate how a disease-modifying drug will do in clinical practice.
- Although newer agents appeal because of convenience (eg, oral dosing) or the perception that they demonstrate superior efficacy to long-standing interferon-β or glatiramer acetate, few data support this. Recent studies show annualized relapse rates for interferon-β or glatiramer acetate in the same range as some of the newer agents.
- Number needed to treat, a measure thought to allow for comparison of efficacy across different studies, is no longer applicable in populations with very low risk of events. In a population with high relapse rates, a low number needed to treat is achievable and reflects efficacy, but in populations with low relapse rates, a higher number needed to treat is seen, owing to the infrequency of attacks.

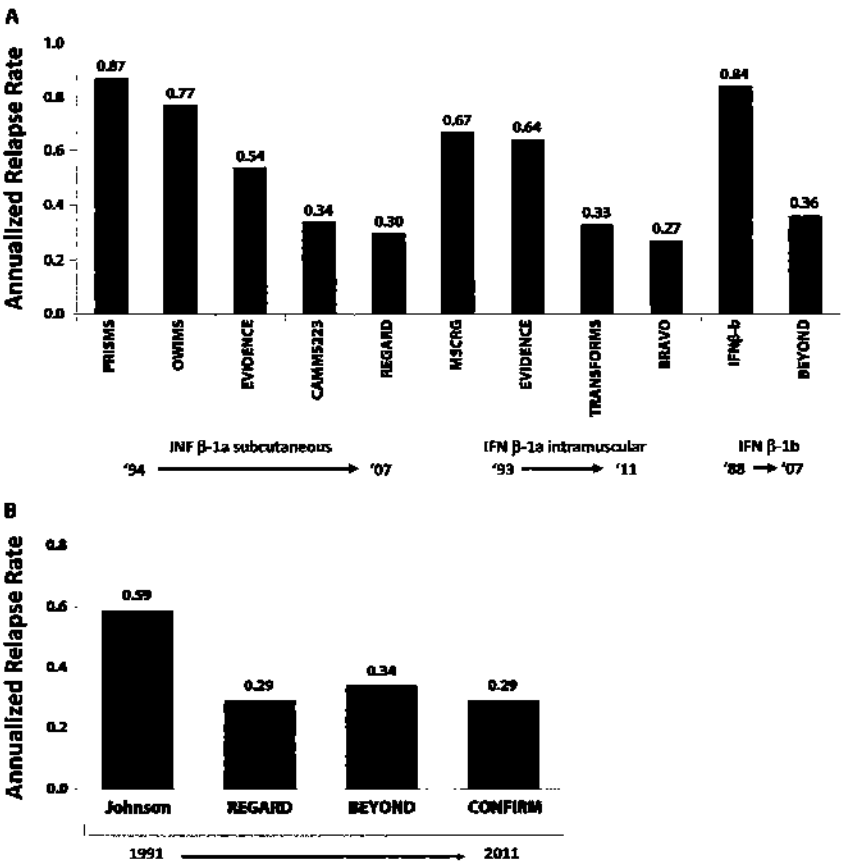

FIGURE 4-3 Relapse response to therapies across the ages—consistent reduction in rates regardless of agent. *A*, Interferon-β treatment-related annualized relapse rate over nearly 2 decades. *B*, Glatiramer acetate treatment-related annualized relapse rate over nearly 2 decades.

PRISMS = Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis; OWIMS = once weekly in MS; EVIDENCE = Evidence of Interferon Dose-Response: European North American Comparative Efficacy; CAMMS223 = A Phase 2 Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Rebif in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis; REGARD = Rebif vs Glatiramer Acetate in Relapsing MS Disease; MSCRG = Multiple Sclerosis Collaborative Research Group; TRANSFORMS = Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis; BRAVO = Laquinimod Double-Blind Placebo-Controlled Study in Relapsing-Remitting Multiple Sclerosis Patients With a Rater-Blinded Reference Arm of Interferon-β-1a; INF β-1b = interferon β-1b; BEYOND = Betaseron Efficacy Yielding Outcomes of a New Dose; CONFIRM = Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.

the patients (except dose in the CARE-MS studies). The other trials with BG-12 or laquinimod included "active comparators" as a reference (to meet the requirements of European regulators), but testing the comparison statistically was not preplanned. Clearly the studies all demonstrate that the various agents are effective, but to perceive that benefit ultimately, patients must be tolerant of the agent and stay on it. The studies' follow-up was typically only 2 years, but the clinical treatment window in practice

is foreseeably much longer. Therefore, there cannot be a substantial downside or risk that develops over time that might offset any perceived short-term benefit. Some agents, such as alemtuzumab, might ideally be used for brief periods to help regain disease control in patients who have broken through their first-line treatments. Once stabilized, patients might then be able to return to these first-line drugs, whose long-term safety may well be better.

It might ultimately be possible, using biomarkers for instance, to choose the best possible treatment for patients at a particular time in the course of their disease. Until then, the treating physician must consider a number of factors before considering a particular agent, weighing always the perceived benefit to risk ratio (and keeping in mind that risks may be delayed or even lifelong as a result of even a short-term exposure).[46,47]

CONCLUSIONS

Already, there are a wide range of agents to choose from for the treatment of relapsing MS, and even more are anticipated in the near future. Neurologists must be prepared to understand the merits of each option along with the recognized risks. Setting up a treatment algorithm is going to be a changing theme as newer agents become available or if new toxicities are realized. We might well be able to start talking about attaining a "disease-activity free" state for patients should the best agent for a given patient be chosen. There is no "one size fits all" empiric treatment for patients today, and much needs to be considered—the duration, course, and burden (clinical and MRI) of disease; previous response to DMT; and most importantly, the perceived risk of progression.

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KEY POINTS

- Short-term studies cannot predict all side effects that can occur with longer-duration therapy; therefore, efficacy in short-term studies cannot be extrapolated to the long term.
- Not all patients present with the same amount of disease or carry the same risk of progression. Risk factors such as disease course, type of relapse and residual disability, MRI burden of disease, or even response to previous disease-modifying drugs must be taken into account when considering a choice for therapy.

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