Published in final edited form as:

Mult Scler Relat Disord. 2014 September 1; 3(5): 639–649. doi:10.1016/j.msard.2014.05.003.

Risk stratification and mitigation in multiple sclerosis

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Abstract

The increasing availability of new agents to treat multiple sclerosis poses new challenges for clinicians who seek therapies that are both safe and effective for their patients. The introduction of additional effective therapies has been accompanied by the recognition of serious side effects. The clinician now must weigh both the benefits and risks of therapies to help patients decide which treatment best fits each patient's risk/benefit profile. An optimal selection of therapies relies on a complete understanding of the risks of therapies and the factors that may help evaluate and mitigate those risks. An individualized treatment approach that incorporates patient and disease factors is needed for each patient. In this review we present risk stratification and mitigation strategies of disease modifying agents for multiple sclerosis.

Keywords

risk; mitigation; stratification; benefits; multiple sclerosis

Introduction

The field of multiple sclerosis (MS) has seen significant changes over the last several years. Clinicians and patients welcomed the introduction of disease modifying agents for multiple sclerosis in the mid-1990s. Injectable agents, all with rather similar risk-benefit profiles, dominated MS care for over a decade. The approval of natalizumab marked a change with

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Author COI Disclosures

Dr. Ontaneda is supported by a National Institutes of Health (Clinical and Translational Science Collaborative of Cleveland, (KL2TR000440) KL2 Award. Dr. Ontaneda has received consulting or speaking fees from Acorda Therapeutics, Biogen Idec, Alkermes, and Novartis.

Mr. Cohn has nothing to disclose.

Dr. Fox has received grants from the National Multiple Sclerosis Society and National Institutes of Health, as well as consulting fees from Avanir, Allozyne, Biogen Idec, Novartis, Questcor, Teva Neuroscience, and Xenoport, and research support from Novartis

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the introduction of an additional effective treatment option, but also the realization of the risks associated with modulation of the immune system. More recently, the introduction of oral agents has opened yet another avenue for patients and clinicians. Currently, there are up to 11 agents available to treat MS, with varying availability around the world. Significant heterogeneity exists in the efficacy and risks associated with these therapies. Therefore, clinicians must tailor treatment to disease activity level and individual patient characteristics in order to identify treatment with the optimal balance between efficacy and safety. In this review we will present risk evaluation and mitigation strategies for approved MS disease modifying agents. Data on the different agents is summarized in table 1.

Individual Disease Modifying Agents

Glatiramer acetate

Glatiramer acetate (GA) is a random polypeptide comprising specific amino acids, which were engineered to simulate myelin basic protein.¹ It serves as a ligand for MHC class II molecules, which may inhibit T-cell activation and induce regulatory T cells in order to reduce inflammation.² The drug is superior to placebo in reducing disease outcomes such as relapse rate and MRI disease progression,^{3,4} and is an effective treatment for clinically isolated syndrome.⁵ GA is administered through daily subcutaneous injection, although a recent trial of three weekly administrations showed clear efficacy, and approval of this preparation is expected in 2014.⁶ GA is generally well tolerated with limited major adverse reactions.⁷ The most common adverse events are injection site reactions (24%), which may include localized erythema (18%), pain (17%), nodules or edema (4%), and long-term use may incur lipoatrophy at injection sites. Immediate post-injection systemic reactions (IPIR) occur in approximately 10% of patients, presenting as transient vasodilation, chest pain, palpitations, tachycardia or dyspnea directly following drug administration.⁸ Risk mitigation strategies for patients on GA include patient education on proper injection technique in order to minimize injection site reactions. Education on the symptoms of IPIR will also minimize unnecessary ED visits, medical workup, and emotional stress.

Interferon β

Interferon β drugs are widely used agents for RRMS and are available as two different compounds. Interferon β -1b is administered as a subcutaneous injection every other day, and interferon β -1a is available in differing doses as weekly intramuscular or thrice weekly subcutaneous injection. They may limit autoimmunity through various mechanisms including downregulation of MHC class II molecules on antigen presenting cells and downregulation of costimulatory signals such as CD40L and CD28 on T cells, thereby inhibiting T cell activation and proliferation. They also may inhibit T cell extravasation across the blood-brain-barrier and induce an anti-inflammatory cytokine profile (e.g. increased levels of IL-10 and TGF- β).⁹ Compared to placebo, IFN reduces relapse rates by approximately 30%,^{10,11} delays disability, and reduces MRI activity by up to 80%,^{12,13} with clinical and MRI benefit sustained through long-term follow up.¹⁴ Similarly to GA, IFN is an effective treatment for CIS.¹⁵

Interferons have been widely used, and long-term follow-up studies demonstrate a favorable safety profile with some characteristic side effects. Flu-like symptoms of fever, myalgia, chills, or headache occur in up to 69% of patients; mild pain, erythema, and pruritus at the injection site develop in 72% of patients.¹⁶ Long-term tolerability studies show that these symptoms are generally mild, occur within the first month of treatment, and tend to improve over time. Common laboratory abnormalities include asymptomatic leukopenia in 37–47% of patients¹⁶ and elevated liver enzymes in 36.9% of patients.¹⁷ Though depression is oft considered a risk of interferon therapy, evidence establishing a clear association is mixed: earlier studies indicated increased rates of depression during the first 2–6 months of interferon treatment,¹⁸ however subsequent investigations show that approximately 24% of MS patients will have depression at any given time, with similar rates seen in interferon and placebo groups on meta-analysis.¹⁹ The occurrence of depression does, however, appear to be correlated with increased disability among patients treated with interferon.²⁰ Despite conflicting data, the risk for depression should still be considered when choosing a disease-modifying therapy. In a patient with significant ongoing depression, an alternative MS therapy should probably be considered. The following strategies can minimize the risks of interferon therapy: flu-like side effects are managed through NSAIDs (particularly long-acting preparations) and hydration for symptomatic relief; hematologic and hepatic effects are evaluated through baseline and longitudinal monitoring CBC and LFTs; for the risk of depression, patients should be routinely screened for the development of depression symptoms.²¹

Natalizumab

Natalizumab is a humanized monoclonal antibody directed at the $\alpha 4$ integrin component of Very Late Antigen-4 (VLA-4) on leukocytes, a target involved in lymphocyte trafficking and homing to the central nervous system. By interrupting the interaction of VLA-4 with vascular cellular adhesion molecules (VCAM) on endothelial cells, natalizumab prevents lymphocytes from migrating across the BBB into the CNS.²² Within twelve years of the discovery of VLA-4 in 1992, natalizumab gained FDA approval in 2004 as a therapy for relapsing forms of MS based on the 1-year data from the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM)²³ and Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL)²⁴ trials. AFFIRM demonstrated natalizumab superiority to placebo: the drug reduced annual relapse rate (ARR) by 68%, disability progression by 42%, new or enlarging T2 lesions by 83%, and gadolinium-enhancing MRI lesions by 92%.^{23, 25} The SENTINEL trial similarly established the superiority of natalizumab and IFN β -1a combination therapy to IFN β -1a monotherapy.²⁴

In phase III trials, 9% of patients developed hypersensitivity reactions, including anaphylaxoid reactions, urticaria, allergic dermatitis, or hives. 24% of patients experienced infusion reactions within two hours of infusion start, most commonly headache (5%), fatigue, dizziness, and nausea.²³ Postmarketing studies have also reported lymphopenia and rare cases of elevated liver enzymes.²⁶

While natalizumab is one of the most potent therapies currently available, it is accompanied by a significant and often fatal risk of progressive multi-focal leukoencephalopathy (PML). In February 2005, three cases of PML were identified in natalizumab-treated patients: two patients with multiple sclerosis and one with Crohn's disease.^{27–29} After the recognition of these cases, natalizumab was temporarily removed from the market. As of June 2013, there have been at least 395 cases of PML reported in patients who received natalizumab treatment over 296,471 patient-years (table 2), representing an overall incidence of 1.3 cases per 1,000 patient-years.³⁰ The most important risk factor for developing PML is prior infection with the John Cunningham virus (JCV), which is the causative agent in PML. There have been just two reported cases of PML that occurred in patients who tested negative for anti-JCV antibodies.³¹ Other significant risk factors include prior immunosuppressant use and prolonged natalizumab treatment, especially for durations greater than 24 months.³² The STRATIFY-1 trial, a longitudinal observational study of MS patients treated with natalizumab in the United States, demonstrated an overall JCV seropositivity of 56% in MS patients. JCV seroprevalence increases with age, with nearly 70% of patients above age 60 demonstrating JCV positivity. Seropositivity is also influenced by gender: 53% of females vs. 64% in males.³³ The risk of developing PML for patients with negative JCV serology, with attention paid to the anti-JCV antibody assay's false negative rate of 2.7%, is estimated to be approximately 0.1 per 1,000 patients treated with natalizumab, although patients with repeated negative test results may have an even lower risk. Conversely, the highest risk exists for patients who exhibit all three key risk factors (present anti-JCV antibodies, prior immunosuppressant use, and extended natalizumab treatment) at 11.1 cases per 1,000 treated patients.³² Emerging research, recently presented as a meeting abstract, seeks to further stratify PML risk by levels of circulating anti-JCV antibodies.³⁴ Indeed, a higher anti-JCV index correlates with a higher risk of developing PML, with a significant increase in risk with an index greater than 1.5. For an anti-JCV antibody index below 1.5, the risk of PML is 0.1, 1.2, and 1.3 per 1,000 patients for natalizumab treatment 1–24 months, 25–48 months, and 49–72 months, respectively. For an index above 1.5, the risk increases to 1.0, 8.1, and 8.5 per 1,000 patients over the same treatment durations.³⁵

If hypersensitivity or significant infusion reactions develop, natalizumab is to be immediately discontinued. In some cases of mild infusion reactions, pretreatment with loratadine and acetaminophen may be attempted. In the AFFIRM trial, hypersensitivity reactions were more common in patients with persistent anti-natalizumab antibodies;²⁵ therefore, while testing for antibodies is typically done to assess loss of drug efficacy, it may also help guide treatment decisions through risk stratification. Patients should also receive baseline and monitoring CBC and LFT panels to monitor for lymphopenia and liver enzyme derangements. Based on the risk factors for developing PML, the FDA recommends baseline MRI for all patients prior to starting natalizumab, with further MRIs to be obtained for patients who demonstrate signs or symptoms of possible PML.³⁶ Prior to initiating natalizumab treatment, each patient's JCV antibody status should be assessed through the anti-JCV antibody assay and reassessed every six months to monitor for seroconversion. Patients who have previously received immunosuppressive therapy may choose to avoid natalizumab, though it is not a strict contraindication for natalizumab use, particularly in

JCV seronegative patients. Should patients develop PML, the drug should be immediately discontinued and the patient treated promptly with 5 sessions of plasmapheresis.^{37, 38}

Fingolimod

Fingolimod is notable among disease-modifying agents in being the first approved oral therapy for multiple sclerosis. The compound binds to and causes the internalization of the sphingosine-1-phosphate receptor 1 on T cells, a molecule involved in T cell egress from lymphoid tissue into systemic circulation. Fingolimod thus appears to limit the autoimmune response in MS by interrupting the movement of lymphocytes to target organs, such as the CNS.³⁹ The FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) trial demonstrated fingolimod superiority to placebo: fingolimod reduces annual relapse rate by 54–60%, disease progression by approximately 30%, the rate of brain volume loss by 30%, and the development of new T2 MRI lesions by 75%.⁴⁰ Through the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), fingolimod was shown to be superior to interferon β in improving clinical and MRI outcomes.^{41, 42}

Cardiac arrhythmias, including dose-related bradycardia and atrioventricular block, were the most common serious adverse events reported in patients who received fingolimod. Cardiac events occurred in 2.2–3.6% of patients treated with fingolimod, typically occurring immediately following initial drug administration. Additionally, there was one reported death from sudden cardiac arrest shortly after treatment initiation, and several other reports of cardiac complications.^{43,44} Additionally, Herpes infection occurred more frequently in the fingolimod-treated groups compared to placebo (3.8% vs. 2.8%) in phase III trials, and was implicated in two deaths during the TRANSFORMS trial: one case of HSV encephalitis and one of disseminated VZV infection in a patient previously naïve to VZV. Other adverse reactions include macular edema (0.5–1.1%), liver enzyme abnormalities (8.3–9.0%), hypertension (10.6–12.6%), and lymphopenia.^{40,41,45,46} Following the regulatory approval of fingolimod, two cases of PML were reported in patients treated with fingolimod. The first occurred in a patient who was previously treated with natalizumab and may represent PML more related to natalizumab treatment.⁴⁷ The second case of PML occurred after eight months of fingolimod treatment in a patient with no previous natalizumab treatment but with a history of prior immunosuppression with azathioprine.⁴⁸

As a result of these adverse reactions, the FDA made several safety recommendations. For cardiovascular risks, a baseline EKG is needed prior to starting fingolimod and the first dose administration is observed for at least 6 hours with hourly measurement of blood pressure and heart rate, and repeated EKG after six hours. Monitoring continues for patients who develop bradycardia below 45 beats per minute, a new EKG abnormality, or symptomatic bradycardia requiring pharmacologic intervention. Fingolimod is contraindicated for patients with a history of cardiac disease, especially those recently diagnosed within the previous 6 months or existing conduction abnormalities such as 2nd or 3rd degree AV block or sick sinus syndrome, as well as patients with a baseline corrected QT interval greater than 500 msec and patients who already take Class I or II antiarrhythmic drugs. To minimize the risk of infection, baseline and monitoring CBCs should be obtained and patients should be

followed clinically for signs of infection. To minimize the risk of disseminated VZV infections all patients starting fingolimod should have VZV antibody testing and should be vaccinated if seronegative. Baseline and monitoring liver function tests should be tested to screen for hepatic injury. Finally an ophthalmologic examination with optical coherence tomography (OCT) is needed prior to starting fingolimod and should be repeated 3 months after treatment initiation, to screen for the development of macular edema. Macular edema occurred in the clinical trials with greater frequency among patients older than 60 and those with diabetes, and therefore should be monitored closely in patients with these risk factors.^{49, 50}

Teriflunomide

Teriflunomide was the second oral therapy for MS approved following fingolimod. It is an active metabolite of leflunomide, which is a treatment for rheumatoid arthritis with activity in several animal models of autoimmune disease, including the MS model experimental autoimmune encephalomyelitis (EAE).^{51, 52} Teriflunomide inhibits the rate-limiting enzyme of de novo pyrimidine synthesis, dehydroorotate dehydrogenase, and thereby selectively depleting rapidly proliferating cells such as activated lymphocytes.⁵³ Teriflunomide also favors an anti-inflammatory TH2 cytokine profile (e.g. increased IL-10) and reduces T cell trafficking to sites of inflammation in a mechanism distinct from pyrimidine depletion.⁵⁴ In clinical trials, teriflunomide was superior to placebo both in reducing ARR (by 31–36%) and in improving MRI outcomes.^{55, 56} When compared to IFN therapy, teriflunomide showed no statistical difference in reducing ARR, but was associated with higher scores on the Treatment Satisfaction Questionnaire for Medication (TSQM) and lower rates of drug discontinuation.^{57, 58}

In phase III trials, the most common adverse events associated with teriflunomide were diarrhea (16.3%), nausea (11.3%), liver enzyme elevations (13.1%), alopecia (11.7%), upper respiratory infections (most commonly nasopharyngitis; 25.8%), headache, parasthesias, back and limb pains, and arthralgias. Additionally, one patient developed an opportunistic intestinal tuberculosis infection.⁵⁶ Furthermore, two of the known risks of leflunomide are presumed to apply to teriflunomide: leflunomide is a known teratogen, and it carries a risk of severe liver injury.⁵⁹

Risk mitigation strategies with teriflunomide include baseline CBC, baseline tuberculin skin tests or interferon gamma release assay to identify latent tuberculosis infection, and baseline LFTs to be repeated monthly for the first 6 months to assess hepatic enzyme derangements. Furthermore, based on the cases of severe liver injury with leflunomide, teriflunomide is contraindicated for patients with existing hepatic disease. Due to the risk of teratogenesis, teriflunomide is also contraindicated during pregnancy or in those considering pregnancy. Cholestyramine may be administered to accelerate drug washout if a patient becomes pregnant while on teriflunomide.⁵⁸ Teriflunomide is the only pregnancy category X medication approved for use in MS.

Dimethyl fumarate

Fumaric acid has been used in Europe for nearly two decades as a treatment for psoriasis. Identified as a potential MS therapy due to its anti-inflammatory effects, the currently approved preparation of dimethyl fumarate is an enterically-coated microtablet formulation that was FDA approved in March 2013 for the treatment of relapsing forms of MS. Fumaric acid activates nuclear factor-E2-related factor 2, which may lead to anti-inflammatory, antioxidant, and neuroprotective effects.⁶⁰ Through independent mechanisms, dimethyl fumarate has also been shown to induce an anti-inflammatory Th2 cytokine profile (i.e. IL-4, IL-5, IL-10) and facilitate apoptosis in activated T cells.⁶¹ Dimethyl fumarate has been shown to be superior to placebo through pivotal phase III trials: Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS (DEFINE)⁶² and Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM).⁶³ DMF reduces the risk of relapse by approximately 50%, the risk of disability progression by 34–38% (DEFINE only), and improves MRI outcomes: patients on DMF had 71–85% reduction in new or enlarging T2 lesions, and approximately 73% lower odds of developing new gadolinium-enhancing lesions.

The adverse effects of oral fumarate therapy were typically mild and had a peak incidence in the first month of therapy. These events included flushing, gastrointestinal events (i.e. diarrhea, nausea, abdominal pain, and vomiting), and pruritus. Flushing occurred in 38% of patients, diarrhea in 15%, nausea in 13%, and abdominal pain, pruritus, and vomiting in 10% of patients each. 16% of patients discontinued the drug due to side-effects.⁶² The long term safety of fumaric acid esters (FAE) with up to 14 years of follow up data in psoriasis patients is reassuring. Among psoriasis patients treated with prolonged courses of fumaric acid esters, the most significant effect was relative lymphocytopenia (<20% of the total leukocyte count) that developed in 76% of patients; on average, patients demonstrated a mean 30% reduction in absolute lymphocyte count that tended to stabilize at 12 months without further declines in lymphocyte count with continued FAE therapy.⁶⁴

As of October 2013, there have been four cases of PML reported in patients with non-MS autoimmune disorders treated with the fumarate preparations Fumaderm® and Psorinovo®. Both of these medications are mixtures of dimethyl fumarate with additional fumaric acid esters (FAE) and metabolites. Ermis⁶⁵ and van Oosten⁶⁶ reported on two of these cases: psoriasis patients on FAE who developed PML in the setting of severe lymphopenia, presumed to be treatment-related, for two and five years, respectively. There were no other immunosuppressing factors identified for either patient. Sweetser⁶⁷ reported two additional cases of PML in psoriasis patients treated with fumarates. The first patient had a history of sarcoidosis that had been treated with methotrexate and steroids and developed PML after only one month of Fumaderm® therapy. The second patient had psoriasis previously treated Fumaderm® as well as a history of cancer for which they had received prolonged treatment with the anti-CD11 monoclonal antibody efalizumab, which itself was withdrawn from clinical use because of its association with PML. In summary, these four cases of PML developed in the setting of prolonged and profound lymphopenia, sarcoidosis with prior immunosuppressive use, or cancer with prior monoclonal antibody treatment. Sarcoidosis, cancer, and efalizumab are known risk factors for PML.⁶⁷ Prior to 2013 there had been no

reported cases of PML in Fumaderm® and Psorinovo® patients; these 4 cases in over 180,000 patient-years of follow up data represent an incidence of 0.02 cases per 1,000 patient-years, or approximately one hundred-fold less frequent than the incidence of PML among natalizumab-treated patients.

The most commonly reported adverse reactions such as flushing, gastrointestinal symptoms, and pruritus may be managed through symptomatic treatment and patient education. Phase III trials found that reactions are typically mild and will improve after the first month of therapy, although in some patients can be severe and preclude continued treatment. Flushing can be reduced with aspirin,⁶⁸ and pruritus may respond to antihistamines. GI symptoms of abdominal pain, nausea, vomiting, and diarrhea may respond to antacids, antiemetics, antidiarrheals, and concomitant administration with food, as needed. Based on the rare occurrence of severe lymphopenia, baseline CBC as well as yearly monitoring CBCs are recommended to identify severe lymphopenia.⁶⁹ Given the low incidence of PML with the use of FAE the role of JCV serology in risk mitigation of patients starting DMF is of undetermined clinical utility.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed at the cell surface antigen CD52. It induces the selective depletion of cells that express CD52, which are primarily lymphocytes and monocytes,⁷⁰ quickly leading to lymphopenia. Recovery of T cells to the lower limit of normal occurs slowly over twelve months and B cells somewhat more rapidly over 6 months.⁷¹ The drug is administered in a fashion distinct from the other available therapies: patients initially receive 5 infusions over 5 consecutive days, followed by 3 additional infusions on consecutive days 12 months later. The International Campath-1H in Multiple Sclerosis trial (CAMMS223) found alemtuzumab to be effective at reducing relapse rates, slowing progression of disability, and improving MRI outcomes in patients as compared to interferon therapy.⁷² The two trials in the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) series established the drug as an effective first line (CARE-MS I⁷³) and in treatment refractory relapsing MS (CARE-MS II⁷⁴). Specifically, CARE-MS I and II described a 49–54% reduction in ARR compared to interferon treatment. Patients experienced sustained benefit through 5-year follow up.^{72–75}

One significant risk of alemtuzumab is infusion reaction: 47% of patients experienced headache, 43% developed rash, 18% experienced nausea, and 17% had pyrexia during the infusion.⁷⁴ Infection is another notable risk, potentially due to the drug-induced lymphopenia. The most common infections reported in alemtuzumab-treated subjects were upper respiratory infections, urinary tract infections, and herpetic infections. Two patients in the CARE-MS I trial developed thyroid papillary carcinoma, representing 0.53% prevalence among the 376 patients who received alemtuzumab.⁷³ A rare, but important, side effect of alemtuzumab is the development of humoral autoimmune syndromes. This autoimmunity may occur due to faulty and early B-cell reconstitution. Nearly one in five patients treated with alemtuzumab developed autoimmune disorders, with thyroid disease representing the most common form and occurring in 18% of patients. Idiopathic Thrombocytopenic Purpura and Goodpasture syndrome were also reported, in 1% and 0.4%, respectively.⁷⁶ Additional

cases of autoimmune endocrine ophthalmopathy, autoimmune hemolytic anemia, type 1 diabetes mellitus, and autoimmune diseases of the skin and connective tissue have also been reported.⁷⁷ Autoimmunity may occur several months and even years after treatment discontinuation. Altered immune reconstitution may contribute to the development of autoimmunity with alemtuzumab.⁷⁷

To minimize risk of infusion reaction, patients may be pretreated with corticosteroids, antipyretics, or antihistamines. To reduce herpetic infections, acyclovir prophylaxis is recommended following each course of alemtuzumab. Finally, patients should be routinely monitored for the development of autoimmunity with routine thyroid stimulating hormone assays and CBC. Intermittent urine testing for signs of Goodpasture syndrome is also recommended. The level of IL-21 has been identified as a possible predictor of the development of autoimmunity, although this assay is not yet clinically available.⁷⁸

Individualizing Risk Stratification and Mitigation Strategies

The specific risks and benefits of the available disease modifying agents have been provided in the sections above, however clinicians will need to place this knowledge in a specific patient context. An understanding of the risk of untreated multiple sclerosis will help drive decisions and a summary of the risks of untreated MS is presented in table 3. Selection of a first line therapy will likely depend on several factors. Traditionally, and due to the availability of extended safety data, injectable agents are obvious first choices. Given the comparable efficacy data between the injectable agents the selection of a therapy will be determined mostly by side effects. Subjects with headaches, depression, and history of liver dysfunction may experience worsening of these comorbidities when exposed to interferons. Monitoring for interferons include following liver function tests, complete blood counts, and monitoring depression. Glatiramer acetate requires little on going risk mitigation but ensuring adequate injection techniques will minimize local side effects. Oral agents may be used as a first line agent and in those with refractory cases. The use of oral therapies as first line agents will continue to increase as safety data becomes available. For fingolimod screening for cardiac pathology, VZV exposure, diabetes and considering age (risk of macular edema) are important factors before starting the medication. First dose observation, monitoring blood counts/liver function, and OCT for macular edema are risk mitigation strategies which should be employed. Use of steroids should be limited as some infectious complications occurred with concurrent steroid use. The use of teriflunomide will depend on child bearing potential (men and women), history of liver dysfunction, and history of latent tuberculosis. Once teriflunomide is initiated frequent liver function testing, blood counts should be instituted. DMF is a viable first line medication, patients with a history of peptic ulcer disease or GI tolerability issues may be at an increased risk of side effects. Subjects should be reminded to take the medications after meals, symptomatic medications should be used to treat side effects, and blood counts should be followed. Natalizumab has traditionally been used when breakthrough disease occurs on a previous medication. Natalizumab may also be used in treatment naïve patients who are JCV negative or who have an aggressive disease course. Repeat JCV testing among those with negative serology, MRI of the brain every 6 months and monitoring of liver function tests will help identify complications early. The possibility of PML with the use of other disease modifying

medications should be considered taking into account the risk of each specific agent (table 2). The risk of PML in JCV positive patients switched from natalizumab to other immunomodulators is not known with certainty, but risk factors are likely to include JCV titer and duration of natalizumab therapy.

If a medication is in use and there are tolerability issues a medication of similar or stronger potency can be selected based on the factors described above. If disease activity is a reason to switch a medication an attempt should be made to use a medication which has better probability of controlling the disease, and this may involve an increase in potential risks. However, there are limited head-to-head studies establishing which therapy is more effective than another. The need for ongoing use of therapy should be considered closely in those patients who go on to develop progressive forms of the disease, as the benefit of anti-inflammatory agents is limited in that stage of the disease.

Conclusion

The increased availability of MS therapies with differing risks and benefits presents an ongoing challenge to MS practitioners. The balance between adequate disease activity control and risks associated with the medications that make that control possible is variable and will depend on several patient and medication factors. Risk associated with control of disease activity must be tailored to the specific needs of patients and to the risk/benefit profile of each individual. The risk mitigation strategies presented in this review are tools which may allow clinicians to select treatments based not only on MS related measures, but also on factors that may predict the development of adverse effects. Clinicians will have to frequently reconsider risks and benefits over time, and the introduction of new agents will make the prediction of adverse effects difficult and uncertain at times. Risk evaluation and mitigation strategies will likely improve the selection of disease modifying agents in MS and will allow clinicians to present patients with efficacious and safe options for treatment of MS.

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Highlights

- Risk stratification and mitigation tools are important for all disease modifying agents in multiple sclerosis
- Selection of disease modifying agents involves an understanding of the risk and benefits of medications
- Tailor treatment to disease activity and patient characteristics to ensure an optimal balance of efficacy and safety

Table 1

Comparative risk and mitigation strategies for currently available disease-modifying agents for multiple sclerosis

Drug	Risks	Mitigation strategies
<i>Glatiramer Acetate</i>	Injection site reactions Immediate post-injection systemic reaction	Patient education, proper injection technique Patient education, and reassurance
<i>Interferon beta</i>	Flu-like symptoms Injection site reactions Leukopenia Elevated liver enzymes Depression	NSAIDs, hydration Patient education, proper injection technique Baseline and monitoring CBC Baseline and monitoring LFT Screen and monitor for depression, suicidal ideation
<i>Natalizumab</i>	PML Hypersensitivity reactions and Infusion reactions Lymphopenia Elevated liver enzymes	Baseline JC virus serology testing, repeated every 6 months Baseline MRI, to be repeated every 6–12 months Reconsideration of risk with anti-JCV antibody seropositivity, greater than 24 infusions, or history of immunosuppressant use Plasmapheresis +/- antiviral therapy Pretreatment with loratadine and acetaminophen Anti-natalizumab antibody testing after 3–6 months of therapy Baseline and monitoring CBC Baseline and monitoring LFT
<i>Fingolimod</i>	Cardiac events (bradycardia, AV block, cardiac arrest, arrhythmias) Herpes infection Macular edema Elevated liver enzymes Lymphopenia	Baseline EKG Cardiology consultation for any abnormal EKG or for patients with cardiac risk factors First dose observation for 6 hours, hourly blood pressure and heart rate monitoring Extended observation and monitoring for patients with events in first 6 hours Contraindication for patients with cardiac disease or who take an antiarrhythmic VZV serology screen; vaccination for patients without prior immunity Acyclovir treatment for suspected herpes infection Baseline and 3 month ophthalmologic testing with OCT Baseline and 3 month LFT Baseline and 3 month CBC
<i>Teriflunomide</i>	Teratogenesis Liver dysfunction Reactivation of latent tuberculosis	Baseline pregnancy test Contraindication in pregnancy Ensure contraceptive use Cholestyramine washout if pregnancy occurs or is planned Baseline LFT, to be repeated monthly for initial 6 months of therapy Contraindication for existing liver disease Baseline TB screen Baseline CBC
<i>Dimethyl fumarate</i>	Gastrointestinal symptoms Flushing Pruritus Lymphopenia	Symptomatic treatment (e.g. antidiarrheals, antiemetics, H2 antagonists) Administer drug with food Aspirin Antihistamines Baseline and monitoring CBC during therapy
<i>Alemtuzumab</i>	Infusion reactions Infections Autoantibody disorders (thyroid, ITP, Goodpasture syndrome)	Pretreatment with corticosteroids, antipyretics, or antihistamines Clinical monitoring for UTI, URI Acyclovir prophylaxis for herpetic infection Baseline and monitoring CBC with platelet count Baseline and monitoring TSH IL-21 screening (elevated IL-21 is reported to indicate increased risk)

Table 2

Comparative risks of progressive multifocal leukoencephalopathy (PML)

Drug	Total cases of PML	Drug exposure (patient-years)	Estimated Incidence (per 1,000 patient-years)
<i>Natalizumab</i>	395	296,471	1.33
<i>Fingolimod</i>	2 ^{47,48,79} <ul style="list-style-type: none"> • Previous natalizumab treatment • Previous immunosuppression with azathioprine, JCV + 	101,000	0.02
<i>Dimethyl fumarate</i>	4 ^{* 65-67} <ul style="list-style-type: none"> • Two years on FAE with severe lymphopenia • Five years on FAE with severe lymphopenia • One month on FAE, history of sarcoidosis, immunosuppression with MTX and steroids • History of cancer treated with efalizumab 	180,000	0.02

* No cases of PML described in MS patients to date. Cases listed represent subjects with psoriasis.

Table 3

Risks of Untreated relapsing multiple sclerosis

Treatment Targets	Evidence of Association	Long-Term outcome
T2 lesion volume	Increase of 0.8–1 ml/year. ^{80,81}	Correlates with increased relapse frequency and long term disability outcomes
T1 black hole conversion	40–50 % of lesions go on to form black holes. ^{82,83}	Correlation with clinical measures and disability progression
Brain Atrophy	0.5–1%/year in MS versus <0.1% in healthy controls. ^{80,8}	Correlation with cognitive outcomes and EDSS in the long term.
Clinical Relapses	Annualized relapse rate in placebo arms: 0.5–1.38. ^{85–87}	Relapses associated with decreased quality of life. Relapses associated with accrual of disability. Earlier onset of SPMS.
Disability accrual	Average change of 0.27 EDSS points/per relapse. ⁸⁸ MRI and lesional activity associated with disability progression. ⁸⁹	Increased likelihood of long term disability.