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Therapeutic Decisions In Multiple Sclerosis: Moving Beyond Efficacy

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Abstract

Importance—Several innovative disease-modifying treatments (DMTs) for relapsing remitting multiple sclerosis (RRMS) 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 one of four properties: (1) immune cell trafficking, (2) cell depletion, (3) immune cell function, or (4) cell replication. In contrast to β-interferons and glatiramer acetate, the first generation DMTs, several newer therapies are imbued with safety issues. In addition to efficacy, understanding the relationship between the mechanism of action (MOA) of the DMTs and their safety profile is essential for decision-making in patient care.

Objective—In this article, we relate safety issues of newer DMTs to their pharmacological characteristics, including molecular targets, MOA, chemical structure, and metabolism. Some newer DMTs also represent repurposing or modifications of previous treatments used in other diseases. Here, we describe how identification and understanding of adverse events (AEs) observed with these established drugs within the same class, provide clues regarding safety and toxicities of newer MS therapeutics.

Conclusions and relevance—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 risk-benefit profiles. Recognizing the individual classes of DMTs described here may be beneficial when considering use of such agents sequentially and possibly in combination.

Keywords

Multiple sclerosis; disease-modifying treatments; safety; mechanism of action; metabolism

Introduction

Multiple sclerosis (MS) is a chronic central nervous system (CNS) inflammatory demyelinating disease,[1] involving both genetic and environmental factors. MS pathology is characterized by focal white and grey 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 that may use these DMTs, it is important to understand and relate their MOAs to benefits and potential safety risks. The first DMTs, interferon-β (IFN-β) and glatiramer acetate (GA), 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-

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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 pre-clinical development is 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 only appear after prolonged exposure; (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 adverse events often represent unwanted pharmacological responses related to MOA, some are idiosyncratic.[8] Some newer therapies also represent repurposing (e.g. rituximab, alemtuzumab) or modifications (e.g. *Fumaderm*, leflunomide) 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.

Here, 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 GA and IFN-β 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, or those in late-stage clinical development. They are grouped into four categories based on their presumed target or MOA: (1) immune cell trafficking, (2) depletion, (3) function and (4) cell replication (Table 1). Better understanding of these properties should assist physicians when choosing such therapies.

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 (BBB). Two types of treatment that impede lymphocyte migration have been developed and are currently licensed. These treatments prevent activated immune cells from crossing the BBB 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; see Fig. 1) that has demonstrated robust reductions in clinical and radiological outcomes in RRMS.[10,11] Natalizumab is directed against the α4 subunit of the cell adhesion molecule VLA-4 expressed on the surface of lymphocytes and monocytes. Binding of VLA-4 to its receptor, VCAM-1, on vascular endothelium is required for transmigration of immune cells across the BBB. As binding of α4 integrin is required for immune cell transmigration into the gut, and after successful testing, natalizumab was also approved for treatment of Crohn's disease.[12]

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Due to blockade of leukocyte migration from blood, natalizumab treatment leads to mild leukocyte elevation[13] and concomitant lymphocyte reduction in cerebrospinal fluid (CSF).[14] Upon treatment discontinuation, the CSF lymphocyte population reconstitutes within 6-12 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 for PML became evident shortly after approval of natalizumab. Two patients in the SENTINEL trial, which tested addition of natalizumab to weekly i.m. IFN-β, developed PML after 28 infusions and 37 infusions, respectively. These observations underscored the need to evaluate treatments for sufficiently long durations, and for carefully-designed Phase IV trials. In this regard, measuring duration of therapy may be more relevant than simply reporting “patient-years” of exposure.

The incidence of PML for MS patients treated ≥2 years is 5.05/1,000 (February 2013).[16] PML may result from reactivation of JC virus within the CNS or possibly mobilization of peripheral viral reserves to the CNS.[17] Three risk factors are recognized for development of PML: evidence of prior JC virus exposure, duration of natalizumab exposure and previous use of immunosuppressants.[16] Recently, a test to detect serum anti-JC virus antibodies was developed and serves as a useful biomarker for risk stratification in natalizumab treatment. This test should be repeated in JC virus-negative patients every six months due to the annual 1-2% seroconversion rate.[18] Similarly, a high incidence of PML (1 in 500) was reported with efalizumab, which was developed for treatment of psoriasis, but later withdrawn. Efalizumab is a mAb directed against another adhesion molecule, CD11a on T and B cells, which binds to ICAM-1.[19] Thus, this elevated PML risk may be a class effect of selective adhesion molecule (SAM) inhibitors.

Chimeric and humanized antibodies contain murine sequences (Fig. 1), which increases 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.[20] Recrudescence of disease activity occurs approximately 3-5 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 one case.[21-23] Unfortunately, predisposing risk factors for rebound after natalizumab withdrawal have not been identified.

Fingolimod

Fingolimod (Fig. 2) is an oral medication approved for treatment of RRMS that has demonstrated superior activity to interferon-β1a *i.m.*[24,25] Fingolimod is a sphingosine-1-phosphate (S1P) agonist that binds to four of the five members of the S1P receptor family (S1P1, 2, 3 and 5). However, following binding and activation of S1P1 receptors, fingolimod acts as a functional antagonist and prevents $CCR7^+$ lymphocytes, including naïve and central memory T cells, from exiting lymph nodes.[26] Consequently, lymphopenia occurs within hours of administration. Since S1P receptors are present on both neurons and glia, and fingolimod penetrates the CNS,[27] fingolimod may exert direct CNS effects.[26]

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Few opportunistic infections have been documented in fingolimod-treated patients. Two deaths occurred from viral infections during phase III trials testing fingolimod, one from herpes simplex virus (HSV) encephalitis and one from disseminated varicella, although both patients were treated with a higher dose (1.25 mg) than was approved (0.5 mg). Since approval, there has been one reported case of varicella encephalitis at 0.5 mg.[28] Currently, a trial is underway to determine whether 0.25 mg may be efficacious and pose less risk of viral infection.[29] VZV vaccination is recommended for patients with no history of chickenpox or prior vaccination.[30] Viral infections associated with use of fingolimod are presumably linked to lymphopenia from lymphocyte sequestration. Persistent lymphopenia after drug withdrawal has been observed,[31] and may also pose concern when considering initiating another therapy soon after fingolimod discontinuation. S1P receptor subtypes 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.[32] 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.[33-35]

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 (Fig. 1), originally developed for treatment of B cell chronic lymphocytic leukemia demonstrated dramatic and sustained reductions in relapses and MRI markers of disease activity in Phase II[36] and Phase III[37,38] studies versus high-dose interferon.

Alemtuzumab is directed against CD52, a surface glycoprotein present on several mature leukocyte subpopulations, including T, B and NK cells.[36] Binding of alemtuzumab to these leukocytes leads to elimination via complement and antibody dependent cellular cytotoxicity (ADCC). However, reconstitution of leukocyte subpopulations varies;[39] B cells recover in approximately six months whereas T cells require more than one year.

Treatment-induced humoral autoimmunity is a major concern associated with alemtuzumab. Grave's disease, idiopathic thrombocytopenic purpura (ITP) and Goodpasture's syndrome have been observed following treatment and may be life-threatening without appropriate clinical management. Grave's disease is the most common iatrogenic autoimmunity and occurs in up to one-quarter of alemtuzumab-treated patients,[36,40,41] most frequently arising 12-18 months after starting treatment.[41] These humoral autoimmune disorders may relate to differences in reconstitution dynamics of B and T cells. Development of autoimmunity may be driven by interleukin-21.[42] Besides autoimmunity, alemtuzumab-treated patients experienced significantly higher infection rates.

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Rituximab and ocrelizumab

Rituximab and ocrelizumab have shown robust reduction in MS disease activity in phase II MS trials.[43,44] Rituximab is a chimeric mAb (Fig. 1) approved for treatment of B cell lymphoma and rheumatoid arthritis (RA).[45] 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 6-8 months, without significant IgG reduction. Reduced MS activity has been attributed to loss of B cell-mediated cellular immunity, namely B cell antigen presentation.[46,47]

Severe infections have been observed in lymphoma patients receiving rituximab. Further, development of ocrelizumab in RA and lupus was discontinued due to occurrence of fatal opportunistic infections.[48] In addition, PML has occurred in a small number of patients with RA or lupus treated with rituximab,[49] and in rituximab-treated lymphoma patients.[50] 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

These DMTs, also called 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 two small molecules, dimethyl fumarate (DMF) and laquinimod, and a 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 two Phase III RRMS trials.[51,52] BG-12 was developed from the fumaric acid ester (FAE) preparation *Fumaderm*®, containing a mixture of dimethylfumarate (DMF) and monoethylfumarate (MEF), used for psoriasis treatment in Germany. BG-12 contains only DMF and is rapidly converted to monomethylfumarate (MMF).[53]

DMF and MMF activate the antioxidant transcription factor nuclear factor (erythroid-derived 2)-related factor 2 (*Nrf2*) pathway,[54,55] leading to expression of detoxifying enzymes, glutathione *S*-transferase A2 (GSTA2), heme oxygenase-1 (HO-1) and NADPH quinone oxidoreductase 1 (NQO1).[56] Fumarates, which are electrophilic, conjugate to glutathione[57,58] and can covalently link to essential thiol groups (nucleophiles) on macromolecules, including Keap1 (Fig. 3A), the inhibitor of the *Nrf2* pathway.[55,59,60] Thus, DMF and its metabolite, MMF activate the *Nrf2* pathway by “inhibiting the inhibitor” (Figure 3B,C).

DMF preserves neurons and glial cells in EAE, while MMF protects murine neurons and human astrocytes from oxidative insult *in vitro*.[55] In contrast, others have reported a neuroprotective effect *in vitro* with DMF, but not with MMF.[61] Treatment of mice with

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DMF induces anti-inflammatory “type II” dendritic cells,[54] which drive anti-inflammatory T cell polarization.[54] Similar effects have been observed with MMF.[54,62] DMF has anti-proliferative effects.[63] While potential neuroprotective effects of DMF are attributed to *Nrf2* activation, whether its anti-inflammatory and immunomodulatory properties are dependent upon triggering *Nrf2* is unknown. In contrast, some animal studies suggest DMF may promote renal tubular hyperplasia and oncogenic activity, also possibly related to *Nrf2* activation.[64]

Safety data are available from two BG-12 phase III RRMS clinical trials[51,52] and their combined extension study.[65] AEs included flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts and elevated liver aminotransferases.[51,52] Renal AEs ranged from 4-14% and proteinuria (<5%) was the most common.[65] Lymphopenia was observed in 4-5% of BG-12-treated patients versus <1% in the placebo group.[65] Although no opportunistic infections were reported in the BG-12 Phase III trials, several PML cases have been reported using FAEs in psoriasis, including two cases using FAE monotherapy where PML was associated with lymphopenia that developed after initiating FAE treatment.[66-68]

Some of these side effects may relate to the MOA of DMF and/or its metabolites, which may be increased at higher doses.[51,52] Following administration, DMF undergoes rapid hydrolysis to MMF and methanol.[55,69] Interestingly, abdominal pain is a common symptom associated with methanol exposure.[70,71] Further metabolism of MMF occurs through the tricarboxylic acid (TCA) cycle, without involvement of cytochrome p450.[64] Exhalation of CO_2 is the primary route of elimination, accounting for approximately 60% of the DMF dose.[64] Drug-protein (e.g. Keap1) adducts,[72] may be responsible for liver enzyme elevations that have been reported for BG-12.[52] Flushing is thought to be attributed to release of prostaglandins causing local vasodilation.[73] Recently, bardoxolone methyl, an *Nrf2* activator, was being advanced for treatment of chronic diabetic nephropathy.[74] However, its development was halted due to deaths in the phase III 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.[75,76] Laquinimod is derived from linomide (Fig. 4), whose development in MS was abandoned after occurrence of fatal serositis and myocardial infarction.[77] In evaluation of structure-activity relationship (SAR), quinolone-3-carboxamide compounds (>60) were designed, synthesized and evaluated in MS models.[78] Individual modifications to the quinolone ring or carboxamide affected efficacy and safety, respectively. Laquinimod, containing one modification in the quinolone and one in the carboxamide, exhibited the best safety and efficacy profile[78] and has since been developed for treatment of MS, Crohn's 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 (APCs). In EAE, laquinimod induces anti-inflammatory APCs, which then down-regulate pro-

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inflammatory Th1 and Th17 T cells and promote development of regulatory T cells.[79] 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 down-regulating NF-κB signalling as well as proinflammatory cytokine and NO production in astrocytes.[80-82] Laquinimod treatment of MS patients was associated with elevation of brain-derived neurotrophic factor (BDNF).[83]

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

Daclizumab

Daclizumab is a humanized non-depleting IgG1 mAb that demonstrated promising results in small pilot MS studies,[84,85] and in a phase II trial testing addition of daclizumab to interferon-β [86] Two phase IIb-III studies are underway to evaluate clinical endpoints.[87]

Daclizumab is directed against the high-affinity α-subunit (CD25) of the interleukin-2 receptor, which is expressed on activated T cells. Interestingly, daclizumab does not block T cell proliferation.[88] Instead, beneficial clinical and radiological measures during MS treatment were associated with expansion of regulatory CD56+(bright) natural killer (NK) cells.[88] No specific AEs emerged from addition of daclizumab to interferon-β,[86] 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 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 (SPMS).[89] It is an anti-neoplastic agent used for treatment of metastatic breast cancer, acute myeloid leukemia and Non-Hodgkin's lymphoma.

Mitoxantrone is an inhibitor of topoisomerase II[90] and can intercalate into double-stranded DNA. Mitoxantrone affects all proliferating cells and is therefore non-selective, although it appears to inhibit B cells more than T cells. Like the related anthracycline chemotherapeutics, mitoxantrone is associated with dose-dependent cardiotoxicity.[91] Initially, the recognized risk of therapy-related acute leukemia (TRAL) in MS treatment was 0.25%, but 10 years after mitoxantrone approval, this risk approached 1.0%.[91] This increased risk of TRAL provides another example underscoring the importance of vigilant

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post-approval safety monitoring. Because of concerns for cardiotoxicity and TRAL, 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 III clinical trials for treatment of RRMS[92] and was recently approved in the USA. Teriflunomide is the active metabolite of leflunomide (Fig. 5), a DMT licensed for treatment of RA.[93] Teriflunomide inhibits mitochondrial dihydroorotate dehydrogenase (DHODH), 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.[94]

AEs associated with teriflunomide include lymphopenia, alopecia, elevated liver enzymes, elevation of blood pressure and nausea. Leflunomide and teriflunomide are considered to be teratogenic in humans and are therefore contraindicated in pregnancy.[95] Teriflunomide can also penetrate into breast milk.[96] As leflunomide treatment of RA is associated with elevated risk of tuberculosis, PPD testing is recommended before commencing teriflunomide treatment in MS patients.[96]

Teriflunomide undergoes extensive enterohepatic recirculation, leading to chronic exposure of the liver to high concentrations that may result in hepatotoxicity,[97] an important safety issue with leflunomide in RA[98,99] and teriflunomide in MS.[96] 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[97] 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 been developed involving administration of cholestyramine or activated charcoal to prevent enterohepatic recirculation. Although genetic polymorphisms of p450 isoforms have been associated with AEs to leflunomide,[100] 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 mechanism(s) of action, duration of effect (i.e. pharmacodynamics) and potential risks. In this article, we have classified DMTs into four categories based upon 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*.[63,101] Nevertheless, categorization of agents with similarities can help us anticipate specific side effects of newer agents. In this regard, it is important to recognize that natalizumab and efalizumab, which are SAM inhibitors and therefore block lymphocyte trafficking, are both associated with PML. While newer S1P agonists (e.g. 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.

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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. TNF receptor antagonists are widely used in 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 lack of 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.

MS physicians 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 (e.g., pregnancy or AE) it may be necessary to accelerate teriflunomide elimination. Metabolites may be active therapeutically, and also responsible for adverse effects. DMF 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 utilize different MOAs, one can envisage combining MS medications that may act in an additive or synergistic manner.[102] Although this is a worthy goal, there are practical concerns. First, to establish that two 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 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-β,[103,104] and it is postulated that this potential antagonistic effect relates to their opposing activity on the pro-inflammatory signaling molecule, STAT1.[105]

Surrogate markers that associate with risk of adverse effects, or response, to DMTs are particularly helpful in clinical practice. As JCV Ab^+ patients have increased risk of PML during natalizumab treatment, anti-JCV 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

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polymorphisms. For example, ABC-transporter gene polymorphisms have been associated with response to mitoxantrone.[106]

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 of established and novel agents with potential anti-oxidative 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 toxicities. 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 future therapies have the most advantageous risk-benefit profiles. Recognizing the individual classifications of DMTs described here may be beneficial when considering use of such agents sequentially, or eventually in combination.

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 side effects, major metabolites and clinical trials. Search was conducted August 14, 2012. Articles were also identified through searches of the authors' own files. Only papers 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.

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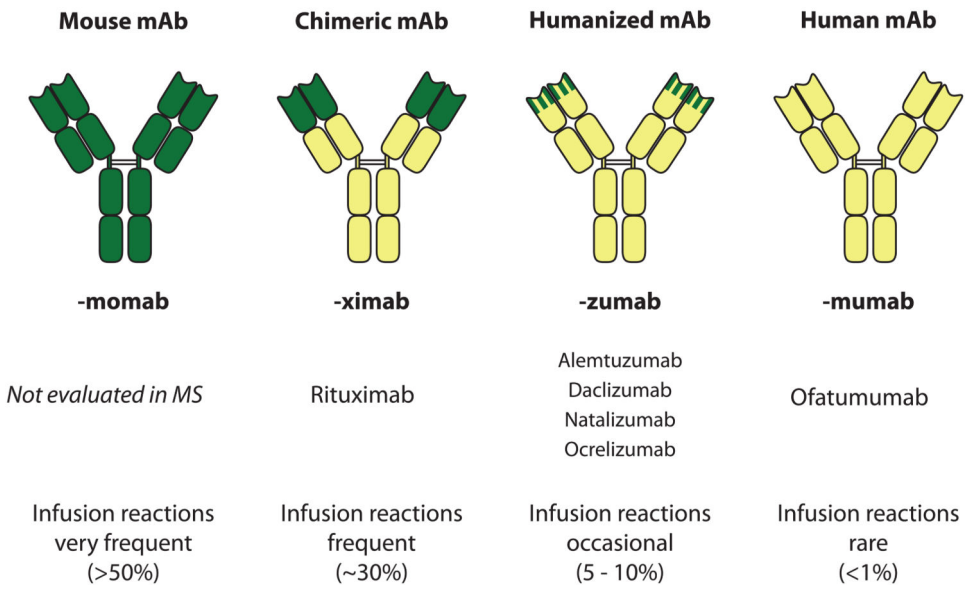

Figure 1.

Classes of therapeutic antibodies. Green: protein sequences of murine origin; yellow: protein sequences of human origin. MS: multiple sclerosis

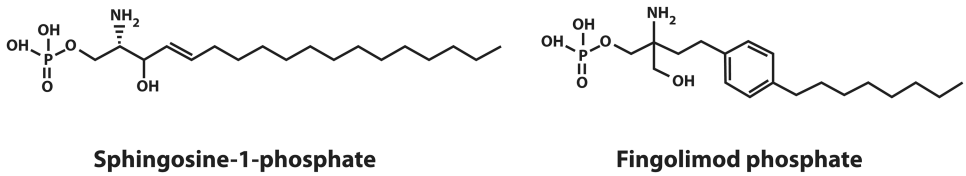

Figure 2.
Chemical structure of sphingosine-1-phosphate and fingolimod.

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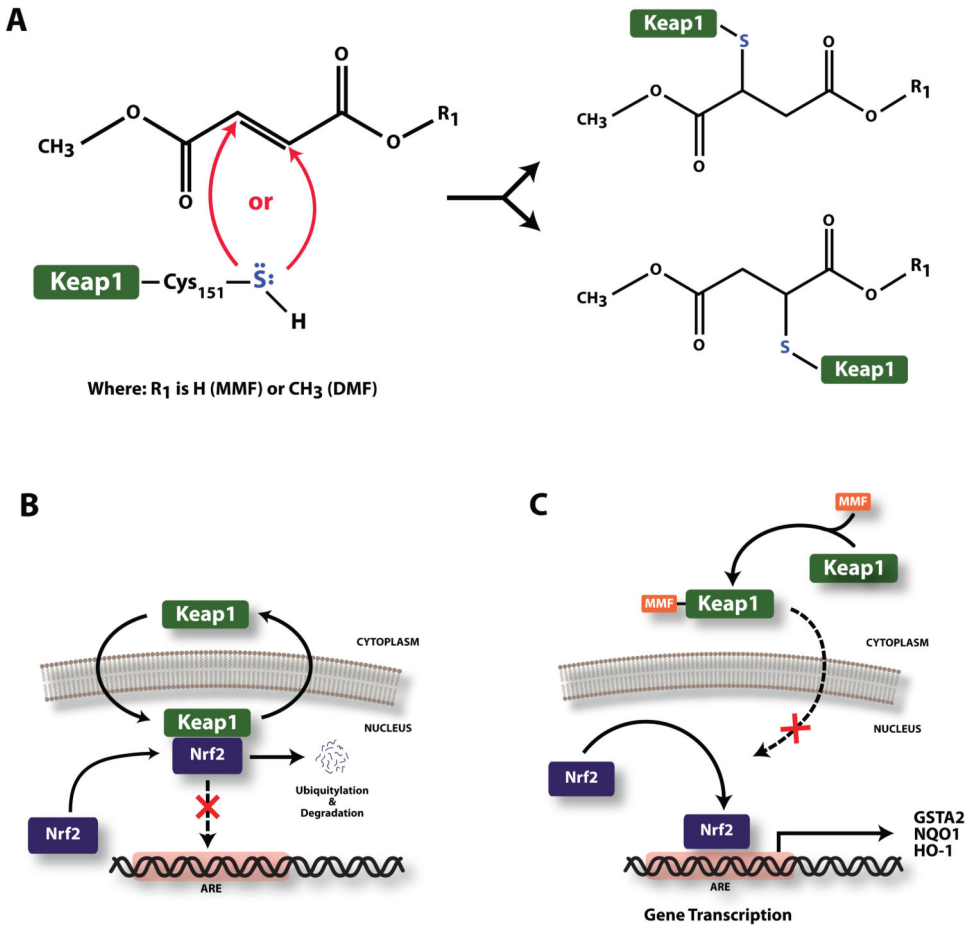

Figure 3.

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}.[55] Two products can be generated depending upon which carbon of the π bond is conjugated. (B) In the absence of MMF, Keap1 binds Nrf2, promoting its ubiquitylation and consequent degradation.[107] (C) Upon covalent binding of MMF to Keap1, interaction between Keap1 and Nrf2 is disrupted, stabilizing Nrf2, which permits it to bind the anti-oxidant response element (ARE), and promote gene transcription.

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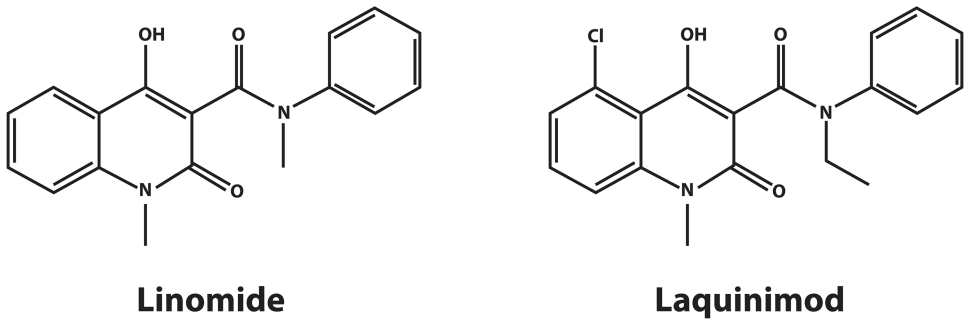

Figure 4.
Chemical structure of linomide and laquinimod.

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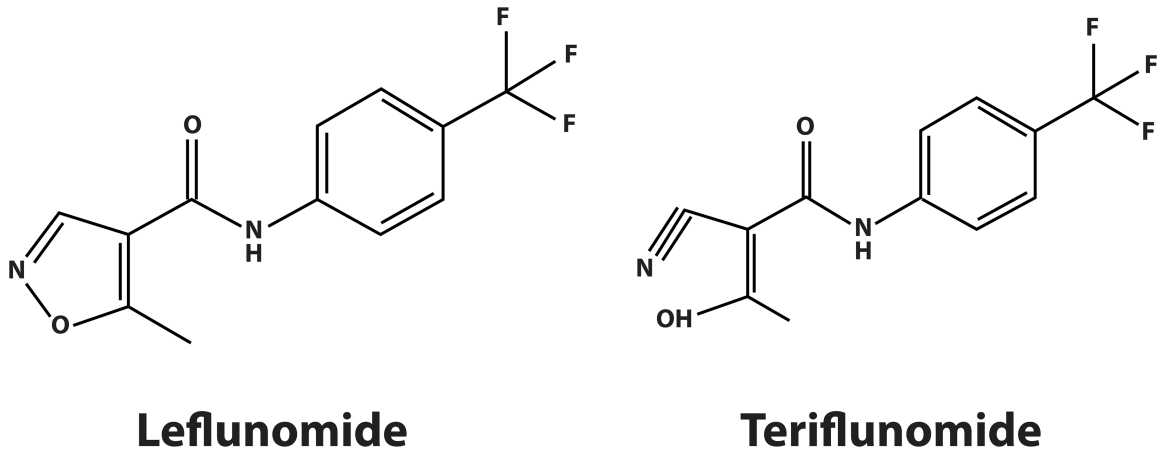

Figure 5.
Chemical structure of leflunomide and teriflunomide.

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Table 1

Categories of DMTs for MS.

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