# Advances in Multiple Sclerosis Neurotherapeutics, Neuroprotection, and Risk Mitigation Strategies

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**KEYWORDS**

• Relapsing multiple sclerosis • Treatment • Disease modifying therapies • Efficacy • Safety • De-escalation • Remyelination • Neurorepair

**KEY POINTS**

- The treatment landscape has improved dramatically over the past few years for patients with multiple sclerosis (MS).
- New treatments for MS can significantly reduce the inflammatory process of relapsing MS.
- Treatments that induce neurorepair are much more limited, and neuroprotection involves preventing or at least limiting the inflammatory component of relapsing MS and encouraging a healthy lifestyle.
- Risk management strategies can help balance the risk of these newer disease-modifying therapies.
- Stopping or de-escalating treatment is an emerging risk management strategy.

## INTRODUCTION

We live in an exciting time for the treatment of patients with multiple sclerosis (MS). We now possess a vast armamentarium of effective therapies, which offer neuroprotection by mitigating neural damage and disability from the inflammatory processes involved in relapsing MS.[1] This is particularly important to do early in the disease course given our limited ability to induce neurorepair. Developing risk management strategies for these disease-modifying therapies (DMTs) can improve their safety and is important to achieve given that they will often need to be used for many years and can induce a variable amount of immunosuppression. This article will focus on recent advances in neurotherapeutics for relapsing MS and risk mitigation strategies.

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## TREATMENT OF MULTIPLE SCLEROSIS ACUTE EXACERBATIONS

Early treatment of acute exacerbations may improve early functional recovery, helping to reduce deconditioning, and provide some neuroprotection.[2,3] The gold standard initial therapy consists of high-dose, short-term glucocorticoids: prednisone (oral 1000–1250 mg daily) or methylprednisolone (intravenous [IV] or oral 1000 mg daily) for 3 to 5 days. Adrenocorticotropic hormone (ACTH) has been postulated to have additional therapeutic advantages over glucocorticoids, but this remains to be shown clinically.[4] For severe relapses or those that do not respond to glucocorticoids, plasmapheresis should be considered.[5]

## TREATMENT OF RELAPSING MULTIPLE SCLEROSIS

When a patient is diagnosed with relapsing MS, one of the most reassuring discussions is the number of available DMT options (**Fig. 1**). Initial strategies on how to use these medications and how to leverage real-world evidence of comparative DMT performance are discussed in other articles in this MS issue. Additionally, further information on B-cell depletion and their role in progressive MS including risk mitigation and the promising therapies of Bruton tyrosine kinase inhibitors (BTKi) and autologous hematopoietic stem cell therapy are also discussed in other articles in this MS issue. Here, we will focus on newer neurotherapeutics and developments in their use.

Because of the number of DMTs that are now available for treating relapsing MS, they are sometimes discussed initially by route of administration (infusion, oral, or injection), efficacy (low, moderate, or high), or mechanism of action, as we will discuss here. See **Table 1** for a summary of DMTs used in patients with MS.

### B-CELL–DEPLETING THERAPIES

It was initially thought that MS was driven by T-cells, based on MS animal models showing the ability to transfer the disease to healthy animals with T-cells from affected animals.[6] However, targeted B-cell therapy was suggested by the presence of B-cells in cerebrospinal fluid and in inflammatory MS lesions, along with the presence of intrathecal antibody production including oligoclonal bands of roughly 95% of patients with MS.[7,8] The use of monoclonal antibodies directed against CD-20 that result in B-cell depletion has highlighted the importance of this cell in driving the pathophysiology of MS given their reduction in clinical and radiological measures of MS. The pathology is likely linked to altered interactions between T-cells, B-cells, and other immune cell populations since the main gene associated with MS is the major histocompatibility II factor by which B-cells (and other antigen-presenting cells) communicate with T-cells.[9]

There are currently 3 approved anti-CD20 monoclonal antibodies by the Food and Drug Administration (FDA) in the United States— ocrelizumab, ofatumumab, and ublituximab. Additionally, rituximab is often used off-label in the treatment of patients with MS. This drug class now accounts for over 50% of new prescriptions written for patients with MS. Ocrelizumab is a humanized anti-CD20 monoclonal antibody, which was approved in 2017 for relapsing MS and remains the only medication also approved for primary progressive MS. Ofatumumab is unique in its dosing as it is a subcutaneous injection monthly. Ublituximab is the most recent addition as it was approved in December 2022 and can be infused over 1 hour. Although rituximab is not approved for MS, it has the longest experience as it was approved initially in 1996 for non-Hodgkin lymphoma and tried in relapsing MS initially in the Heart failure

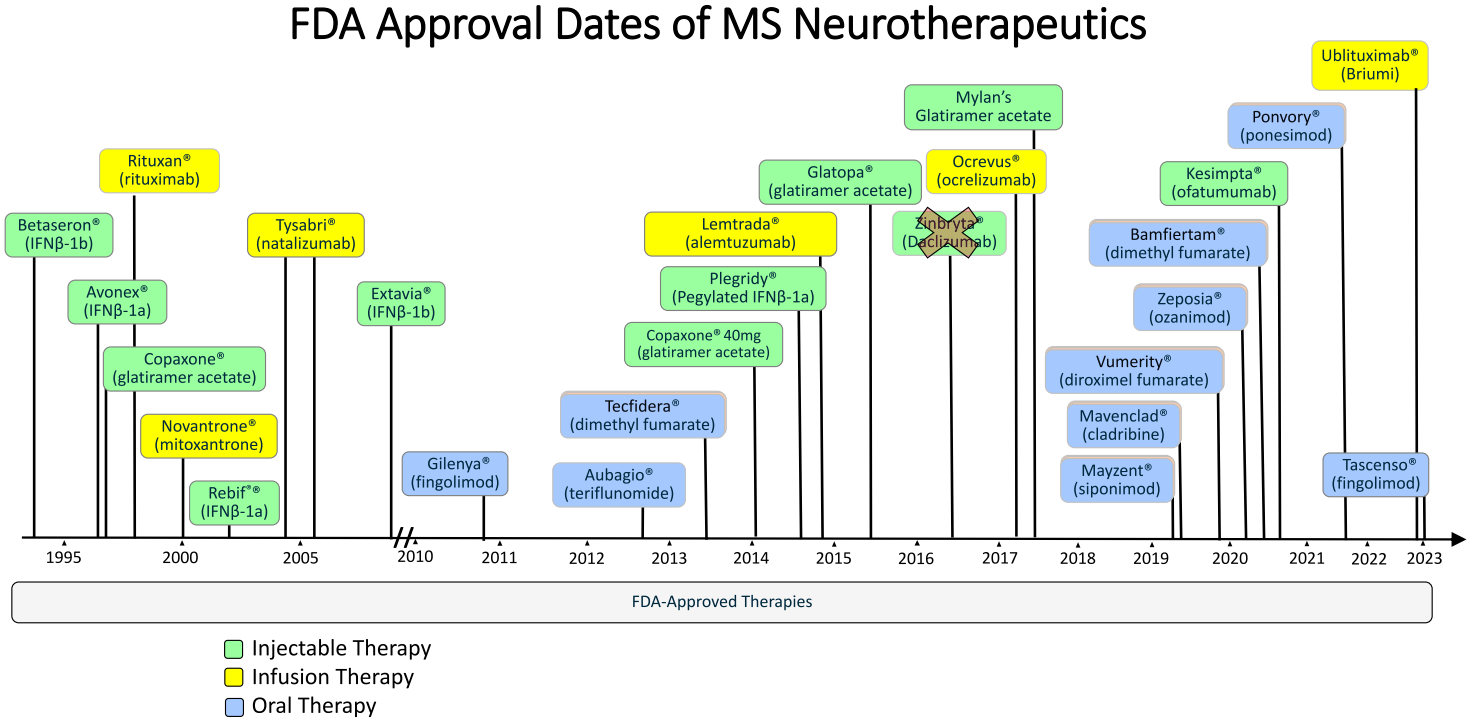


**Fig. 1.** Dates of approval of multiple sclerosis (MS) disease-modifying therapies by the Food and Drug Administration (FDA). Natalizumab was withdrawn in 2015 due to 3 cases of progressive multifocal leukoencephalopathy and reapproved in 2016. Daclizumab was withdrawn in 2018 due to safety concerns. mg, milligrams.

**Table 1**
**Disease-modifying therapies used for the treatment of patients with multiple sclerosis**

| Drug Name | Mechanisms of Action | Dosage and Route of Administration |
|---|---|---|
| Ocrelizumab | Anti-CD20 humanized monoclonal antibody; B-cell depletion | 600 mg infused intravenously every 6 mo;<br>1st dose is split with 300 mg on day 1 and 15<br>Premedications can include (administered 30–60 min prior to infusion)<br>1. 100–125 mg IV methylprednisolone<br>2. Antihistamine (eg, diphenhydramine, cetirizine)<br>3. Acetaminophen |
| Rituximab | Anti-CD20 chimeric monoclonal antibody; B-cell depletion | 500–1000 mg infused intravenously every 6 mo;<br>Sometimes an additional 1000 mg is infused at 2 wk.<br>Premedications–same as ocrelizumab. |
| Ofatumumab | Anti-CD20 fully humanized monoclonal antibody; B-cell depletion | 20 mg administered via subcutaneous injection<br>Initial titration–at week 0, 1, 2<br>Maintenance dosing—every 4 wk starting on week 4 |
| Ublituximab | Glycoengineered anti-CD20 chimeric monoclonal antibody; B-cell depletion | 450 mg infused intravenously every 6 mo starting 2 wk after the initial dose of 150 mg<br>Premedications—same as ocrelizumab |
| Natalizumab | Humanized monoclonal antibody to alpha-4 integrin; blocks transmigration of activated lymphocytes into the CNS | 300 mg infused intravenously every 4–6 wk |
| Alemtuzumab | Anti-CD52 humanized monoclonal antibody; depletion of T-cells and B-cells predominantly with some effect on natural killer cells and monocytes | 12 mg infused intravenously for 5 consecutive days, followed by 12 mg daily for 3 consecutive days 12 months later. This can be repeated as needed every 12 mo. Monitor blood pressure.<br>Premedication—1000 mg methylprednisolone or equivalent and herpes prophylaxis for 2 mo or CD4+ cells are $\leq$ 200 cells/microliter. |

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**Table 1**
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| Drug Name | Mechanisms of Action | Dosage and Route of Administration |
|---|---|---|
| Dimethyl Fumarate | Nuclear factor erythroid-derived 2-related factor (Nrf2)–dependent and independent pathways | 240 mg orally twice daily<br>Initial titration—120 mg orally twice daily for 7 d |
| Diroximel Fumarate | Nuclear factor erythroid-derived 2-related factor (Nrf2)–dependent and independent pathways | 462 mg orally twice daily<br>Initial titration—231 mg orally twice daily for 7 d |
| Monomethyl Fumarate | Nuclear factor erythroid-derived 2-related factor (Nrf2)–dependent and independent pathways | 190 mg orally twice daily<br>Initial titration—95 mg orally twice daily for 7 d |
| Teriflunomide | Inhibits dihydro-orotate dehydrogenase, involved in the de novo pyrimidine synthesis pathway | 7 or 14 mg orally once daily |
| Fingolimod | Sphingosine 1-phosphate receptor (S1PR) modulator | 0.5 mg orally once daily<br>Requires a first dose observation which must be repeated if there is a 2-wk interruption |
| Siponimod | Sphingosine 1-phosphate receptor (S1PR) modulator | 1 mg orally once daily (no CYP2C9*3 allele)<br>2 mg orally once daily (if CYP2C9*1/*3 or *2/*3) and contraindicated if CYP2C9*3/*3<br>Initial titration—start 0.25 mg daily and increase to these doses; repeat if there is a 4-d interruption |
| Ozanimod | Sphingosine 1-phosphate receptor (S1PR) modulator | 0.92 mg orally once daily<br>Initial titration—0.23 mg daily on day 1–4 followed by 0.46 mg daily on days 5–7, which must be repeated if there is a 2-wk interruption |
| Ponesimod | Sphingosine 1-phosphate receptor (S1PR) modulator | 20 mg orally once daily<br>Initial titration—start 2 mg orally daily and increase over 15 d; repeat if there is a 4-d interruption |
| Cladribine | Deoxyadenosine analog that is activated only in selected cell types, resulting in a reduction of B and T-cells | 3.5 mg/kg of body weight orally divided into 2 yearly treatment courses. Each course is separated into 2 treatment cycles of 4 to 5 days separated by roughly 4 weeks |

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**Table 1**
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| Drug Name | Mechanisms of Action | Dosage and Route of Administration |
|---|---|---|
| Interferon beta-1b | Increases anti-inflammatory signals while downregulating proinflammatory cytokines | 0.25 mg (1 mL) subcutaneous injection every other day<br>Initial titration—0.25 mL every other day for weeks 1–2, followed by 0.50 mL every other day for weeks 3–4, and then 0.75 mL every other day for weeks 5–6 |
| Interferon beta-1a | Increases anti-inflammatory signals while downregulating proinflammatory cytokines | 30 mcg weekly intramuscular injection<br>Initial titration—7.5 mcg increasing by 7.5 mcg weekly until reach 30 μg. |
| Interferon beta-1a | Increases anti-inflammatory signals while downregulating proinflammatory cytokines | 22 or 44 mcg subcutaneous injection 3 times per week<br>Initial titration—For 22 mcg dose, 4.4 mcg 3 times per week for 2 wk, then 11 mcg 3 times per week for 2 wk.<br>For 44 mcg dose, 8.8 mcg 3 times per week for 2 wk, then 22 mcg 3 times per week for 2 wk. |
| Pegylated Interferon beta-1a | Increases anti-inflammatory signals while downregulating proinflammatory cytokines | 125 mcg subcutaneous or intramuscular injection every 2 wk.<br>Initial titration—63 mcg on day 194 mcg on day 15, and 125 mcg on day 29 and thereafter. |
| Glatiramer acetate | Binds major histocompatibility complex and inhibits inflammatory responses. Induces anti-inflammatory cytokines. | 20 mg daily or 40 mg 3 times per week subcutaneously |

*Abbreviations:* CNS, central nervous system; IV, intravenous; mcg, micrograms; mg, milligrams; ml, milliliter.

Events reduction with Remote Monitoring and eHealth Support trial.[10] Here, the proportion of patients with clinical relapses was statistically significantly reduced by 58% at 24 weeks ($P = .02$) and 49% at 48 weeks ($P = .04$) compared to patients receiving placebo. These medications have achieved relapse rate reductions in the range of 50% to 60% against active comparators including interferon beta-1a and teriflunomide.[11–13] They also showed reductions of 94% or greater in the number of contrast-enhancing lesions.

Treatment with B-cell–depleting therapies is commonly associated with infusion-related reactions (IRRs). These reactions are common (20%–48%) but are seldom life-threatening.[11–13] Although often thought to be a reaction to the drug themselves, they are more likely related to the release of cytokines upon B-cell apoptosis, creating

a cytokine storm type reaction. These reactions are more common in patients who still have B-cells present during an infusion.[14] Ofatumumab has been associated with fewer treatment reactions likely because the subcutaneous route of administration causes a more gradual destruction of B-cells. Premedication with steroids is helpful in reducing IRRs.[15] Acetaminophen is also likely to be helpful as IRRs were more common with ublituximab, which omitted acetaminophen in the phase 3 trials.[13] In subsequent infusions, premedication may be simplified, as intravenous diphenhydramine can often cause sedation. Additionally, infusions can be done at a slower rate if IRRs in a patient are common.

Due to the immunosuppression associated with B-cell depletion, infections need to be monitored in patients receiving these medications. Upper respiratory tract, lower urinary tract, and skin infections are the most common infections.[11] Other infections and immune-mediated conditions reported in the post-marketing setting include herpes simplex virus and varicella zoster virus infections, hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML), and colitis.[16–18] In the event of an active infection, treatment should be delayed until the infection has resolved. Patients are encouraged to receive all necessary live or live-attenuated vaccines at least 4 weeks prior to starting ocrelizumab infusions. They are also not recommended until B-cells have been repleted after discontinuing treatment. All non-live vaccines may be taken up to 2 weeks prior to starting infusions.

## NATALIZUMAB

Natalizumab disrupts the leukocyte-endothelial interaction and prevents the transmigration of activated leukocytes from the circulating bloodstream into the central nervous system by blocking the alpha-4 subunit on integrin.[19–21] In the phase III study versus placebo, natalizumab decreased sustained progression of disability by 42%, annualized relapse rate by 68%, new and enlarging T2 lesions by 83%, and the mean number of contrast-enhancing lesion by 92% over placebo.[20] Natalizumab was initially approved by the FDA in November 2004 but was withdrawn in February 2005 after 3 deaths from PML. After development of the risk-minimization and monitoring TOUCH program, natalizumab was reapproved in June 2006. The main safety concern is the development of PML that has been associated with longer natalizumab exposure, older age, and higher titers of the John Cunningham virus serology.[22,23] Infusions can be extended to every 6 weeks, which appears to reduce the rates of PML.[24] IRRs can occur but are much less common than with B-cell–depleting treatments and have been associated with anti-natalizumab antibodies. These antibodies should be checked when IRRs occur, as well as when breakthrough disease is suspected, as they have been associated with reduced efficacy of natalizumab.[25]

## ALEMTUZUMAB

Alemtuzumab is a monoclonal antibody directed against CD52-expressing T-cells, B-cells, natural killer cells, and monocytes.[26] The reduction in relapse rates versus interferon beta-1a ranges from 49.4% to 55%.[27,28] The main concern with the use of alemtuzumab is the type of adverse events, which include IRRs, infections, and autoimmune disorders (thyroid disorders, hemophagocytic lymphohistiocytosis, acquired hemophilia A), malignancy (thyroid cancer, melanoma, lymphoproliferative disorders), and vascular events (ischemic stroke, hemorrhagic stroke, arterial dissection, and myocardial infarction occurring shortly after initiation of alemtuzumab

treatment).[27–33] Because of these concerns, alemtuzumab is recommended in the following settings: (1) for highly active relapsing-remitting multiple sclerosis (RRMS) that has been unresponsive to at least 2 or more DMTs by the FDA and (2) for highly active RRMS unresponsive to at least 1 DMT or in patients with rapidly worsening disease according to the European Medicines Agency.

## FUMARATES

The fumarate class of DMTs includes dimethyl fumarate, diroximel fumarate, and monomethyl fumarate.[33–35] Dimethyl and diroximel fumarate are both metabolized to monomethyl fumarate, which is believed to be the active component of these medications. In the CONFIRM and DEFINE phase 3 trial of dimethyl fumarate versus placebo, reductions of 44% and 53% were seen for relapses and 74% and 90% were observed for contrast-enhancing lesions.[34,35] Diroximel fumarate had similar efficacy to diroximel fumarate. However, it was better tolerated with fewer gastrointestinal-related side effects and missed days of work.[36,37] This is likely due to less methanol (<10%) produced with diroximel fumarate.[37] These effects can be ameliorated by taking the medication with food and improve after the first month of being on treatment. Although dimethyl fumarate is associated with more discontinuations due to gastrointestinal side effects, its efficacy is similar to that of fingolimod in several real-world studies.[38–41] Aspirin can help with flushing if this side effect becomes clinically significant.

## TERIFLUNOMIDE

Teriflunomide, the active metabolite of leflunomide, inhibits pyrimidine biosynthesis and disrupts the interaction between antigen-presenting cells, such as B-cells and T-cells.[36] Teriflunomide has become the comparator DMT in most of the newer clinical trials for higher efficacy therapies. However, teriflunomide demonstrated annualized relapse rate (ARR) reductions of 31.5% and 36.3% versus placebo and 80% reduction in contrast-enhancing lesions.[42,43] Although side effects associated with teriflunomide are common (**Table 2**), they can often be easily mitigated, especially given the long-term experience with leflunomide in rheumatological conditions (see **Table 1**).

## SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATORS

The sphingosine 1-phosphate receptor (S1PR) modulators include fingolimod, siponimod, ozanimod, and ponesimod. The efficacy of these medications appears to be similar, although comparative studies are currently difficult as the number of patients on siponimod, ozanimod, and ponesimod remains limited.[44] Fingolimod demonstrated an ARR reduction of 54% and had an 82% reduction in contrast-enhancing lesions versus placebo.[45] The efficacy of fingolimod appears to be similar to that of dimethyl fumarate although with better tolerability.[38,39,42]

The newer S1PR modulators gradually became more selective with the hope of minimizing their side effect profiles.[44] However, their side effect profile has remained similar and described in **Table 2**. Due to these similarities, complete blood count including lymphocyte counts, electrocardiogram, liver functions tests, and ophthalmic evaluation are recommended prior to starting S1PR modulators. The dosing for siponimod is variable and dependent on the *CYP2C9* genotype due to metabolism of this drug. Otherwise, all S1PR modulators can prolong the QT interval, resulting in the first dose observation required for fingolimod. This has been resolved with the newer generation

**Table 2**
**Most common risk mitigations associated with disease-modifying therapies used in patients with multiple sclerosis**

| Disease Modifying Therapy | Risk Factor | Risk Mitigation |
|---|---|---|
| Anti-CD20 therapies (ocrelizumab, rituximab, ofatumumab, ublituximab) | Infusion Reactions | Infuse slower. Consider additional premedication or eliminating part of premedication if the reaction is to current premedication. If B-cells have reconstituted, then consider infusing more frequently or a higher dose |
| | Infections | Baseline and surveillance CBC with differential. Baseline hepatitis B core antibody, consider getting surface antibody if will vaccinate and surface antigen; monitor lymphocyte and immunoglobulin levels. Reconsideration of risk-benefit as disability and/or age increases |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs throughout treatment |
| Natalizumab | PML | JCV serology testing every 6 mo. Repeat monitoring MRI every 6–12 mo. Infuse at extended interval – 6 wk. Reconsideration of risk-benefit though REMS program (TOUCH®) |
| | Infusion Reaction | Consider pretreatment medication. Check for natalizumab neutralizing antibodies |
| | Lymphopenia | Baseline and surveillance CBC with differential auto diff throughout treatment |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs throughout treatment |

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**Table 2**
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| Disease Modifying Therapy | Risk Factor | Risk Mitigation |
|---|---|---|
| Alemtuzumab | Infusion Reaction | Pretreatment with corticosteroids, antipyretics, and antihistamines. Control blood pressure |
| | Infection | Monitor for UTI, URI. REMS: baseline VZV IgG (consider vaccination if negative), TB testing |
| | Humoral Autoimmunity (thyroid, ITP, Goodpasture) | REMS: baseline and monthly for 48 mo after last dose—CBC with differential, serum creatinine, urinalysis with urine cell counts, LFTs, and TSH (every 3 mo) |
| | Malignancy | Monitor for thyroid cancer, melanoma, lymphoproliferative disorders, and lymphoma |
| Fumarates (dimethyl fumarate, diroximel fumarate, monomethyl fumarate) | Gastrointestinal Symptoms | Symptomatic treatment. Administer with food |
| | Flushing | Aspirin |
| | Pruritis | Antihistamine |
| | Lymphopenia | Baseline and surveillance CBC with differential throughout treatment. Absolute lymphocyte count of >500 cells/microliter recommended to reduce PML risk |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs throughout treatment |
| Teriflunomide | Teratogenic | Baseline pregnancy test. Reliable method of contraception. Immediate washout with cholestyramine if become or planning on becoming pregnant |
| | Liver Toxicity | Baseline and surveillance LFTs, monthly for the first 6 mo and then periodically |
| | Lymphopenia | Baseline and surveillance CBC with differential throughout treatment |
| | Reactivation of Latent TB | Baseline TB screening with purified protein derivative or QuantiFERON |
| | Hair Thinning | Biotin supplementation |

| | | |
|---|---|---|
| Sphingosine 1-phosphate receptor (S1PR) modulator (fingolimod, siponimod, ozanimod, ponesimod) | Cardiac Anomalies (bradycardia, AV block, cardiac arrest, arrhythmias) | Baseline ECG and 6-h observation during the first dose (fingolimod). Avoid in patients with QT prolongation or medications that can increase the QT interval |
| | Zoster Infections (Herpes, Varicella) | Zoster virus serology screening and vaccinations. Early and/or chronic preventative treatment |
| | Macular Edema | Ophthalmologic monitoring or OCT at baseline and 3 mo after starting treatment |
| | Lymphopenia | Baseline and surveillance CBC with differential |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs |
| Cladribine | Teratogenic | Baseline pregnancy test. Reliable method of contraception |
| | Lymphopenia | Baseline and surveillance CBC with differential. ALC reconstitution to within normal limits necessary for starting Year 2 of treatment |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs |
| | Infection | Exclude HIV infection, TB, and active hepatitis at baseline. Monitor for zoster infections and consider vaccination |
| | Malignancy | Avoid if there is a current malignancy and monitor |
| Interferon (interferon beta-1a, interferon beta-1b, pegylated interferon beta-1a) | Flu-like Symptoms | NSAIDs, hydration |
| | Leukopenia | Baseline and surveillance CBC with differential |
| | Elevated Liver Enzymes | Baseline and surveillance LFTs |
| | Depression/Suicidal | Screening and monitoring for depression and suicidal ideation. Consider antidepressant medications and/or referral to therapy. |
| Glatiramer acetate | Acute post-injection systemic reaction | Reassurance that reaction is self-limiting. |

*Abbreviations:* CBC, complete blood count; ECG, electrocardiogram, HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; JCV, john cunningham virus; LFT, liver function tests; NSAIDS, nonsteroidal anti-inflammatory drugs; OCT, optical coherence tomography; PML, progressive multifocal leucoencephalitis; REMS, risk evaluation and mitigation strategy; TB, tuberculosis; TSH, thyroid-stimulating hormone; URI, upper respiratory infection; UTI, urinary tract infection; VZV, varicella zoster virus.

S1PR modulators by using a dose titration to gradually start medication. It is too early to compare infections between these medications, but the newer generation S1PR modulators also appear to have better vaccine responses than fingolimod.[46] These differences may provide an advantage of the newer S1PR modulators over fingolimod.

### CLADRIBINE

Cladribine works by suppressing purine synthesis and targets specific lymphocyte subtypes by controlling activation of this medication. Over 96 weeks, the ARR was reduced by 57.6% over placebo and contrast-enhancing lesions by 85.7%.[47] The percentage of patients who had a relapse gradually increased over the following 2 years to 25%.[48] The concern for malignancies delayed the approval of this medication, and it is usually reserved as a second-line therapy. It is contraindicated in patients with active chronic infections, malignancy, pregnancy, breastfeeding, and patients of reproductive potential not willing to use effective contraception for at least 6 months after treatment.[49] Due to these contraindications and adverse events, patients should be screened for pregnancy, malignancies, and active infections prior to initiating cladribine therapy.

### INTERFERON BETA-1

Interferons (IFN) are cytokines that regulate the responsiveness of the immune system via multiple mechanisms. Four medications are included in this group: recombinant human interferon beta (IFN-b)1b, intramuscular IFN-b1a, subcutaneous IFN-b1a, and pegylated IFN-b1a. The first approved medication for patients with MS was IFN-b1b in 1993 by the FDA. IFN-b1a is produced in mammalian hosts and is glycosylated, while IFN-b1b is produced in bacterial hosts and is not glycosylated. These DMTs have lower efficacy, reducing relapses by about a third with the lower dose once weekly intramuscular IFN-b1a being at the lower end of the group.[50–52] Adverse events are similar and include injection site reactions (eg, abscess, cellulitis, or necrosis), flu-like symptoms, liver abnormalities, thyroid dysfunction, leukopenia, and decreased mood. The low efficacy and difficulty with tolerability have led to decreased use of these DMTs over the past few years.

### GLATIRAMER ACETATE

Glatiramer is composed of random polymers of the 4 amino acids most commonly found in myelin basic protein. Glatiramer affects the immune system by binding to major histocompatibility complex molecules and competes with various myelin antigens in presenting to T-cells. Glatiramer is also a potent inducer of specific T helper 2 type suppressor cells that migrate to the brain, resulting in bystander suppression and anti-inflammatory cytokine production.[50] Glatiramer acetate has a similar level of efficacy as subcutaneous INF-b1a and INF-b1b.[53,54] Glatiramer is not associated with an increased risk of infection but can be associated with local injection site reactions and, less commonly, transient systemic post-injection reactions (eg, chest pain, flushing, dyspnea, palpitations, and/or anxiety). The safety of glatiramer acetate has led to the development of a monthly depot formulation with an ongoing phase 3 clinical trial being conducted (NCT04121221).

### NOVEL TREATMENTS UNDER DEVELOPMENT

New therapies for relapsing MS include BTKi and stem cell transplantation, which are discussed more in other sections. Phase 3 studies are currently underway for multiple

BTKi in treating relapsing and progressive MS including evobrutinib, tolebrutinib, fenebrutinib, remibrutinib, and BIIB091, with results for evobrutinib expected at the end of 2023. Phase 3 studies are also underway for IMU-838 (vidofludimus calcium),a more selective inhibitor of dihydroorotate dehydrogenase than teriflunomide, which is being compared to placebo. Additionally, biosimilars are being developed for natalizumab, which may acquire FDA approval by the end of 2023. Xacrel, a biosimilar to ocrelizumab, is currently being studied in Iran. Frexalimab (SAR441344) is a monoclonal antibody that binds CD40 L and will soon be entering phase 3 studies after reporting an 89% reduction in contrast-enhancing lesions in patients with relapsing MS (NCT04879628). Many other compounds have completed phase 1 and 2 trials, suggesting that we will continue to see drugs with new mechanisms of action for the treatment MS.

## REMYELINATION

A pathway to consider in neurorepair is neuronal remyelination. Remyelination is mediated by the recruitment and differentiation of surrounding oligodendroglial precursor cells to restore conduction through axons.[55] Because of the increasing loss of neurons, it may prove difficult to achieve this goal later in the disease. However, since dalfampridine is theorized to work on demyelinated neurons, remyelination should be achievable in at least some patients. Current drugs being explored in clinical trials for possible remyelinating potential include clemastine, GSK239512, opicinumab, GNbAC1, simvastatin, biotin, and domperidone (**Table 3**).[55] Despite the extraordinary strides being made in identifying remyelinating therapies, there has yet to be an effective treatment.

## MULTIPLE SCLEROSIS RISK MITIGATION

Risk mitigation strategies refer to the identification of therapy risks based on the individual patient's characteristics.[56] As with any medication, DMTs are associated with different risks and adverse events. Therefore, it is vital to not only know what those risks/adverse events are but also how to minimize and address them if they are precipitated. **Table 2** summarizes the most common risk mitigation strategies associated with each of the MS DMTs.

One of the most important aspects in risk mitigation is determining whether a patient still needs to be on a DMT. Much like there can be therapeutic inertia, which can slow down therapy escalation when breakthrough disease occurs, there can be therapeutic inertia that keeps patients on treatment that they may not need. In the past, this was less common as patients often tired of using the frequent injectable platform medications, and they would self-discontinue treatment. There was also a recognition that patients tended to have less inflammatory activity as they aged and remained stable for several years. This led to the first randomized trial evaluating DMT discontinuation. The Discontinue Disease Modifying Therapies in MS (DISCOMS) study randomized patients over the age of 55 years who were clinically stable for 5 years and radiologically stable for 3 years to continue or stop treatment. In this patient population, DMT discontinuation was not non-inferior to continuing therapy (ie, 12.2% of patients who discontinued DMT had a relapse or a new/expanding brain MRI lesion vs 4.7% who continued therapy).[57] It therefore appears to be safe to discontinue medication in this patient population, although most of these patients were on platform medications.

There was a shift toward the approval of more highly efficacious and tolerable DMTs following the approval of natalizumab and fingolimod. With patients increasingly likely to be on higher efficacy therapies, another risk mitigation approach to be considered is de-escalation when appropriate (eg, increased safety concerns, aging patient

**Table 3**
**Remyelinating treatments tried in patients with MS**

| Medication | Mechanism of Action | Study Information |
|---|---|---|
| Clemastine | First-generation histamine H1 receptor blocker | Remyelinating potential identified in a high-throughput in vitro screening.[62]<br>The ReBUILD clinical study involved 50 RRMS patients and investigated the remyelinating potential of clemastine in chronic demyelinating optic neuropathy. Remyelination was assessed using the shortening of the P100 latency delay in VEP, which was reduced by 3.2 ms/eye if the results were analyzed as a "delayed treatment trial," or 1.7 ms/eye when analyzed as a "crossover trial."[63] |
| GSK239512 | CNS-penetrant antihistamine that targets $H_3$ receptors | Phase II, randomized, parallel-group, placebo-controlled, double-blind, multicenter study of adults with relapsing MS (NCT01772199). While the study failed to meet its primary and secondary endpoints, post hoc analysis using MTR to assess in vivo myelin content showed small mean improvements in lesional MTR relative to placebo.[64] |
| Opicinumab | Antibody against LINGO-1 (leucine-rich repeat and immunoglobulin-like domain–containing nogo receptor–interacting protein 1).[65,66]<br>Loss of LINGO-1 enhances myelin sheath formation and myelination.[65,66] | The Phase 2 RENEW showed non statistically significant improvement in the recovery of optic nerve conduction latency by measuring VEP in patients with ON. The phase 2b SYNERGY trial also did not meet its primary endpoint, but post hoc analyses showed an increased clinical effect in a subgroup of patients with earlier disease and certain baseline MRI characteristics. Based on these results a third phase 2 trial, AFFINITY, was done which was not successful. |
| GNbAC1 | Antibody against the envelope protein (ENV) of multiple sclerosis–associated retrovirus.<br>ENV protein can be silenced via epigenetic control and certain environmental factors such as viruses (eg, EBV and HHV8) result in its re-expression. ENV can limit OPC differentiation via toll-like receptor 4.[67,68] | In the CHANGE-MS trial, 270 patients were enrolled and showed significant benefit of GNbAC1 on cortical and thalamic atrophy, with relative volume loss reductions of 31% and 72%. Furthermore, there was a 63% reduction in the number of T1 hypointense lesions when compared to the control group. Finally, a benefit in magnetization transfer ratio in both normal appearing white matter and cerebral cortex, suggests an effect on remyelination. |

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| Simvastatin | β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitor | Previous trials showed that statins stimulated OPC differentiation. The phase 4 SIMCOMBIN trial assessed whether simvastatin could be efficacious as an add-on therapy to interferon beta-1a in relapsing MS.[69] No difference in the annualized relapse rate was seen. However, a second trial (MS-STAT) which enrolled 140 secondary progressive MS patients showed that simvastatin led to a 43% reduction in mean annualized brain atrophy rate. A larger 3-y MS-STAT2 study is now planned to enroll 1180 patients.[70] |
| Biotin | Vitamin B Coenzyme<br>May increase myelin production by increasing adenosine triphosphate and stimulating fatty acid synthesis.[71] | The MS-SPI trial enrolled 154 patients and increased the proportion of patients with disability reversal by 12.6% vs placebo. However, the phase 3 SPI2 with 642 subjects failed to show a significant improvement in disability.[72] |
| Domperidone | A D2/D3 dopamine receptor antagonist<br>May increase production of prolactin.[73] | Prolactin can stimulate remyelination in animal models which prompted the initiation of a phase 2 clinical trial in secondary progressive MS (NCT02308137).[74] |
| Elezanumab | Fully human monoclonal antibody directed against repulsive guidance molecule A (RGMa)<br>RGMa is a modulator of axonal growth, myelination, and downstream immunoregulatory molecules that inhibiting oligodendroglial regeneration[75] | Phase 2 trials involving 123 patients in progressive MS (RADIUS-P) and 208 patients in relapsing MS (RADIUS-R) vs placebo in addition to their standard of care disease modifying therapy were completed in 2021. However, elezanumab did not outperform placebo.[76] |

*Abbreviations:* ENV, envelope protein; MS, multiple sclerosis; ms, millisecond; MTR, magnetization transfer ratio; ON, optic neuritis; OPC, oligodendrocyte precursor cells; VEP, visual evoked potentials.

population with associated immunosenescence that may incur additional risks).[58] Although advancing age remains an important factor in considering when a patient may no longer need a DMT to treat their MS, another factor to consider is increasing disability due to its association with serious infections.[59] For example, patients with MS on rituximab were 8.56 times more likely to have a serious infection than if they did not require a walking device.[60] In this multivariable model using stepwise selection, age became non-significant. Additionally, during the coronavirus disease 2019 pandemic, mortality was much more associated with being non-ambulatory (OR = 25.4) than age (OR = 1.77 for every 10-year increase) or treatment, which was not significant.[61] However, B-cell–depleting therapies were associated with higher rates of hospitalizations.

In summary, risk management of being on a DMT should include monitoring when a patient should discontinue or de-escalate their treatment.

## SUMMARY

There have been great advances in the treatment of relapsing MS. Since the introduction of the first FDA approved DMT for relapsing MS in 1993, new therapies have continued to be developed with higher efficacy and better safety profiles and tolerability. The inflammation associated with relapses results in neuronal damage that disproportionally affects patients when they are younger. The risks of infections associated with higher efficacy DMTs escalate with increasing disability. This proves another reason to maximize neuroprotection early in the disease course as part of the risk mitigation strategy. By controlling relapses, the contribution of progressive MS has become clearer and highlights the continued need to pursue therapies to stop progression and offer neurorepair.

## CLINICS CARE POINTS

- Once a diagnosis of relapsing MS is secured, treatment options should be discussed with the patient to minimize the risk of future disabling relapses and maximize neuroprotection.
- A risk mitigation strategy should be developed early to maximize the benefit-risk potential of the disease-modifying therapy.
- More investigation is needed in the treatment of progressive disease and inducing neurorepair.

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