

# Multiple Sclerosis: Current and Emerging Disease-Modifying Therapies and Treatment Strategies

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## Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating central nervous system disease that typically strikes young adults, especially women. The pathobiology of MS includes inflammatory and neurodegenerative mechanisms that affect both white and gray matter. These mechanisms underlie the relapsing, and often eventually progressive, course of MS, which is heterogeneous; confident prediction of long-term individual prognosis is not yet possible. However, because revised MS diagnostic criteria that incorporate neuroimaging data facilitate early diagnosis, most patients are faced with making important long-term treatment decisions, most notably the use and selection of disease-modifying therapy (DMT). Currently, there are 10 approved MS DMTs with varying degrees of efficacy for reducing relapse risk and preserving neurological function, but their long-term benefits remain unclear. Moreover, available DMTs differ with respect to the route and frequency of administration, tolerability and likelihood of treatment adherence, common adverse effects, risk of major toxicity, and pregnancy-related risks. Thorough understanding of the benefit-risk profiles of these therapies is necessary to establish logical and safe treatment plans for individuals with MS. We review the available evidence supporting risk-benefit profiles for available and emerging DMTs. We also assess the place of individual DMTs within the context of several different MS management strategies, including those currently in use (sequential monotherapy, escalation therapy, and induction and maintenance therapy) and others that may soon become feasible (combination approaches and “personalized medicine”). We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials, from January 1, 1990, to August 31, 2013. The following search terms were used: *multiple sclerosis, randomized controlled trials, interferon-beta, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, BG-12, alemtuzumab, rituximab, ocrelizumab, daclizumab, neutralizing antibodies, progressive multifocal leukoencephalopathy.*

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**M**ultiple sclerosis (MS) is an idiopathic, putatively autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS) with genetic and environmental effects.<sup>1-3</sup> The median clinical onset of MS is approximately 29 years of age, and the female/male ratio in this group approaches 3:1 and may be increasing.<sup>4</sup> Multiple sclerosis causes bothersome or disabling physical symptoms involving mobility problems, vision problems, problems with coordination, cognitive dysfunction, fatigue, and pain. Quality of life may be further reduced by mood disorders and limitations in employment and social functioning.<sup>5-7</sup> It is the second most common cause of disability in young adults, and it is one of the costliest chronic diseases, with total annual costs per affected individual exceeding

US\$50,000 (2007 dollars), which is similar to that of congestive heart failure.<sup>8,9</sup>

Lesions of CNS white matter with loss of myelin, neuronal axons, and myelin-producing oligodendrocytes characterize the multifocal pathology of MS.<sup>10</sup> Recent research has also highlighted an underappreciated involvement of gray matter, which may be especially relevant to irreversible disability.<sup>11,12</sup> Acute inflammatory lesions are initiated by activated peripheral leukocytes that enter the CNS through a breached blood-brain barrier (BBB).<sup>13</sup> The clinical correlate of this process is a clinical attack (synonyms include relapse, exacerbation, or flare), which consists of subacute neurological symptoms (eg, visual impairment and imbalance) that worsen over days to a few weeks and, early in the disease, often recover

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## ARTICLE HIGHLIGHTS

- Ten disease-modifying therapies (DMTs) are approved for relapsing forms of multiple sclerosis (MS).
- First-generation self-injectable DMTs, interferon beta drugs and glatiramer acetate, have moderate efficacy and good safety profiles but relatively low adherence rates.
- Natalizumab is highly effective for relapsing multiple sclerosis but is associated with the risk of progressive multifocal leukoencephalopathy.
- The risk factors for progressive multifocal leukoencephalopathy include exposure to John Cunningham virus, previous immunosuppressive drug use, and natalizumab therapy for more than 2 years.
- Fingolimod is a once-daily oral DMT with moderate efficacy, but several important cardiovascular contraindications and requirements for specific laboratory and ophthalmological monitoring.
- Teriflunomide is a once-daily oral DMT with efficacy similar to that of self-injectable drugs and key characteristics that necessitate special safety evaluation and monitoring (pregnancy category X, potential hepatotoxicity, and long half-life).
- Dimethyl fumarate/BG-12 is a twice-daily oral DMT with moderate efficacy and, thus far, a favorable safety profile with self-limited flushing and gastrointestinal symptoms and side effects.
- Multiple sclerosis DMTs may be used as sequential monotherapies or as part of escalation or induction strategies. Combination therapies and personalized medicine are future therapeutic opportunities.

spontaneously and completely.<sup>14</sup> Current preventive disease-modifying therapies (DMTs) for MS primarily target attacks, reducing their frequency and severity. Brain magnetic resonance imaging (MRI) may detect several new asymptomatic lesions for every clinically apparent attack and is used as a sensitive, objective, and quantifiable instrument for the measurement of MS activity in both clinical practice and therapeutic trials.<sup>15</sup>

Eighty-five percent of the patients have relapsing-remitting multiple sclerosis (RRMS), in which a clinical attack heralds the onset of the disease.<sup>16</sup> If insufficient brain MRI evidence is present at first clinical presentation, a temporary diagnosis of “clinically isolated syndrome” may be applied, implying high risk for future confirmed MS, awaiting evidence of further

clinical relapses or new MRI lesions (“dissemination in time and space”).<sup>17,18</sup> The remaining 15% of the patients have primary progressive multiple sclerosis (PPMS), defined as gradually progressive and unremitting loss of neurological function for more than 1 year. It usually manifests as a gait disorder, is associated with less evidence of inflammatory activity (subsequent clinical relapses and MRI lesions) than RRMS, and likely represents a neurodegenerative process.<sup>19</sup> Distinguishing RRMS from PPMS is crucial because all available MS DMTs have presented efficacy for attack reduction in relapsing MS, but none has yet proven to affect PPMS.

The natural history of MS is notoriously variable and largely unpredictable on an individual level. In RRMS, residual effects of clinical relapses may result in accumulating neurological impairment,<sup>20</sup> typically quantified in practice and clinical trials with the Expanded Disability Status Scale (EDSS), an ordinal scale ranging from 0 (normal) to 10 (death from MS).<sup>21</sup> However, the most important predictor of future disability for patients with RRMS is the development of secondary progressive multiple sclerosis (SPMS). Conversion to SPMS occurs in approximately 60% to 70% of those with RRMS, usually 1 to 3 decades after disease onset, and when EDSS scores range from 2 to 5, reflecting mild to moderate disability in an ambulatory patient.<sup>22,23</sup> Secondary progressive MS behaves much like PPMS, usually manifesting as a gradually worsening gait disorder and causing ambulatory dysfunction requiring mobility assistance with cane (EDSS score 6), walker (6.5), or wheelchair (8). Remarkably, up to 15% of the patients with RRMS may ultimately prove to have “benign” MS, escaping both major attack-related disability and conversion to SPMS.<sup>24</sup> Unfortunately, there is limited ability to predict which outcome is likely for an individual patient with early-stage disease.

Many people with newly diagnosed or early-stage MS are overwhelmed by the combination of uncertain prognosis, the often-unsettling prospect of embarking on preventive immunotherapy with no defined time frame, and the lengthy roster (10 and growing) of available DMTs with different benefit-risk profiles. Herein, we review currently available and emerging DMTs, focusing on recent developments, and various strategies to incorporate them into contemporary patient-

**TABLE 1. First-Generation Self-Injectable Multiple Sclerosis Disease-Modifying Therapies**

Characteristic	Disease-modifying therapy				
	Interferon beta-1b		Interferon beta-1a		Glatiramer acetate
Brand name	Betaseron	Extavia	Avonex	Rebif	Copaxone
Year approved	1993	2009	1996	2002	1997
Dose	250 µg	250 µg	30 µg	22 or 44 µg	20 mg
Route	SC	SC	IM	SC	SC
Frequency	Every other day	Every other day	Weekly	Thrice weekly	Daily

IM = intramuscular; SC = subcutaneous.

physician shared-decision models. We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1, 1990, through August 30, 2013. The following search terms were used: *multiple sclerosis, randomized controlled trials, interferon beta, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, BG-12, alemtuzumab, rituximab, ocrelizumab, daclizumab, neutralizing antibodies, and progressive multifocal leukoencephalopathy*. Articles addressing MS DMTs and MS management strategies were selected for inclusion.

**APPROVED DMTs**

**“First-Generation” Self-Injectable Therapies**

Four interferon beta preparations and glatiramer acetate (GA) are approved for relapsing MS (Table 1). Their mechanisms of action are not fully understood, but interferon beta reduces BBB disruption and modulates T-cell, B-cell, and cytokine functions, whereas GA probably stimulates regulatory T cells.<sup>25</sup> These immunomodulatory drugs have comparable efficacy, reducing the clinical relapse rate by about one-third and moderating the development of new brain MRI lesions over periods of 1 to 3 years for both clinically isolated syndrome<sup>26-29</sup> and relapsing MS.<sup>30-35</sup> The interferon beta drugs also slow EDSS worsening in relapsing MS but have minimal effect on established progressive MS.<sup>36-39</sup> The development of persistent high-titer interferon beta neutralizing antibodies, especially with subcutaneous preparations, is associated with reduced efficacy of all drugs in the class.<sup>40,41</sup>

Because interferon beta and GA have favorable long-term safety profiles and minimal

monitoring requirements, they remain common first-line choices despite competition from new oral therapies. There are no available biological markers or pharmacogenomic profiles that predict better outcome with a specific drug for an individual patient. Concomitant medical conditions and patient preferences for injection type and frequency and avoidance of certain adverse effects (such as interferon beta-associated flu-like symptoms) are factors that affect the selection of a specific agent.<sup>42</sup> Adherence and persistence with therapy is a problem, with greater than 25% of the patients discontinuing therapy within 1 to 2 years.<sup>43</sup>

The development of oral DMTs and parenteral DMTs with infrequent dosing requirements has spurred new developments within this first generation of therapies. A placebo-controlled study found that double-dose (40 mg) of GA administered thrice weekly reduced the annualized relapse rate by 34%, which is similar to the 29% value originally achieved with standard 20 mg of GA administered daily, and with a lower incidence of injection site reactions.<sup>44</sup> A supplemental new drug application is under review at the Food and Drug Administration (FDA). Similarly, a PEGylated form of subcutaneous interferon beta-1a with a longer half-life permits reduced injection frequency (every 2-4 weeks) than did current interferon beta preparations. An ongoing phase 3 study found relapse, disability progression, and MRI benefits that support a Biologics Licensing Application currently under review by the FDA.<sup>45</sup>

**General Immunosuppression: Mitoxantrone**

Mitoxantrone is a general immunosuppressive drug approved for rapidly worsening relapsing MS and is the only agent approved to treat SPMS.<sup>46</sup> At standard doses, its use is limited

TABLE 2. Summary of Efficacy Data From Pivotal Controlled Trials for Recently Developed Multiple Sclerosis Disease-Modifying Therapies<sup>a,b</sup>

Characteristic	Disease-modifying therapy				
	Natalizumab	Fingolimod	Teriflunomide	Dimethyl fumarate	Alemtuzumab
Brand name	Tysabri	Gilenya	Aubagio	Tecfidera	Lemtrada
Year approved	2004, 2006	2010	2012	2013	Under review
Dose	300 mg	0.5 mg	7 or 14 mg	240 mg	12 mg
Route	IV	Oral	Oral	Oral	IV
Frequency	Every 4 wk	Daily	Daily	BID	Annual course
Clinical relapses					
Relative RR	68%	54%	31% (both doses)	51%-53%	55% (naive) 49% (treated)
Absolute RR	0.50	0.18	0.37 (both doses)	0.17	0.21 (naive) 0.26 (treated)
NNT (2 y)	2	5	6	5	5 (naive) 4 (treated)
Disability progression					
Relative RR	42%	30%	NS (7 mg) 26% (14 mg)	38%	NS (naive) 42% (treated)
Absolute RR	0.120	0.064	NS (7 mg) 0.071 (14 mg)	0.110	NS (naive) 0.084 (treated)
NNT (2 y)	8	14	NA (7 mg) 14 (14 mg)	9	NA (naive) 12 (treated)

<sup>a</sup>BID = twice a day; IV = intravenously; MS = multiple sclerosis; NA = not applicable; NNT = number needed to treat; NS = not significant; RR = risk reduction.

<sup>b</sup>All data represent comparisons of individual therapies and a parallel placebo arm with the exception of alemtuzumab, which was compared with subcutaneous interferon beta-1a, and results from both the DMT-naïve and previously DMT-treated trials of alemtuzumab are included. These data are presented for reference purposes rather than as direct comparisons of efficacy between DMTs. All values are statistically significant unless otherwise indicated.

to 2 years because of cumulative dose-related cardiomyopathy. After initial widespread use, it became apparent that mitoxantrone was associated with higher than expected rates of cardiomyopathy and delayed treatment-related acute leukemia, markedly reducing its use in the United States.<sup>47</sup>

### Natalizumab

Natalizumab is a humanized monoclonal antibody that selectively targets the  $\alpha$ 4 subunit of the cell adhesion molecule “very late antigen 4” expressed on the surface of lymphocytes and monocytes.<sup>48</sup> It prevents the interaction between the very late antigen 4 integrin and its ligand vascular cell adhesion molecule-1 on brain vascular endothelium. This interaction is necessary for the transmigration of immune cells across the BBB; thus, circulating lymphocytes could not enter the CNS and trigger acute MS lesions.

Two pivotal trials found remarkable efficacy of natalizumab against clinical relapses, EDSS-measured disability, and MRI measures, leading to FDA approval of natalizumab for

relapsing MS in late 2004 (Table 2).<sup>49-51</sup> Natalizumab was associated with a slightly increased rate of common infections (eg, pharyngitis) but was otherwise well tolerated. However, it was soon recognized that 2 trial participants developed progressive multifocal leukoencephalopathy (PML), a CNS infection with the John Cunningham virus (JCV), which leads to death or irreversible neurological disability from progressive cognitive, motor, or visual dysfunction and for which there is no proven effective treatment.<sup>52-54</sup> The ubiquitous JCV is harbored by 50% to 60% of the population. CNS infection occurs rarely in people with immunodeficiency disorders or people receiving long-term immunosuppressive therapy (eg, transplant recipients).<sup>54</sup> An interruption to normal immune surveillance by natalizumab results in the escape of JCV to the CNS from sequestration in peripheral organs or primary CNS reactivation. The temporary withdrawal of natalizumab from the market was followed by its reintroduction in 2006 with a risk mitigation strategy (the TOUCH program), which is meant to provide

**TABLE 3. Stratified PML Risk Data Associated With Natalizumab Therapy for JCV Seropositive Patients<sup>a,b,c</sup>**

Duration of natalizumab therapy (mo)	Prior immunosuppressive therapy exposure?	
	No	Yes
0-24	0.7 (0.5-1.0)	1.8 (1.1-2.7)
25-48	5.3 (4.4-6.2)	11.2 (8.6-14.3)
49-72	6.1 (4.8-7.8)	Insufficient data

<sup>a</sup>JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.

<sup>b</sup>Risk estimates are expressed per 1000 treated patients (95% CI) and were updated September 1, 2013.<sup>56</sup>

<sup>c</sup>The risk of PML for JCV seronegative patients is estimated at 0.1 per 1000 patients (95% CI, 0.01-0.35).

continuous PML surveillance. The PML experience with natalizumab has affected the design of long-term safety assessments in subsequent MS clinical trials and postmarketing studies.

Risk factors for PML include evidence of prior JCV exposure, duration of natalizumab therapy, and prior use of immunosuppressants such as mitoxatrone, azathioprine, or methotrexate (but not the immunomodulators interferon beta and GA or routine use of bolus corticosteroids for clinical relapses).<sup>55</sup> The risk of PML emerges primarily in JCV seropositive patients who have received natalizumab therapy for more than 2 years, after which the incidence exceeds 1 per 200 (5.51 per 1000; 95% CI, 4.95-6.11; as of September 2013).<sup>56</sup> Only 2 PML cases have thus far been noted in patients documented to be JCV seronegative beforehand. Other biomarkers are under evaluation; a particularly low level of L-selectin-expressing CD4 T cells appears to portend a higher PML risk.<sup>57</sup>

Risk stratification data for PML, summarized in Table 3, may be used to counsel individual patients regarding initiation or discontinuation of natalizumab. Anti-JCV serological testing is now routinely used to assess JCV exposure status.<sup>58</sup> The seroconversion rate is 1% to 2% per year; therefore, retesting every 6 months is recommended for seronegative patients using natalizumab. Of note, recent data suggest that serological methods may underestimate JCV infection rates because more than one third of the seronegative patients have detectable JC viremia or viremia.<sup>59,60</sup> Therefore, vigilance for early signs of PML, such as progressive speech deficits, hemiparesis, or seizures, even in seronegative patients

is important. Seropositive patients using natalizumab should undergo routine brain MRI surveillance every 6 months to detect early, potentially subtle signs of PML. Clinical or MRI evidence suggestive of PML should prompt natalizumab discontinuation, further investigation with cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction, and consideration of plasma exchange to rapidly remove circulating natalizumab.<sup>61,62</sup> There is a risk of additional neurological symptoms from immune reconstitution inflammatory syndrome after rapid natalizumab removal, but this can often be controlled with corticosteroids.<sup>63</sup>

Owing to PML risk, natalizumab is generally reserved for use in patients with “breakthrough” disease activity on one or more of the first-line DMTs. Some MS specialists also use it as a first-line therapy for early aggressive MS for 1 to 2 years, to be followed by transition to another agent once disease activity appears controlled, especially in JCV seropositive individuals. The natalizumab molecule contains murine sequences that increase immunogenicity, resulting in infusion reactions and neutralizing antibodies.<sup>64</sup> Patients with persistent anti-natalizumab neutralizing antibody titers should discontinue therapy because of loss of efficacy and increased risk of hypersensitivity reactions, which may be fatal.<sup>65</sup> Inflammatory activity of MS may return 3 to 6 months after the discontinuation of natalizumab.<sup>66</sup> Although not detected in an analysis of controlled trial participants, some patients have been reported to exhibit “rebound” activity far exceeding their baseline rate but prediction of this outcome is not currently possible.<sup>66,67</sup> Strategies such as tapering the natalizumab with increased infusion intervals or using pulse corticosteroids do not appear beneficial, but earlier transition to other DMTs may reduce the risk of rebound activity.<sup>68-71</sup>

**Oral DMTs**

Three oral DMTs are approved for relapsing MS: fingolimod, teriflunomide, and dimethyl fumarate/BG-12 (Table 2).

**Fingolimod.** Fingolimod is a once-daily oral medication approved for relapsing MS. It is superior to both placebo and intramuscular interferon beta-1a on measures of clinical relapse (~ 50% reduction in relapse rate vs placebo) and

MRI activity.<sup>72,73</sup> It is a sphingosine-1-phosphate (S1P) agonist, binding to 4 of the 5 S1P receptor subtypes, but acts as a functional antagonist. Fingolimod interferes with a key S1P mechanism that lymphocytes use to exit lymph nodes.<sup>74</sup> Nodal trapping of lymphocytes renders them unavailable for entering the CNS to initiate MS lesions and causes mild lymphopenia. Fingolimod also enters the CNS and affects neurons and supporting glia that express S1P receptors.<sup>75</sup>

Adverse effects of fingolimod reflect the effects of lymphopenia as well as the fact that subtypes of S1P receptors are expressed on many other tissues. Although few opportunistic infections have been recorded, there is a notable risk of viral infections, especially varicella zoster, for which documentation of an adequate serological response or immunization is required before therapy. Disseminated zoster infection has occurred.<sup>76</sup> Owing to significant effects on cardiac smooth muscle, fingolimod is contraindicated for patients who, within 6 months, have experienced ischemic heart disease syndromes, symptomatic cerebrovascular disease, or heart failure, who have Mobitz type II second-degree or third-degree atrioventricular block or sick sinus syndrome (unless the patient has a functioning pacemaker), prolonged corrected QT interval  $\geq 500$  ms, or current treatment with class Ia or class III antiarrhythmic drugs.<sup>77</sup> Bradycardia is a near-universal occurrence that requires clinical observation for 6 hours after the first dose of fingolimod, but it is rarely symptomatic in individuals without cardiovascular risk factors. The FDA has recently clarified the management of patients with relevant risk factors, including need for specialty consultation or prolonged cardiac monitoring for patients at highest risk or in whom cardiac events occur during the first-dose monitoring session.<sup>77</sup>

The retina expresses S1P receptors, likely accounting for an approximately 0.5% risk of macular edema (usually reversible) that requires pretreatment and 3-month follow-up ophthalmological examinations for all treated patients. The risk of macular edema is higher in people with diabetes mellitus or prior uveitis, and such individuals should have annual ophthalmological assessments indefinitely.<sup>78</sup> Other potential adverse events include hypertension, asymptomatic reduction in pulmonary forced vital capacity, and elevated liver

transaminases. Selective S1P modulators are in development and should have narrower adverse event profiles. A recently reported case of PML in a patient who received fingolimod for 7 months, and who was not previously exposed to natalizumab, remains under investigation.<sup>79</sup> Otherwise, PML has not been associated with fingolimod. Fingolimod is a suitable first- or second-line DMT for individuals without cardiovascular risk factors who desire once-daily oral therapy and have a high likelihood of adherence with required monitoring.

**Terifunomide.** Teriflunomide, a once-daily oral DMT, is the active metabolite of the rheumatoid arthritis drug leflunomide. It exerts immunological effects by inhibiting dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis in proliferating (but not resting) cells.<sup>80</sup> Two doses—7 and 14 mg/d—were approved on the basis of the results of 2 large placebo-controlled phase 3 trials that presented efficacy for the primary outcome of relapse rate as well as secondary MRI measures.<sup>81,82</sup> Disability progression data indicated significant benefit in both studies only for the 14 mg dose. An as yet unpublished trial found that neither teriflunomide dose was superior to subcutaneous interferon beta-1a dose.<sup>83</sup>

Teriflunomide is generally well tolerated at both approved doses. Common adverse effects include lymphopenia, elevated liver transaminases (it carries a black box warning for potentially serious hepatotoxicity on the basis of experience with leflunomide), hypertension, nausea, diarrhea, peripheral neuropathy (1%-2%), acute renal failure (1%), and alopecia.<sup>84,85</sup>

Some unique safety considerations of teriflunomide include its teratogenicity (pregnancy category X) and prolonged half-life. It is contraindicated in pregnancy and is excreted in breast milk and semen. It has an extended half-life (18-19 days) because of enterohepatic recirculation, and it may take several months or up to 2 years to fully eliminate the drug after discontinuation,<sup>86</sup> a concern in patients who become pregnant during therapy, want to conceive shortly after discontinuing the drug, or experience a serious adverse event such as hepatotoxicity. In these cases, cholestyramine or activated charcoal may be used to facilitate accelerated elimination over a period of 11 days.<sup>83</sup> These characteristics

make teriflunomide less suitable for selected patients, particularly women with childbearing potential, those who have a history of nonadherence to medication use and monitoring, and those with preexisting hepatic conditions or using other potentially hepatotoxic drugs.

**Dimethyl Fumarate/BG-12.** Dimethyl fumarate (DMF) is a newly approved twice-daily oral DMT for relapsing MS. On ingestion, it is hydrolyzed to monomethyl fumarate, which is eliminated through respiration and has little hepatic or renal excretion. The mechanism of DMF action has not been completely elucidated, but it is known to activate the nuclear-related factor 2 transcriptional pathway, which reduces oxidative cell stress, as well as to modulate nuclear factor  $\kappa$ B, which could have anti-inflammatory effects.<sup>87,88</sup> Fumaric acid compounds have been used for decades; for example, the German Fumaderm preparation is used for psoriasis.<sup>89</sup> The DMF preparation for MS, also known as BG-12, is an enteric-coated tablet designed to improve gastrointestinal tolerability. Two pivotal MS trials compared DMF (240 mg twice-daily and thrice-daily dosage arms) with placebo.<sup>90,91</sup> DMF achieved its primary outcome of significant reduction in the annualized relapse rate and MRI activity in both studies. It also outpaced GA, which was a “reference comparator” required by the European regulatory agency, on measures of relapse and MRI, although there was no benefit on EDSS progression.<sup>90</sup>

The safety and tolerability profile of DMT appears favorable. Approximately 30% of individuals will experience self-limited symptoms of flushing (lasting about 1 week and mitigated by taking DMT with food or aspirin) or gastrointestinal symptoms and gastrointestinal side effects, such as nausea, abdominal pain, or diarrhea (lasting 2-4 weeks). No other adverse events were more common with DMT than with placebo. Although renal pathological changes were noted in all species studied during preclinical investigations, renal dysfunction was not a significant adverse event in human trials.<sup>92</sup> Four European cases of PML were recently reported in association with the use of Fumaderm or compounded fumaric acid esters for the treatment of psoriasis.<sup>93-95</sup> However, confounding factors in these cases included concomitant or recent immunosuppressant use or cancer and excessive drug dosing causing profound and prolonged leukopenia.<sup>95</sup>

To date, PML has not been reported with DMF. However, a 30% mean lymphocyte count reduction is routinely observed with DMF and regular complete blood cell count monitoring is recommended. The known benefit-risk profile of DMF makes it a reasonable initial or later stage DMT option for most patients with RRMS.

## EMERGING THERAPIES

### Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell surface marker present on monocytes and lymphocytes. One course of intravenous treatment depletes T, B, and natural killer cell types, especially CD4<sup>+</sup> T cells. Although B cells repopulate within 5 to 6 months, T cells deplete for more than 1 year. Treatment is repeated at 1 year and may be extended annually thereafter.

Two recently reported phase 3 studies—CARE-MS I and CARE-MS II—found efficacy of alemtuzumab in single-blind comparisons vs thrice-weekly subcutaneous interferon beta-1a.<sup>96,97</sup> Both protocols were designed for patients with recently diagnosed relapsing MS and relatively mild disability in the hope that early aggressive therapy might “reset” the immune system and favorably affect the longer-term disease course. CARE-MS I recruited treatment-naïve individuals, whereas CARE-MS II enrolled individuals who had continued disease activity on at least 1 first-line therapy. The coprimary outcomes of the annualized relapse rate and EDSS progression were used in each trial. In CARE-MS I, the annualized relapse rate was significantly reduced with 12 mg of alemtuzumab but confirmed EDSS progression was not, possibly owing to the low event rates (11% for placebo and 8% for alemtuzumab). Multiple MRI end points and the proportion of patients who were “disease activity free” on both clinical and MRI measures favored alemtuzumab. CARE-MS II used a similar design but 2 doses (12 and 24 mg) of alemtuzumab. Reductions in both the annualized relapse rate (49%) and the sustained accumulation of disability (42%) favored alemtuzumab, as did virtually all MRI measures. There was no treatment advantage, and more adverse events, in the 24-mg alemtuzumab arm.

Alemtuzumab is associated with significant adverse effects, especially secondary autoimmune

**TABLE 4. Key Risks and Adverse Events of Multiple Sclerosis Disease-Modifying Therapies: Monitoring, Detection, and Evaluation<sup>a</sup>**

Disease-modifying therapy	Pregnancy category	Neutralizing antibodies <sup>b</sup>	Routine monitoring	Adverse events	Evaluation and management strategies
Interferon beta preparations	C	Yes	Baseline and regular CBC, LFTs	Injection-site reactions Flu-like symptoms  LFT elevation  Leukopenia  Depression	Dose titration, topical methods (eg, ice); usually self-limited Dose titration, NSAIDs/acetaminophen, usually self-limited Review other potential hepatotoxic medications, consider temporary interferon beta suspension, rechallenge at lower dose Lower dose or temporarily discontinue drug and then rechallenge Consider psychiatric evaluation and antidepressant therapy; if severe, consider discontinuing interferon beta
Glatiramer acetate	B	No	None	Injection-site reactions Benign systemic reaction (dyspnea, palpitations)	Topical methods None (self-limited, usually nonrecurrent)
Mitoxantrone	D	No	Baseline and regular (eg, every 6 mo) CBC, LFT  Baseline echocardiography; repeat before each dose	Cardiac toxicity  Leukemia	Predose echocardiogram or MUGA scan; annual follow-up scans even after course completion to detect delayed cardiac toxicity Regular CBC; follow-up recommended for years after course completion
Natalizumab	C	Yes	Baseline and routine (eg, every 6 mo) CBC, LFTs JCV serology and brain MRI every 6 mo in JCV seronegative patients	Infusion reactions  PML	If recurrent, check neutralizing antibody titer  TOUCH program surveillance; if suspected, discontinue natalizumab and complete clinical, MRI, and CSF evaluation
Fingolimod	C	No	Baseline and regular (eg, every 6 mo) CBC, LFTs  Baseline ECG and VZV serology Baseline and 3-mo ophthalmological examination (minimum)	Bradyarrhythmia  Macular edema  Herpes virus infections (especially VZV)	First-dose observation protocol (6-h monitoring of heart rate and blood pressure) Cardiology consultation if risk factors or abnormal baseline ECG results Prolonged cardiac monitoring if risk factors or events during first-dose observation Ophthalmological monitoring; consider indefinitely in patients with diabetes mellitus or history of uveitis Prompt antiviral therapy; consider prophylaxis in patients with recurrence
Teriflunomide	X	No	Baseline and regular (eg, every 6 mo) CBC Baseline and monthly LFTs for 6 mo, then every 6 mo Baseline pregnancy test, tuberculosis test Baseline and regular blood pressure	Teratogenic risk  Hepatotoxicity	Emphasize need for reliable contraception; discontinue drug and use accelerated drug washout protocol if pregnancy occurs while on drug or is planned after discontinuation  Monthly LFT monitoring, for 6 mo, then every 6 mo; discontinue drug and use accelerated washout protocol for moderate or severe toxicity

*Continued on next page*

**TABLE 4. Continued**

Disease-modifying therapy	Pregnancy category	Neutralizing antibodies <sup>b</sup>	Routine monitoring	Adverse events	Evaluation and management strategies
Dimethyl fumarate/ BG-12	C	No	Baseline and regular (eg, every 6 mo) CBC	Flushing (dose-related)  Gastrointestinal symptoms and gastrointestinal side effects  Leukopenia	Self-limited; may take with food or aspirin  Self-limited; symptomatic  Laboratory monitoring
Alemtuzumab	C	No	Baseline and regular (eg, every 6 mo) thyroid function and monthly platelet (and possibly urinalysis) monitoring	Secondary autoimmunity	Laboratory monitoring

<sup>a</sup>CBC = complete blood cell count; CSF = cerebrospinal fluid; ECG = electrocardiogram; LFT = liver function test; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSAID = nonsteroidal anti-inflammatory drug; PML = progressive multifocal leukoencephalopathy; VZV = varicella zoster virus.

<sup>b</sup>The "Neutralizing Antibodies" column indicates whether such antibodies affect drug efficacy or safety for each drug or drug class.

disorders such as autoimmune thyroid disease (18%, including Graves' disease), idiopathic thrombocytopenic purpura (0.8%, including 1 fatal case that led to a risk mitigation strategy with monthly platelet count monitoring), and Goodpasture syndrome (rare).<sup>98</sup> This secondary autoimmunity may be associated with interleukin 21.<sup>99</sup> Infusion reactions, herpes infections, and other common infections were more frequent in patients treated with alemtuzumab; a protocol amendment recommended additional acyclovir during and, for 28 days, after alemtuzumab infusions. Thyroid papillary carcinoma was seen in 2 patients treated with alemtuzumab, and malignant disease is a potential ongoing risk owing to the long duration of immunosuppression induced by the drug. Alemtuzumab is currently under FDA review; if approved, a risk mitigation program will likely be mandated and it will probably find the most use as a second- or later-line agent for breakthrough disease (partly on the basis of CARE-MS II data as well as a recent open-label study suggesting benefit after other DMT failure<sup>100</sup>) or as an induction-type therapy for aggressive MS.

**Ocrelizumab**

Ocrelizumab is a humanized anti-CD20 monoclonal antibody structurally similar to the chimeric anti-CD20 agent rituximab. Anti-CD20 therapies deplete B cells (except progenitor B cells and plasma cells), resulting in the depletion of B cells for 6 to 9 months but a mild effect on immunoglobulin production.

The use of rituximab resulted in significant relapse and MRI benefits in a phase 2 study of relapsing MS, and the effects were evident early in the study, suggesting that it may act by interfering with B-cell antigen presentation.<sup>101,102</sup> A phase 2 relapsing MS study comparing high-dose and low-dose ocrelizumab against placebo and intramuscular interferon beta-1a arms revealed significant relapse (vs placebo; low-dose only vs interferon beta-1a) and MRI benefits (vs placebo and interferon beta-1a).<sup>103</sup> Two phase 3 relapsing MS trials and 1 phase 3 PPMS trial are underway.

**Laquinimod**

Laquinimod is a potentially safer derivative of the immunomodulatory drug linomide, development of which was halted after cardiovascular events and deaths during phase 3 trials.<sup>104</sup> The mechanism of action of laquinimod is unknown but may be related to its ability to enter the CNS. Two phase 3 studies of oral laquinimod are complete; both were placebo controlled and 1 included an active comparator (interferon beta-1a) arm.<sup>105,106</sup> The data presented modest effects on relapses and MRI lesions lagging those of available DMTs, and further studies are being done to determine whether the more significant effects detected on outcomes of EDSS progression and brain atrophy provide an advantage.

**Daclizumab**

Daclizumab is a humanized monoclonal antibody that targets the high-affinity  $\alpha$  subunit

(CD25) of the interleukin 2 receptor that is expressed on activated T cells.<sup>107-109</sup> A phase 2 study found positive results when daclizumab was added to interferon beta-1a.<sup>109</sup> Clinical and MRI benefits are associated with the expansion of regulatory CD56<sup>+</sup> (bright) natural killer cells, a new mechanism of action and potential therapeutic biomarker.<sup>110</sup> A 1-year placebo-controlled phase 2b study found efficacy of daclizumab vs placebo.<sup>111</sup> Hepatic enzyme elevation and cutaneous reactions were the main adverse events. A phase 3 study comparing daclizumab and interferon beta-1a is underway.

### THERAPEUTIC STRATEGIES

Shared decision making between a person with MS and his or her neurologist typically results in a mutually satisfactory selection of an initial DMT. Recommendations and decisions are affected by recent MS activity (recent attack frequency, severity, and recovery), the degree of neurological impairment, the “lesion burden” (and the presence of active enhancing lesions) evident on brain and spinal cord MRI, drug availability and cost, concomitant medical illnesses and medications, adverse effect profiles, monitoring requirements, and patient preferences, among other factors (Table 4). Increased decision-making complexity has brought patient preferences (eg, a female patient’s imminent plans to conceive a child; desire to avoid

self-injections or specific adverse effects) to the forefront, especially early in the disease. However, patients who experience more active disease, especially with residual neurological deficits, are more likely to accept the trade-off of more risk for greater efficacy. Further confounding the situation is uncertainty regarding whether, and how much, DMT therapy affects long-term outcomes such as need for gait aid or life expectancy.<sup>112,113</sup> In this section, we review general treatment strategies, some currently in use and others destined for future deployment.

### Sequential DMT Monotherapy

This strategy is the most common current MS treatment strategy and is partially supported by available controlled trials. Patients initiate their first DMT treatment and begin a period of surveillance for clinical or MRI disease activity as well as tolerability, adherence, and safety issues. The ideal outcome is an extended clinical and radiological remission (no relapses, disability progression, or new MRI lesions) without significant adverse events; if achieved, therapy continues indefinitely but with periodic reassessment.

Even if a selected drug is providing benefit, most patients will eventually experience some degree of “breakthrough” relapse or MRI activity owing to the partial efficacy of all DMTs. The clinical challenge is when to declare treatment failure and revise the treatment plan. This approach may be termed *treatment escalation* if the next drug has greater apparent efficacy, though in many instances the rationale may be to try a DMT with a difference mechanism of action even if efficacy estimates for the current and next drugs are similar. Unfortunately, there is sparse high-quality evidence to support clinical decision making in this scenario. First, it has proven difficult to validate definitions of treatment failure for clinical use; some factors for consideration are listed in Table 5.<sup>114-117</sup> Second, more work is needed to understand the types of short-term change that might predict longer-term prognosis.<sup>118</sup> Third, there are few head-to-head DMT trials or trials that assess specific DMTs as a next option specifically in the setting of failure of another DMT. Despite these challenges, declaration of treatment failure is straightforward in instances in which disability has increased. Whether to escalate from first-line self-injectable therapies to an oral drug or

**TABLE 5. Considerations for Determination of Multiple Sclerosis Disease-Modifying Therapy Failure or Loss of Efficacy**

#### Patient factors

- Drug tolerability
- Drug toxicity
- Adherence to dose regimen
- Adherence to monitoring requirements

#### Clinical factors

- Comparison of pretreatment and on-treatment relapse rates
- On-treatment relapse rate (eg,  $\geq 1$  per year), severity, and degree of recovery
- Increased neurological impairment (eg, EDSS score increase by 1 point in 1 y)
- Increased cognitive dysfunction
- Presence of neutralizing antibodies (for interferon beta drugs and natalizumab)

#### MRI factors

- Increase in brain lesion number (serial MRI scans)
- Occurrence of on-treatment active (gadolinium-enhancing) lesions
- Increase in brain stem or spinal cord lesions
- Increase in brain MRI T1 “black holes” (marker of irreversible axonal loss)
- Development or worsening of cerebral atrophy

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging.

**TABLE 6. Rationale and Evidence for Sequential Monotherapy With Multiple Sclerosis Disease-Modifying Therapies<sup>a,b</sup>**

Current DMT	Next DMT	Rationale and evidence			
		Efficacy escalation	Different MOA	Other factors	Evidence for efficacy from controlled trials
IM interferon beta-1a	GA	Yes	Yes	NAbs	CombiRx <sup>126</sup>
	SC interferon beta-1a	Yes	No		EVIDENCE <sup>35</sup>
	Fingolimod	Yes	Yes	NAbs	TRANSFORMS <sup>73</sup>
	Teriflunomide	Possibly	Yes	NAbs	None
	DMF/BG-12 Natalizumab Alemtuzumab	Yes	Yes	NAbs	None
SC interferon beta-1a	Alemtuzumab	Yes	Yes	NAbs	CARE-MS I <sup>96</sup> CARE-MS II <sup>97</sup>
SC interferon beta (any)	Other DMT (non-interferon beta)	Yes	Yes	NAbs	None
GA	Interferon beta	No	Yes		None
	DMF/BG-12	Yes	Yes		CONFIRM <sup>90</sup>
	Other DMT	Yes	Yes		None
Fingolimod	Natalizumab	Yes	Yes		None
Teriflunomide DMF/BG-12	Other DMT	No	Yes		None
Natalizumab	Other DMT	No	Yes	NAbs PML risk >2 y	None
Alemtuzumab	Other DMT	No	Yes		None

<sup>a</sup>CARE-MS = Comparison of Alemtuzumab and Rebif Efficacy for Multiple Sclerosis; CONFIRM = Comparator and an Oral Fumarate in Relapsing Remitting Multiple Sclerosis; DMF = dimethyl fumarate; DMT = disease-modifying therapy; EVIDENCE = Evidence of Interferon Dose-response: European North American Comparative Efficacy; IM = intramuscular; GA = glatiramer acetate; MOA = mechanism of action; NAb = neutralizing antibody; PML = progressive multifocal leukoencephalopathy; SC = subcutaneous; TRANSFORMS = Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing Remitting Multiple Sclerosis.

<sup>b</sup>Rationale for efficacy escalation is based on the magnitude of DMT effect on relapses in placebo-controlled trials, recognizing that caution is required when comparing between trials. Efficacy evidence indicates whether and which head-to-head studies found superior efficacy of 1 DMT vs another, though not necessarily in the context of treatment failure.

natalizumab is a key decision point that is often affected by JCV antibody status. For patients already using fingolimod, teriflunomide, or DMF, switching to natalizumab is likely an efficacy “escalation” (though direct evidence for this is lacking) whereas switching between the oral agents may or may not be. Clear failure of 2 or more drugs usually prompts serious consideration of natalizumab, even in JCV seropositive individuals, even if it is to be used for 2 years or less in the hope of inducing disease remission with minimal PML risk. Natalizumab has exhibited efficacy in highly inflammatory MS and in the setting of breakthrough disease.<sup>119</sup> When available, alemtuzumab would be a serious consideration for such patients. The rationale and evidence for switching between specific therapies is summarized in Table 6.

In addition to efficacy issues, risk must be considered with any therapeutic change. There may be overlapping immunosuppressive effects of sequentially used drugs and some toxicity (PML, secondary autoimmunity, and malignant disease) may be delayed by months or years. There are many other unanswered questions regarding DMT switching, including

whether washout periods between current and subsequent DMTs are necessary, how long they should be for specific DMT transitions, and appropriate long-term surveillance approaches for risks such as PML and malignant disease.

**Induction and Maintenance Strategy**

If a causative relationship exists between early inflammatory activity of MS and future development of a degenerative SPMS course, it seems sensible to consider early and aggressive immunotherapy in hopes of postponing or preventing the latter outcome. Once in sustained remission, patients could then transition to “safer” immunomodulatory therapies, reasoning that the more aggressive therapy might provoke a long-term immunological “reset” with benefits such as reduction in epitope spreading and protection of neurons from a toxic inflammatory environment. This “induction and maintenance” strategy parallels approaches used to treat cancer and other chronic illnesses.<sup>120,121</sup> Uncontrolled studies found benefits using mitoxantrone followed by GA or interferon beta for patients with aggressive RRMS.<sup>122,123</sup> The pivotal alemtuzumab trials were also partly predicated on

the “reset” hypothesis, but the trial outcomes were mixed for disability measures; longer-term observations from extension studies may provide more insight.

The use of the induction strategy in routine clinical practice awaits more definitive data. In continuation with the example of alemtuzumab, some patients might be attracted by the infrequent dose regimen but this may be counterbalanced by the needs for years of clinical and laboratory surveillance for secondary autoimmunity. It is more challenging to convincingly endorse this strategy in most patients with early “average” MS activity who are considering their first therapy and who will likely not have aggressive inflammatory disease and may or may not develop SPMS decades on. Furthermore, epidemiologic studies<sup>124</sup> and therapeutic studies in established SPMS<sup>125</sup> suggest that there may be an important dissociation between the inflammatory and neurodegenerative phases of MS. In other words, successful elimination of early inflammation may not necessarily translate into an effect on degenerative progression, the mechanisms of which could be operative even early in relapsing disease. Well-designed controlled trials followed by long-term observational studies using robust disability outcomes stand the best chance of answering these questions.

### Combination Strategies

Combination therapies are widely used in other fields such as rheumatologic disease and cancer. Although conceptually attractive because of the promise that 2 mechanistically distinct therapies may have greater efficacy than either of them, there have been few successful large trials. The largest and longest duration combination therapy study, CombiRx, compared with 2 other arms: interferon beta-1a plus placebo injections and GA plus placebo injections.<sup>126</sup> The data revealed no advantage of the combination therapy for the annualized relapse rate or disability compared with the better performing single agent (GA) over 3 years of treatment. Several combinations of current DMTs are attractive in theory, but there are safety concerns, risks of interactions that can actually reduce efficacy or aggravate the disease,<sup>127,128</sup> few regulatory incentives, and, even if successful, the fact that the combined cost of the already expensive drugs could be prohibitive. Nevertheless, a sound biological rationale and careful,

valid study design could make this a feasible approach for selected areas of MS therapeutic research, if not routine practice.<sup>129</sup>

### Personalized DMT Strategies

The heterogeneous natural history of MS is vexing to both patients and their physicians. Our current MS course categorization schema (relapsing vs progressive) is primitive and relies on historical information with little prognostic significance. Although we can make some limited predictions for risk (eg, interferon beta neutralizing antibodies or development of PML), we lack DMT-specific biomarkers that predict a beneficial response. Although some attempts at identifying therapeutic biomarkers have been reported,<sup>130-132</sup> none has been fully validated and some could not be replicated.<sup>132,133</sup> Our patients remain confronted with the entire undifferentiated “menu” of DMT options, largely within the sequential monotherapy paradigm. However, we foresee gradual steps toward truly personalized medicine for MS as large-scale genomics and related disciplines are applied to explain the individual heterogeneity of the disease and believe that this approach will ultimately prove as, or more, important an advance as the establishment of randomized controlled trials.<sup>134</sup>

### CONCLUSION AND UNMET NEEDS

The past 2 decades have witnessed remarkable advances in treatment options for MS. New drugs have been developed on the basis of the knowledge of the pathobiology of MS; in turn, we have made discoveries about MS (and other diseases such as PML) from the therapies themselves. Ten current therapies have convincingly altered the short- and intermediate-term natural history of the disease, and many more are poised to do so. It is likely that the current sequential monotherapy or treatment failure schema will eventually give way to personalized approaches, guided by valid predictive biomarkers and pharmacogenomics. Available DMTs provide both immediate options and hope for people suffering from MS, but many unmet needs remain. Two of the greatest are lack of therapies that convincingly slow or halt progressive forms of the disease and absence of treatments that could repair or regenerate neurons, oligodendrocytes, and supporting glia. Fortunately, clinical investigators worldwide and organizations

such as the National Multiple Sclerosis Society have focused their attention on these problems, promising even greater advances toward and beyond the horizon of the next decade.

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**Abbreviations and Acronyms:** **BBB** = blood-brain barrier; **CNS** = central nervous system; **DMF** = dimethyl fumarate; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FDA** = Food and Drug Administration; **GA** = glatiramer acetate; **JCV** = John Cunningham virus; **MRI** = magnetic resonance imaging; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **PPMS** = primary progressive multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **SIP** = sphingosine-1-phosphate; **SPMS** = secondary progressive multiple sclerosis

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