Review

Therapeutic Decisions in Multiple Sclerosis
Moving Beyond Efficacy

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Several innovative disease-modifying treatments (DMTs) for relapsing-remitting multiple sclerosis have been licensed recently or are in late-stage development. The molecular targets of several of these DMTs are well defined. All affect at least 1 of 4 properties, namely (1) trafficking, (2) survival, (3) function, or (4) proliferation. In contrast to β-interferons and glatiramer acetate, the first-generation DMTs, several newer therapies are imbued with safety issues, which may be attributed to their structure or metabolism. In addition to efficacy, understanding the relationship between the mechanism of action of the DMTs and their safety profile is pertinent for decision making and patient care. In this article, we focus primarily on the safety of DMTs in the context of understanding their pharmacological characteristics, including molecular targets, mechanism of action, chemical structure, and metabolism. While understanding mechanisms underlying DMT toxicities is incomplete, it is important to further develop this knowledge to minimize risk to patients and to ensure future therapies have the most advantageous benefit-risk profiles. Recognizing the individual classes of DMTs described here may be valuable when considering use of such agents sequentially or possibly in combination.

JAMA Neurol. doi:10.1001/jamaneurol.2013.3510
Published online August 5, 2013.

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Section Editor: David E. Pleasure, MD.

Multiple sclerosis (MS) is a chronic central nervous system (CNS) inflammatory demyelinating disease,[1] involving both genetic and environmental factors. Its pathology is characterized by focal white and gray matter lesions with myelin, oligodendrocyte, and neuroaxonal loss[2]; the latter is thought to be responsible for irreversible accumulation of disability.[3]

There is excitement in MS therapeutics as new disease-modifying treatments (DMTs) are rapidly becoming available. However, some of this enthusiasm is tempered by risks engendered by certain newer agents. To optimally manage patients who may use these DMTs, it is important to understand and relate the DMTs' mechanisms of action (MOAs) to benefits and potential safety risks. The first DMTs, interferon beta and glatiramer acetate, reduce risk of new attacks and are generally well tolerated and safe. While activity of these agents was originally attributed to their influence on T cells, it now appears these drugs also influence innate immunity.[4,5] Although potentially more effective and convenient, recent DMTs have been associated with risks of potentially serious adverse events (AEs), altering risk to benefit ratios. Consequently, treatment decisions have become more complex and require detailed information regarding drug properties.[6] For many reasons, understanding risks associated with novel treatments is imperfect: (1) data collected during preclinical development are limited and extrapolation from animal to humans can be unreliable; (2) clinical studies often recruit insufficient patients to detect less common AEs, recruit highly selected patients, and may be too short to detect AEs that appear only after prolonged exposure; and (3) identifying causal relationships between treatment and an AE may be difficult. Safety issues are identified after approval for around one-quarter of pharmaceutical treatments.[7]

While AEs often represent unwanted pharmacological responses related to MOA, some are idiosyncratic.[8] Some newer therapies (eg, rituximab, alemtuzumab, BG-12, teriflunomide) also represent repurposing or modifications of previous treatments used in other diseases. Identifying and understanding AEs observed with other members of the same class, or with use of the same drug in other populations, can provide clues regarding safety and toxicities.

Herein, the safety profile of DMTs for MS is reviewed from the perspective of their molecular targets, chemical structure, MOA, and metabolism. As first-generation therapies glatiramer acetate and interferon beta present few, well-defined safety issues that have been described previously,[9] these medications are not discussed. Instead, we focus on more recently approved therapies and those in late-stage clinical development. They are grouped into 4 categories based on their presumed target or MOA: (1) immune cell trafficking; (2) cell depletion; (3) immune cell function; and (4) cell replication (**Table**). Better understanding of these properties should assist physicians when choosing such therapies.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed with the following key words: drug name (chemical and

brand name), mode of action, specific adverse effects, major metabolites, and clinical trials. The search was initially conducted August 14, 2012. Articles were also identified through searches of the authors' own files. Only articles published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

DMTs Inhibiting Immune Cell Trafficking

Acute focal CNS inflammation is triggered, particularly at early stages of disease, by influx of activated lymphocytes across the blood-brain barrier. Two types of treatment that impede lymphocyte migration have been developed and are currently licensed. These treatments prevent activated immune cells from crossing the blood-brain barrier into the CNS (natalizumab) or from exiting lymph nodes into the circulation (fingolimod). While these therapies may offer substantial efficacy, as a consequence of their MOAs they alter lymphocyte distribution, which may influence immune surveillance.

Natalizumab

Natalizumab is a humanized monoclonal antibody (mAb) (**Figure 1**) that has demonstrated robust reductions in clinical and radiological outcomes in relapsing-remitting MS (RRMS).[10,11] Natalizumab is directed against the α4 subunit of the cell adhesion molecule very late antigen 4 (VLA-4) expressed on the surface of lymphocytes and monocytes. Binding of VLA-4 to its receptor, vascular cell adhesion molecule 1 (VCAM-1), on vascular endothelium is required for transmigration of immune cells across the blood-brain barrier. Binding of α4 integrin is also required for immune cell transmigration into the gut. After successful testing in Crohn disease, natalizumab was approved for treatment of this condition.[12]

Due to blockade of leukocyte migration from blood, natalizumab treatment leads to mild leukocyte elevation[13] and concomitant lymphocyte reduction in cerebrospinal fluid.[14] On treatment discontinuation, the cerebrospinal fluid lymphocyte population reconstitutes within 6 to 12 months.[14]

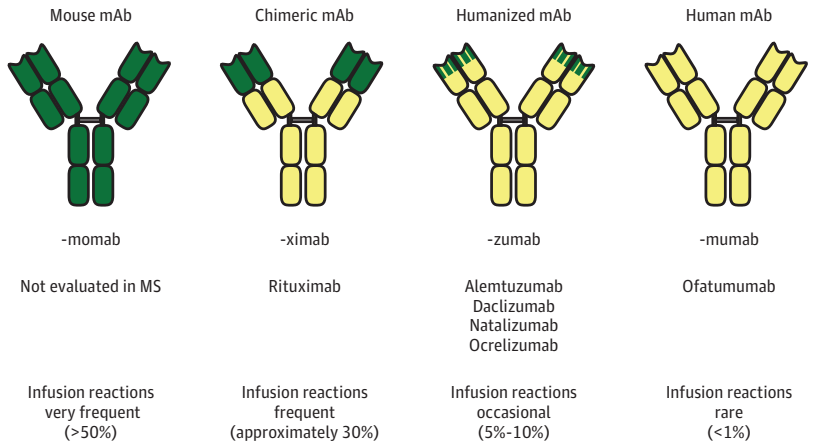
The principal safety issue with use of natalizumab is the increased risk of progressive multifocal leukoencephalopathy (PML),[15] which can be fatal or result in permanent disability. The risk of PML became evident shortly after approval of natalizumab. Two patients in the SENTINEL trial,[15,16] which tested addition of natalizumab to weekly intramuscular interferon beta, developed PML after 28 and 37 infusions. These observations underscored the need to evaluate treatments for sufficiently long durations and for carefully designed phase 4 trials. In this regard, measuring duration of therapy may be more relevant than simply reporting "patient-years" of exposure.

The incidence of PML for patients with MS treated for at least 2 years is 5.05 in 1000 (as of February 2013).[17] It may result from reactivation of JC virus within the CNS or possibly mobilization of peripheral viral reserves to the CNS.[18,19] Three risk factors are recognized for development of PML: evidence of prior JC virus exposure, duration of natalizumab exposure, and previous use of immunosuppressants.[18] A test to detect serum anti–JC virus antibodies was recently developed and serves as a useful biomarker for risk stratification in natalizumab treatment. This test should be repeated in JC virus–negative patients every 6 months owing to the annual 1% to 2% seroconversion rate.[20] Similarly, a high incidence of PML (1 in 500 patients) was reported with efalizumab, which was developed for treatment of psoriasis but later withdrawn. Efalizumab is an mAb directed against the adhesion molecule CD11a on T and B cells, which binds to intercellular adhesion molecule 1 (ICAM-1).[21] Thus, this markedly elevated PML risk likely represents a class effect of these selective adhesion molecule inhibitors.

Table. Categories of Disease-Modifying Treatments for Multiple Sclerosis

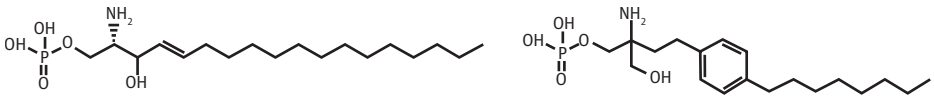
Purpose	Disease-Modifying Treatment
Inhibit immune cell trafficking	Natalizumab
	Fingolimod
Promote immune cell depletion	Alemtuzumab
	Rituximab
	Ocrelizumab
Influence immune cell function	BG-12
	Laquinimod
	Daclizumab
Inhibit cell replication	Mitoxantrone
	Teriflunomide

Figure 1. Classes of Therapeutic Antibodies



Green indicates protein sequences of murine origin; yellow, protein sequences of human origin; mAb, monoclonal antibody; and MS, multiple sclerosis.

Figure 2. Chemical Structure of Sphingosine-1-Phosphate and Fingolimod



Sphingosine-1-phosphate Fingolimod phosphate

Chimeric and humanized antibodies contain murine sequences (Figure 1), which increase their immunogenicity. Use of mAbs can be associated with infusion reactions and persistent neutralizing antibodies; for natalizumab, neutralizing antibodies are associated with loss of therapeutic response and increased risk of hypersensitivity reactions.[22] Recrudescence of disease activity occurs approximately 3 to 5 months after natalizumab discontinuation and corresponds to desaturation of VLA-4 binding. In some cases, natalizumab discontinuation has been associated with a rebound (overshoot) beyond baseline activity and was fatal in 1 case.[23-25] Unfortunately, predisposing risk factors for rebound after natalizumab withdrawal have not been identified.

Fingolimod

Fingolimod (**Figure 2**) is an oral medication approved for treatment of RRMS. It has demonstrated superior activity to intramuscular interferon beta-1a.[26,27] Fingolimod is a sphingosine-1-phosphate (S1P) agonist that binds to 4 of the 5 members of the S1P receptor family (S1P1, S1P2, S1P3, and S1P5). However, following binding and activation of S1P1 receptors, fingolimod acts as a functional antagonist and prevents C-C chemokine receptor type 7 (CCR7)–positive lymphocytes, including naive and central memory T cells, from exiting lymph nodes.[28] Consequently, lymphopenia occurs within hours of administration. Because S1P receptors are present on both neurons and glia and fingolimod penetrates the CNS,[29] fingolimod may exert direct CNS effects.[28]

Few opportunistic infections have been documented in fingolimod-treated patients. Two deaths occurred from viral infections during phase 3 trials testing fingolimod, one from herpes simplex virus encephalitis and one from disseminated varicella-zoster virus, although both patients were treated with a higher dose (1.25 mg) than was approved (0.5 mg). Since approval, there has been 1 reported case of varicella-zoster virus encephalitis at 0.5 mg.[30] Currently, a trial is under way to determine whether 0.25 mg may be efficacious and pose less risk of viral infection.[31] Varicella-zoster virus vaccination is recommended for patients with no history of chickenpox or prior vaccination.[32] Viral infections associated with use of fingolimod are presumably linked to lymphopenia from lymphocyte sequestration. Persistent lymphopenia after drug withdrawal has been observed[33] and may also pose concern when considering initiation of another therapy soon after fingolimod discontinuation. Subtypes of S1P receptors are found in other tissues and may contribute to AEs associated with fingolimod, notably bradycardia, dyspnea, and macular edema. For example, S1P3 receptors are found in cardiac smooth muscle, vascular endothelium, and airways.[34] More selective S1P1 agonists are under development with the aim of eliminating certain AEs such as macular edema, a consequence from binding retinal S1P2 receptors.[35-37]

DMTs Producing Immune Cell Depletion

While attention has focused primarily on the role of T cells in MS pathogenesis, recent successes using B-cell–depleting agents have provided greater appreciation of the importance of this lymphocyte subset. Several mAbs originally developed for treatment of hematological malignancies, targeting B and T cells or B cells alone, are being evaluated for potential use in MS. These antibodies are IgG1 and cause cell depletion.

Alemtuzumab

Alemtuzumab, a humanized mAb (Figure 1) originally developed for treatment of B-cell chronic lymphocytic leukemia, demonstrated dramatic and sustained reductions in relapses and magnetic resonance imaging markers of disease activity in a phase 2 study[38] and in phase 3 studies[39,40] vs high-dose interferon.

Alemtuzumab is directed against CD52, a surface glycoprotein present on several mature leukocyte subpopulations, including T, B, and natural killer cells.[38] Binding of alemtuzumab to these leukocytes leads to elimination via complement and antibody-dependent cellular cytotoxicity. However, reconstitution of leukocyte subpopulations varies[41]; B cells recover in approximately 6 months, whereas T cells require more than 1 year.

Treatment-induced humoral autoimmunity is a major concern associated with alemtuzumab. Graves disease, idiopathic thrombocytopenic purpura, and Goodpasture syndrome have been observed following treatment and may be life threatening without appropriate clinical management. Graves disease is the most common iatrogenic autoimmunity and occurs in up to one-quarter of alemtuzumab-treated patients,[38,42,43] most frequently arising 12 to 18 months after starting treatment.[43] These humoral autoimmune disorders may relate to differences in reconstitution dynamics of B and T cells. Development of autoimmunity may also be driven by interleukin 21 (IL-21).[44] Besides autoimmunity, alemtuzumab-treated patients experienced significantly higher infection rates.

Rituximab and Ocrelizumab

Rituximab and ocrelizumab have shown robust reduction in MS disease activity in phase 2 MS trials.[45,46] Rituximab is a chimeric mAb (Figure 1) approved for treatment of B-cell lymphoma and rheumatoid arthritis (RA).[47] Ocrelizumab is a humanized mAb. Rituximab and ocrelizumab are directed against CD20, a glycoprotein primarily found on B cells, with the exception of early progenitor (pro-B) cells and plasma cells. Binding of rituximab and ocrelizumab leads to rapid B-cell elimination that persists for 6 to 8 months without significant IgG reduction. Reduced MS activity has been attributed

to loss of B-cell–mediated cellular immunity, namely B-cell antigen presentation.[48,49]

Severe infections have been observed in patients with lymphoma receiving rituximab. Further, development of ocrelizumab in RA and lupus was discontinued owing to occurrence of fatal opportunistic infections.[50] In addition, PML has occurred in a small number of patients with RA or lupus treated with rituximab[51] and in rituximab-treated patients with lymphoma.[52] So far, no PML cases have been associated with rituximab or ocrelizumab treatment in MS, where these agents are tested in monotherapy.

DMTs Targeting Immune Cell Function

The DMTs targeting immune cell function, or *immunomodulators*, correspond to treatments that primarily influence functional characteristics of both innate and adaptive immunity. They may affect multiple signaling pathways that alter cytokine production or effector cell functions, or both. This class includes 2 small molecules, dimethyl fumarate (DMF) and laquinimod, and an mAb, daclizumab. A preparation of DMF, BG-12, was recently approved and laquinimod is in late-stage development. BG-12 and laquinimod may have direct central effects due to passive entry into the CNS.

BG-12

BG-12, an oral treatment, has demonstrated efficacy in 2 phase 3 RRMS trials.[53,54] BG-12 was developed from the fumaric acid ester preparation Fumaderm, containing a mixture of DMF and monoethyl fumarate, used for psoriasis treatment in Germany. BG-12 contains only DMF and is rapidly converted to monomethyl fumarate (MMF).[55]

Dimethyl fumarate and MMF activate the antioxidant transcription factor nuclear factor (erythroid-derived 2)–related factor 2 (Nrf2) pathway,[56,57] leading to expression of detoxifying enzymes, glutathione *S*-transferase A2 (GSTA2), heme oxygenase 1 (HO-1), and reduced nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1 (NQO1).[58] Fumarates, which are electrophilic, conjugate to glutathione[59,60] and can covalently link to essential thiol groups (nucleophiles) on macromolecules, including Keap1 (**Figure 3**A), the inhibitor of the Nrf2 pathway.[57,62,63] Thus, DMF and its metabolite, MMF, activate the Nrf2 pathway by "inhibiting the inhibitor" (Figure 3B and C).

Dimethyl fumarate preserves neurons and glial cells in experimental autoimmune encephalomyelitis, while MMF protects murine neurons and human astrocytes from oxidative insult in vitro.[57] In contrast, others have reported a neuroprotective effect in vitro with DMF but not with MMF.[64] Treatment of mice with DMF induces anti-inflammatory type II dendritic cells,[56] which drive anti-inflammatory T-cell polarization.[56] Similar effects have been observed with MMF.[56,65] Dimethyl fumarate has antiproliferative effects.[66] While potential neuroprotective effects of DMF are attributed to Nrf2 activation, whether its anti-inflammatory and immunomodulatory properties are dependent on triggering Nrf2 is unknown. In contrast, some animal studies suggest that DMF may promote renal tubular hyperplasia and oncogenic activity, also possibly related to Nrf2 activation.[67]

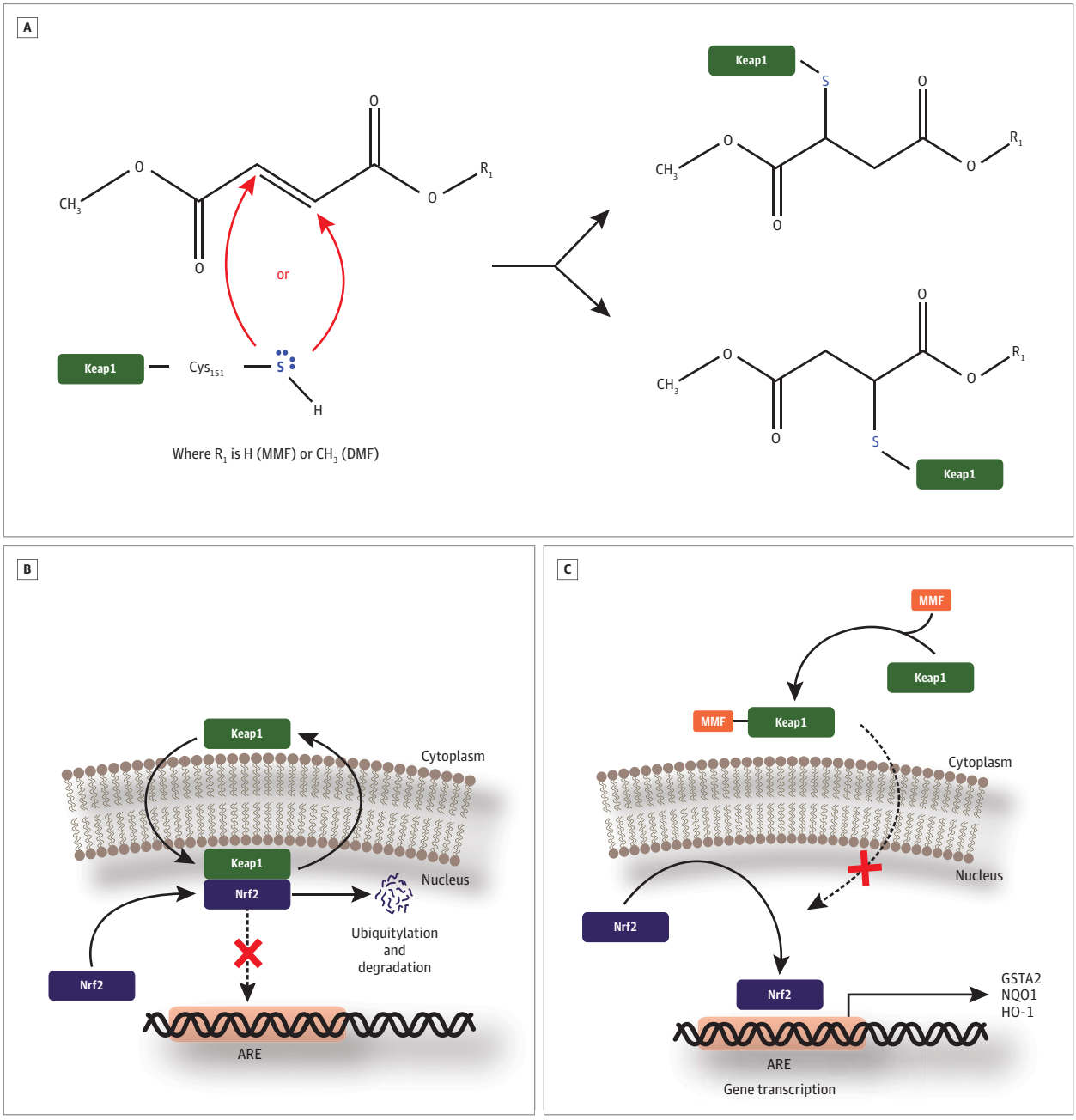
Safety data are available from 2 BG-12 phase 3 RRMS clinical trials[53,54] and their combined extension study.[68] Its AEs included flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts, and elevated liver aminotransferases.[53,54] Renal AEs ranged from 4% to 14% and proteinuria (≤5%) was the most common.[68] Lymphopenia was observed in 4% to 5% of BG-12–treated patients vs less than 1% in the placebo group.[68] Although no opportunistic infections were reported in the BG-12 phase 3 trials, several PML cases have been reported using fumaric acid esters in psoriasis, including 2 cases using fumaric acid ester monotherapy where PML was associated with lymphopenia that developed after initiating fumaric acid ester treatment.[69-71] Thus, it may be important for physicians to monitor lymphocyte counts when treating patients who have MS with BG-12.

Some of these AEs may relate to the MOA of DMF and/or its metabolites, which may be increased at higher doses.[53,54] Following administration, DMF undergoes rapid hydrolysis to MMF and methanol.[57,72] Interestingly, abdominal pain is a common symptom associated with methanol exposure.[73,74] Further metabolism of MMF occurs through the tricarboxylic acid cycle, without involvement of cytochrome P450.[67] Exhalation of carbon dioxide is the primary route of elimination, accounting for approximately 60% of the DMF dose.[67] Drug-protein (eg, Keap1) adducts[75] may be responsible for liver enzyme elevations that have been reported for BG-12.[54] Flushing is thought to be attributed to release of prostaglandins causing local vasodilation.[76] Recently, bardoxolone methyl, an Nrf2 activator, was being advanced for treatment of chronic diabetic nephropathy.[77] However, its development was halted owing to deaths in the phase 3 trial testing its efficacy. Whether bardoxolone methyl toxicity is related to its activation of Nrf2, its structure, or its metabolites is not clear.

Laquinimod

Laquinimod, a quinolone-3-carboxamide, is an orally active immunomodulator that appears to have more pronounced beneficial effects on disease progression and brain atrophy than on clinical and radiological markers of inflammation in RRMS.[78,79] Laquinimod is derived from linomide (**Figure 4**), whose development in MS was abandoned after occurrence of fatal serositis and myocardial infarction.[80] In evaluation of the structure-activity relationship, quinolone-3-carboxamide compounds (>60) were designed, synthesized, and evaluated in MS models.[81] Individual modifications to the quinolone ring or carboxamide affected efficacy and safety, respectively. Laquinimod, containing 1 modification in the quinolone and 1 in the carboxamide, exhibited the best safety and efficacy profile[81] and has since been developed for treatment of MS, Crohn disease, and lupus. Laquinimod affects the peripheral immune system and acts within the CNS. Its targets include innate immune cells, including monocytes and dendritic cells, which function as antigen-presenting cells. In experimental autoimmune encephalomyelitis, laquinimod induces anti-inflammatory antigen-presenting cells, which then downregulate proinflammatory Th1 and Th17 T cells and promote development of regulatory T cells.[82] Glial cells, including astrocytes and microglia, are CNS targets. Laquinimod treatment reduced CNS invasion of inflammatory monocytes and prevented demyelination and subsequent axonal loss in rodents by downregulating NF-κB signaling as well as proinflammatory cytokine and nitric oxide production in astrocytes.[83-85] Laquinimod treatment of patients with MS was associated with elevation of brain-derived neurotrophic factor.[86]

Figure 3. Methylfumarates Promote Activation of the Nrf2 Pathway via Regulation of Keap1, the Nrf2 Inhibitor



A, Methylfumarates are electrophiles that covalently bind the nucleophilic thiol group (-S-H) of Keap1 residue Cys_{151}.[57] Two products can be generated depending on which carbon of the π bond is conjugated. DMF indicates dimethyl fumarate; MMF, monomethyl fumarate. B, In the absence of MMF, Keap1 binds Nrf2, promoting its ubiquitylation and consequent degradation.[61] ARE indicates antioxidant response element. C, On covalent binding of MMF to Keap1, interaction between Keap1 and Nrf2 is disrupted. This stabilizes Nrf2, which permits it to bind the ARE and promote gene transcription.

Laquinimod was studied in 2 phase 3 trials using annualized relapse rate reduction as its primary end point. Because of its more pronounced beneficial effect on disability progression, a third trial is being conducted using disability as its primary end point. Safety data from the first phase 3 trials demonstrated that laquinimod was well tolerated and not associated with serious AEs; notably, serositis and myocardial infarction were not observed. Laquinimod undergoes slow hepatic metabolism, which may correlate with transient transaminase elevation seen in 5% of laquinimod-treated patients compared with 2% in placebo-treated patients.

Daclizumab

Daclizumab is a humanized nondepleting IgG1 mAb that demonstrated promising results in small pilot MS studies[87,88] and in a phase 2 trial testing addition of daclizumab to interferon beta.[89] Two phase 2b-3 studies are under way to evaluate clinical end points.[90]

Daclizumab is directed against the high-affinity α subunit (CD25) of the IL-2 receptor, which is expressed on activated T cells. Interestingly, daclizumab does not block T-cell proliferation.[91] Instead, beneficial clinical and radiological measures during MS treatment were associated with expansion of regulatory CD56$^+$ (bright) natural killer cells.[91] No specific AEs emerged from addition of daclizumab to interferon beta,[89] although liver enzyme elevations and cutaneous reactions were observed.

DMTs Targeting Immune Cell Replication

The recognized role of lymphocytes in MS pathogenesis has provided the foundation for advancing drugs that inhibit their expansion. In this class, mitoxantrone hydrochloride and teriflunomide are agents approved for MS treatment that target DNA.

Mitoxantrone

Mitoxantrone is an anthracenedione approved for treatment of rapidly evolving relapsing or secondary progressive MS.[92] It is an antineoplastic agent used for treatment of metastatic breast cancer, acute myeloid leukemia and non-Hodgkin lymphoma.

Mitoxantrone is an inhibitor of topoisomerase II[93] and can intercalate into double-stranded DNA. Mitoxantrone affects all proliferating cells and is therefore nonselective, although it appears to inhibit B cells more than T cells. Like the related anthracycline chemotherapeutics, mitoxantrone is associated with dose-dependent cardiotoxic effects.[94] Initially, the recognized risk of therapy-related acute leukemia in MS treatment was 0.25%, but 10 years after mitoxantrone approval, this risk approached 1.0%.[94] This increased risk of therapy-related acute leukemia provides another example underscoring the importance of vigilant postapproval safety monitoring. Because of concerns for cardiotoxic effects and therapy-related acute leukemia, use of mitoxantrone for MS is generally confined to second- or third-line treatment.

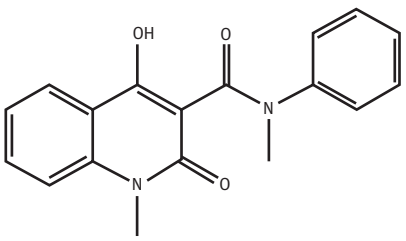
Teriflunomide

Teriflunomide is an oral agent that demonstrated efficacy in phase 3 clinical trials for treatment of RRMS[95] and was recently approved in the United States. Teriflunomide is the active metabolite of leflunomide (**Figure 5**), a DMT licensed for treatment of RA.[96] Teriflunomide inhibits mitochondrial dihydroorotate dehydrogenase, an enzyme used for de novo synthesis of pyrimidine nucleotides in proliferating cells. However, teriflunomide does not inhibit the salvage pathway used by resting cells.[97]

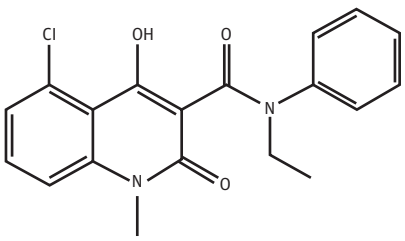
The AEs associated with teriflunomide include lymphopenia, alopecia, elevated liver enzymes, elevated blood pressure, and nausea. Leflunomide and teriflunomide are considered to be teratogenic in humans and are therefore contraindicated in pregnancy.[98] Teriflunomide can also penetrate into breast milk.[99] As leflunomide treatment of RA is associated with elevated risk of tuberculosis, purified protein derivative testing is recommended before commencing teriflunomide treatment in patients with MS.[99]

Teriflunomide undergoes extensive enterohepatic recirculation, leading to long-term exposure of the liver to high concentrations that may result in hepatotoxic effects,[100] an important safety issue with leflunomide in RA[101,102] and teriflunomide in MS.[99] As a consequence of its enterohepatic recycling, substantial time is required to achieve steady-state plasma concentrations of teriflunomide. The extended 10-day half-life[100] is of potential clinical relevance in case of serious AE or pregnancy, when rapid drug elimination is necessary. In this context, wash-out procedures have

Figure 4. Chemical Structure of Linomide and Laquinimod

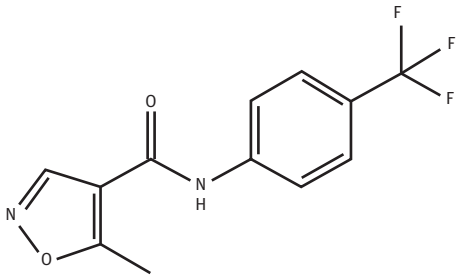


Linomide

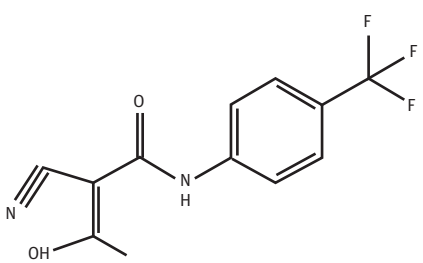


Laquinimod

Figure 5. Chemical Structure of Leflunomide and Teriflunomide



Leflunomide



Teriflunomide

been developed involving administration of cholestyramine or activated charcoal to prevent enterohepatic recirculation. Although genetic polymorphisms of cytochrome P450 isoforms have been associated with AEs from leflunomide,[103] cytochrome P450 may have a limited role in teriflunomide metabolism.

Discussion

With introduction of several new MS medications, treatment decisions are becoming more complex. Whereas efficacy remains paramount, choosing new agents necessitates careful consideration of other characteristics, including MOA, duration of effect (ie, pharmacodynamics), and potential risks. In this article, we have classified DMTs into 4 categories based on their ability to (1) inhibit cell trafficking, (2) promote immune cell depletion, (3) influence immune function, or (4) inhibit cell replication. While we have provided a framework, it is important to recognize that each category is not mutually exclusive. Agents that reduce lymphocyte proliferation may induce immune modulation and vice versa.[66,104] Nevertheless, categorization of agents with similarities can help us anticipate specific AEs of newer agents. In this regard, it is important to recognize that natalizumab and efalizumab, which are selective adhesion molecule inhibitors and therefore block lymphocyte trafficking, are both associated with PML. While newer S1P agonists (eg, BAF312 and ONO-4641) selectively activate S1P1 receptors on lymphocytes and reduce trafficking, these agents also bind the S1P1 receptors expressed by cells directing atrioventricular conduction and therefore, like fingolimod, can be associated with some level of bradycardia. A potential hazard of DMTs like mitoxantrone and teriflunomide, which interact with DNA or inhibit DNA metabolism, respectively, is that such agents may affect DNA within stem cells and/or germ cells.[94,99]

Agents specific for one molecular target or immune pathway may have pleiotropic effects. While the intended mechanism of a given DMT may shift immune balance favorably for one disease, it may have paradoxical activity in others. Tumor necrosis factor receptor antagonists are widely used for RA and were considered for MS therapy until their use was associated with increased risk of CNS demyelination. Although T- and B-cell depletion by alemtuzumab is associated with potent therapeutic effects in MS, its use promotes humoral autoimmunity targeting the thyroid and, more rarely, platelets, kidney, or lung. Whether this iatrogenic autoimmunity relates to distinct kinetics of T- and B-cell reconstitution or abnormal T-cell cytokine secretion is not clear. Prolonged lymphopenia after alemtuzumab treatment may be an important consideration when using other agents sequentially. Specifically, should one wait until there is full reconstitution of both B cells and T cells prior to treatment with another agent? Similarly, if a patient does not respond to fingolimod, one may consider delaying sequential treatment until the fingolimod-associated lymphopenia resolves. Interestingly, prolonged lymphopenia and associated immunosuppression, rather than concern related to its clinical benefit in MS, probably halted development and use of cladribine. When treating MS with newer agents, we may need to think beyond our next therapy.

Physicians who treat MS will need to pay particular attention to metabolic properties when prescribing certain newer agents. In contrast to interferons (natural endogenous proteins) and glatiramer acetate (a polypeptide-based agent), newer oral therapies are synthetic organic molecules and may be metabolized and excreted differently. Teriflunomide undergoes prolonged hepatobiliary circulation; in certain situations (eg, pregnancy or AE) it may be necessary to accelerate teriflunomide elimination. Metabolites may be active therapeutically and also responsible for adverse effects. Dimethyl fumarate is rapidly metabolized to MMF, considered the predominant bioactive form responsible for Nrf2 activation. As methanol is produced in metabolism of DMF to MMF, methanol or other DMF metabolites could possibly contribute to its adverse effects.

With introduction of new agents that use different MOAs, one can envisage combining MS medications that may act in an additive or synergistic manner.[105] Although this is a worthy goal, there are practical concerns. First, to establish that 2 effective drugs are more efficacious together than either one alone may require enrolling large numbers of patients. Second, as the price of many MS agents increases, it may be unreasonable to consider the added cost in combination. In general, one should be cautious when combining pharmacological agents as their metabolism may interfere with one another and further paradoxical effects can occur. In this regard, clinical trials have suggested that widely used cholesterol-lowering statins may interfere with the efficacy of interferon beta,[106,107] and it is postulated that this potential antagonistic effect relates to their opposing activity on the proinflammatory signaling molecule STAT1.[108]

Surrogate markers that associate risk of adverse effects, or response, to DMTs are particularly helpful in clinical practice. As JC virus antibody–positive patients have increased risk of PML during natalizumab treatment, anti-JC virus seropositivity has become an important biomarker for stratification of this risk. Serum IL-21 levels could be considered to estimate risk of thyroid autoimmunity in alemtuzumab-treated patients. Stratification may include gene polymorphisms. For example, *ABC*-transporter gene polymorphisms have been associated with response to mitoxantrone.[109]

In stark contrast to the excitement surrounding our increasing repertoire of treatments for RRMS, the paucity of useful agents for progressive MS is sobering. Thus far, our successes primarily target the peripheral inflammation characterizing RRMS, but not the CNS-resident inflammatory and neurodegenerative processes of progressive MS. Hopefully, this therapeutic gap will be breached through better understanding of MS progression, refining our clinical and imaging metrics of MS progression, and testing established and novel agents with potential antioxidative and neuroprotective MOAs.

While no drug to date cures MS, it is clear that major advances have been made in therapeutics of RRMS. However, several current drugs have serious, sometimes life-threatening toxic effects. Although the understanding of mechanisms underlying DMT toxicities is incomplete, it is important to develop this knowledge to minimize risk to patients and to ensure that future therapies have the most advantageous benefit to risk profiles. Recognizing the individual classifications of DMTs described here may be beneficial when considering use of such agents sequentially or eventually in combination.

ARTICLE INFORMATION

Accepted for Publication: May 14, 2013.

Published Online: August 5, 2013. doi:10.1001/jamaneurol.2013.3510.

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Obtained funding: Zamvil.
Administrative, technical, and material support: Brück, Prat, Spencer, Zamvil.
Study supervision: Brück, Gold, Oreja-Guevara, Steinman, Weber, Ziemssen, Zamvil.

Conflict of Interest Disclosures: Brück receives research support from Teva Pharmaceutical Industries Ltd, Biogen Idec, and Novartis; is member of scientific advisory boards of Teva Pharmaceutical Industries Ltd, Biogen Idec, Novartis, and Genzyme/Sanofi; serves on speaker's bureaus for Bayer Vital, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries Ltd, Genzyme/Sanofi, and Novartis; and serves on the editorial boards of *Acta Neuropathologica*, *Neuropathology and Applied Neurobiology*, and *Therapeutic Advances in Neurological Disorders*. Gold receives research support from Teva Pharmaceutical Industries Ltd, Biogen Idec, Novartis, Merck Serono, and Elan; is a member of scientific advisory boards of Teva Pharmaceutical Industries Ltd, Biogen Idec, Novartis, Baxter, and Genzyme/Sanofi; serves on speaker's bureaus for Bayer Vital, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries Ltd, Genzyme/Sanofi, ZLB Behring, and Novartis; and serves on the editorial boards of *American Journal of Pathology*, *Aktuelle Neurologie*, and *Therapeutic Advances in Neurological Disorders*. Lund receives research support from Teva Pharmaceutical Industries Ltd, Genzyme/Sanofi, and Novartis and has served as a consultant for and received honoraria from Teva Pharmaceuticals Inc. Oreja-Guevara has received honoraria as a consultant on scientific advisory boards for Biogen Idec, Bayer Schering, Merck Serono, Teva, and Novartis and has participated in clinical trials and other research projects promoted by Biogen Idec, GlaxoSmithKline, Teva, and Novartis. Prat receives research grant support from the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada, the Fonds de recherche du Québec–Santé, Teva Pharmaceuticals Inc, and Elan and has served as a consultant for and received honoraria from Elan, Biogen Idec, EMD Serono, Genzyme/Sanofi, Novartis, and Teva Pharmaceuticals Inc. Spencer has received travel compensation from Teva Pharmaceuticals Inc. Steinman receives research grant support from the National Institutes of Health (grants RO1 NS55997 and R21AI0955055), the National Multiple Sclerosis Society, and the Guthy-Jackson Charitable Foundation; has served as a consultant for and received honoraria from Biogen Idec, Genzyme, MedImmune, Novartis, Questcor, Roche, Sanofi, and Teva Pharmaceuticals Inc; and has received honoraria from Teva Pharmaceuticals Inc, Biogen Idec, Novartis, and Pfizer. Tintoré has received compensation for consulting services and speaking from Bayer Schering, Merck Serono, Biogen Idec, Teva, Sanofi-Aventis, Genzyme, and Novartis. Vollmer receives research grant support from the National Institutes of Health, Teva Neuroscience, Biogen Idec, Ono Pharmaceuticals, Genzyme, and Janssen Research & Development and has served as a consultant for and received honoraria from Biogen Idec, Teva Neuroscience, EMD Serono, Genzyme, Novartis, Questcor, Roche, Elan, Bristol-Myers Squibb, Accord Pharmaceuticals, Ono, Accelerated Cure Project, Eli Lilly, Medical Logix, MSDx, Esai Pharmaceuticals, Schering-Plough Biopharma, Xenoport, and Daiichi Sanyko. Weber has received research support from Teva Pharmaceutical Industries Ltd and Roche; has participated on the scientific advisory boards of Teva Pharmaceutical Industries Ltd and Roche; has served as a consultant for and received honoraria from Genzyme, Novartis, Roche, and Teva Pharmaceuticals Inc; and serves on the editorial board of *PLoS One*. Weiner serves as a consultant to Teva; has received ancillary grants from Teva; has served on an advisory board for Novartis; is the University of Southern California principal investigator for an alemtuzumab study sponsored by Genzyme/Sanofi; is a member of the safety board for an adrenocorticotropic hormone–Solu-Medrol study; and was appointed by the National Institutes of Health and National Multiple Sclerosis Society as chair of the Data Safety Monitoring Committee for the phase 2 estriol trial. Ziemssen has received speaker honoraria from Biogen Idec, Genzyme, GlaxoSmithKline, Sanofi-Aventis, Merck Serono, MSD, Novartis, Teva, and Bayer Healthcare and serves as a consultant for Biogen Idec, Genzyme, Teva, Novartis, and Bayer HealthCare. Zamvil receives research grant support from the National Institutes of Health (grants RO1 AI073737 and RO1 NS063008), the National Multiple Sclerosis Society (grant RG 4124), the Guthy-Jackson Charitable Foundation, the Maisin Foundation, Biogen Idec, Teva Pharmaceuticals Inc, Five Prime Inc, and Boehringer-Ingelheim Inc; has served as a consultant for and received honoraria from Biogen Idec, EMD Serono, Genzyme, Novartis, Questcor, Roche, and Teva Pharmaceuticals Inc; and has served or serves on the editorial boards of *The Journal of Clinical Investigation*, *The Journal of Immunology*, *Neurotherapeutics*, and *The Journal of Neurological Sciences*.

Funding/Support: This work was supported by Teva Pharmaceuticals Inc.

Additional Information: This article is the result of a working group meeting held in Tel Aviv, Israel, in August 2012, supported by Teva Pharmaceuticals Inc, during which a panel of MS experts addressed safety considerations in immune modulation in MS therapy.

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