



Infection Mitigation Strategies for Multiple Sclerosis Patients on Oral and Monoclonal Disease-Modifying Therapies

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Abstract

Purpose of Review The newer, higher-efficacy disease-modifying therapies (DMTs) for multiple sclerosis (MS)—orals and monoclonals—have more profound immunomodulatory and immunosuppressive properties than the older, injectable therapies and require risk mitigation strategies to reduce the risk of serious infections. This review will provide a systematic framework for infectious risk mitigation strategies relevant to these therapies.

Recent Findings We classify risk mitigation strategies according to the following framework: (1) screening and patient selection, (2) vaccinations, (3) antibiotic prophylaxis, (4) laboratory and MRI monitoring, (5) adjusting dose and frequency of DMT, and (6) behavioral modifications to limit the risk of infection. We systematically apply this framework to the infections for which risk mitigations are available: hepatitis B, herpetic infections, progressive multifocal leukoencephalopathy, and tuberculosis. We also discuss up-to-date recommendations regarding COVID-19 vaccinations for patients on DMTs.

Summary We offer a practical, comprehensive, DMT-specific framework of derisking strategies designed to minimize the risk of infections associated with the newer MS therapies.

Keywords Multiple sclerosis · Disease-modifying therapy · Treatment · Infections · Risk mitigation · Adverse events

Introduction

The older, injectable disease-modifying therapies (DMTs) for MS—glatiramer acetate and interferon β —are of modest efficacy, but are not immunosuppressive, and have excellent long-term safety profiles [1, 2]. Most of the newer orals and monoclonal antibody DMTs have better efficacy than the older drugs but also a more profound effect on the immune system, necessitating the implementation of derisking strategies to prevent serious infections [3]. Currently, nine orals, four infusible monoclonals therapies, and one injectable monoclonal antibody therapies are FDA-approved for MS. These drugs fall into several classes: ocrelizumab, ofatumumab, and rituximab (which is

widely used off-label for MS) are CD20-depleting therapies that remove B-cell lineage cells from the peripheral circulation [4]; natalizumab is an $\alpha 4\beta 1$ -integrin-blocker, which prevents lymphocyte migration into the central nervous system [5]; fingolimod, siponimod, and ozanimod are sphingosine-1-phosphate (S1P) modulators that prevent lymphocyte egress from lymph nodes [6]; monomethyl fumarate, dimethyl fumarate, and diroximel fumarate are fumarates that exert anti-inflammatory activity via Nrf2-dependent and Nrf2-independent pathways [7]; alemtuzumab is an anti-CD52 antibody, which depletes CD52-bearing lymphocytes [8]; teriflunomide blocks proliferation of activated lymphocytes [9]; and cladribine disrupts cell metabolism and DNA synthesis and repair, leading to lymphocyte death [10]. As of 2020, these newer DMTs were used by more than two-thirds of the MS patients in the USA.

In this review, we classify risk mitigation strategies for preventing infections in MS patients on the newer DMTs according to the following framework: (1) screening and patient selection, (2) vaccinations, (3) antibiotic prophylaxis while on DMT, (4) laboratory and MRI monitoring while on DMT, (5) DMT dose/frequency adjustment, and (6) behavioral modifications. In this review, we focus only on the infections that are

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associated with the newer DMTs for which risk mitigations strategies are available.

Hepatitis B Infection

Chronic hepatitis B virus (HBV) is estimated to affect up to 2.5 million people in the USA and 291 million worldwide [11]. Chronic and resolved hepatitis B may be reactivated with anti-CD20 therapy, which may lead to fulminant hepatitis, hepatic failure, and death [12–16]. Therefore, screening for HBsAg and anti-HBc Ab is mandatory before starting anti-CD20 therapy [14, 17–19]. Patients with positive HBsAg or hepatitis B core Ab may have chronic or resolved HBV infection, and should be referred to a specialist in managing hepatitis B. Hepatitis B seropositive patients may still be eligible for anti-CD20 therapies as long as they start anti-HBV prophylaxis, such as entecavir or tenofovir, prior to anti-CD20 therapy and continue on it for at least 12 months after discontinuation of anti-CD20 therapy [17]. Unvaccinated patients who are at risk for contracting hepatitis B via infected sexual contact(s), intravenous drug use, exposure to percutaneous or mucosal fluids in healthcare or other at-risk occupations, and patients who travel to endemic regions should be offered hepatitis B vaccination and provided with guidance on behavioral modifications that decrease the risk of acquiring HBV [20]. Hepatitis B vaccination series should be completed at least 6 weeks before initiating anti-CD20 therapy, if possible [14]. The Advisory Committee on Immunization Practices (ACIP) does not offer guidance on hepatitis B vaccination in adult patients without risk factors for acquiring hepatitis B who are starting anti-CD20 therapy. The authors' practice is not to vaccinate such patients so as not to delay treatment unless it is patient's preference to be vaccinated.

Screening for hepatitis B—as well as for hepatitis C—is required before starting cladribine [21]. It is reasonable to offer hepatitis B (and hepatitis C, in the case of alemtuzumab) screening prior to starting S1P modulators, natalizumab or alemtuzumab as there are case reports of hepatitis B reactivation on fingolimod [22], natalizumab [23], and alemtuzumab [24]. Unvaccinated patients should be offered vaccination, and seropositive patients should be referred to hepatologist for consideration of antiviral prophylaxis.

Varicella-Zoster Virus and Other Herpes Infections

Prior to the introduction of varicella-zoster virus (VZV) vaccination in 1995, VZV infected more than 90% of individuals worldwide [25]. Following primary infection (chickenpox), typically during childhood, VZV becomes latent in the sensory ganglia and may manifest later in life as cutaneous herpes zoster (shingles) [26, 27]. In immunocompromised individuals, disseminated VZV infection can be life-threatening. Sphingosine 1-phosphate receptor (S1P) modulators

[27–31], alemtuzumab [32], and cladribine [33] have been associated with increased incidence of VZV infection with the potential for severe infection. Therefore, before starting these therapies, patients should be screened for immunity to varicella with VZV IgG antibody. Although varicella vaccine-induced immunity may not always be detected via VZV IgG assays [34], a VZV Ab-seronegative patient who does not have a history of VZV infection or vaccination should receive varicella vaccination before starting S1P modulators, alemtuzumab, or cladribine. Because the varicella vaccine is a live vaccine, it is contraindicated for patients who are treated with S1P modulators and for a variable duration after the drug discontinuation (see Table 1 for DMT-specific vaccine recommendations) [28–30].

Shingrix is a highly effective vaccine for preventing shingles, with an efficacy of 97.2% [37]. It is recommended for all immunocompetent adults aged ≥ 50 years [38, 39]. The ACIP also recommends Shingrix for those on low-dose immunosuppressive therapy [38]. The incidence of shingles is increased in patients on S1P modulators [31], and it is, therefore, reasonable to recommend Shingrix even for patients who are younger than 50 if they plan to start on these drugs. Shingrix is not a live vaccine and can be offered to patients who are taking S1P modulators, though the efficacy of vaccines is possibly blunted in patients on these S1P therapies [40]. VZV IgG seronegative individuals, who do not have a history of prior varicella infection or vaccination, should receive varicella vaccine rather than Shingrix, as the latter is not indicated for the prevention of primary varicella infection [38].

Anti-herpes prophylaxis is recommended for patients on alemtuzumab [27]. Acyclovir (200–400 mg bid) should be started on the first day after alemtuzumab infusion and continued until CD4+ lymphocytes recover to at least 200 cells/mm³, or for 2 months after infusion, whichever takes longer [32, 41]. Anti-herpes prophylaxis should also be administered to patients on cladribine until lymphocyte counts rise above 200 cells/mm³ [21]. Natalizumab may also increase the risk of herpetic reactivation (including acute retinal necrosis and herpes encephalitis or meningitis) [42], while the data on fumarates and anti-CD20 therapies are less clear. Fumarates were associated with an increased risk of zoster in some reports [43, 44], but the review of post-marketing reports did not identify increased risk [45]. Ocrelizumab was associated with an increase in herpes infections compared to no treatment (4.7% vs 3.3%) [46] and when compared to interferon beta-1a (5.9% vs 3.4%) [47], while herpes antiviral drug use during rituximab treatment was similar to that of injectable therapies and lower than that of natalizumab and fingolimod in a large population-based study [48]. Although the authors generally do not recommend anti-herpes prophylaxis with these agents, in patients with frequent or serious herpetic outbreaks (VZV, HSV1, HSV2), valacyclovir or acyclovir prophylaxis should be considered.

Table 1 A review of vaccination schedules by disease-modifying therapy, grouped by mechanism of action

Disease-modifying therapy (brand name)	Non-live, inactivated vaccinations	Live or live-attenuated vaccination
Ofatumumab (Kesimpta) [19]	Administer at least 2 weeks prior to initiation of ofatumumab	Administer at least 4 weeks prior to ofatumumab initiation. Not recommended during treatment and after discontinuation, until B-cell repletion (mean 9.7 months in one study [35])
Rituximab (Rituxan) [18]	Administer at least 4 weeks prior to a course of rituximab	Do not administer prior to or during treatment. No recommendation for post-discontinuation period
Ocrelizumab (Ocrevus) [14]	Administer at least 6 weeks prior to ocrelizumab initiation	Administer at least 6 weeks prior to ocrelizumab initiation. Not recommended during treatment and after discontinuation, until B-cell repletion
Fingolimod (Gilenya) [28]	May be less effective during and for 2 months after discontinuation of therapy	Avoid during therapy, and for 2 months after stopping fingolimod. VZV is a live-attenuated vaccine, and treatment initiation with fingolimod should be postponed for 1 month after VZV vaccination
Siponimod (Mayzent) [29]	May be less effective during therapy. For needed vaccinations, it is recommended to discontinue siponimod 1 week prior to vaccination and resume 4 weeks after vaccination	Avoid during therapy and for up to 4 weeks after stopping Siponimod. VZV is a live-attenuated vaccine, and treatment initiation with siponimod should be postponed for 4 weeks after VZV vaccination
Ozanimod (Zeposia) [30]		Avoid use during therapy and for up to 3 months after stopping ozanimod. VZV is a live-attenuated vaccine, and treatment initiation with ozanimod should be postponed for 1 month after VZV vaccination
Alemtuzumab (Lemtrada) [32]	Complete all vaccinations at least 6 weeks prior to treatment	
Dimethyl Fumarate (Tecfidera) [36]	Vaccination guidelines not provided	
Cladribine (Mayzent) [21]	All vaccines should be administered prior to starting cladribine. Separate recommendations for non-live vaccines are not provided	Administer at least 4–6 weeks prior to start cladribine

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic brain infection caused by JC virus (JCV) that occurs in the setting of immunosuppression or immunodeficiency [49]. Among the approved therapies for MS, the incidence of PML is highest with natalizumab [50]. As of August 2020, there have been 839 cases of PML among 213,000 patients exposed to natalizumab (Biogen, data on file). Screening for JCV antibody before and during natalizumab therapy is critical for mitigating the risk of PML. The risk of natalizumab-associated PML is less than 1:10,000 among JCV antibody seronegative patients and as high as 1:31 among patients with high levels of anti-JCV antibodies, prolonged duration of natalizumab therapy, and prior use of immunosuppressants [49, 51–54]. JCV Ab titers can be falsely negative in patients who underwent plasmapheresis within 2 weeks of testing [42] and in patients on anti-CD20 therapies [55] and falsely positive in patients who received intravenous immunoglobulin within 6 months of testing [42]. After starting natalizumab, JCV antibody titer should be monitored every 6 months in seronegative individuals as the rate of JCV seroconversion is 3–8% annually [42]. For JCV seropositive patients who received natalizumab for more than 18 months, regular monitoring with MRI of the brain every 3–4 months to screen for asymptomatic PML is recommended [56, 57].

Another key risk mitigation strategy for decreasing natalizumab-associated PML risk is extending the interval between natalizumab infusions from the approved every 4-week dosing to every 6–8 week dosing. This strategy has been shown to dramatically reduce the risk of PML in JCV seropositive individuals [52••]. In observational studies [58, 59], the efficacy of extended-dose natalizumab was comparable to standard dosing, and a prospective trial to confirm the equivalence of every 6-week and every 4-week dosing is ongoing (NCT03689972). The authors' practice is to always extend the frequency of NTZ dosing for JCV seropositive patients to reduce the risk of PML.

As of March 2021, there have been 11 cases of PML among more than 501,000 patients exposed to dimethyl fumarate (DMF) (Biogen, data on file). The majority of cases of DMF-associated PML occurred in the setting of prolonged moderate-to-severe lymphopenia, predominantly in older patients (median 61 years old) (Biogen, data on file). It is recommended to monitor lymphocyte counts in DMF and to consider discontinuing DMF in patients with serious infections [36]. The authors' practice has been to decrease the fumarate dose to once a day or discontinue it when lymphocyte count is <800 cells/ μ L in older individuals since fumarate-associated PML cases can occur even in patients with lymphocyte count in 500–800 cells/ μ L range (Biogen, data on file).

PML has also been reported in 40 out of more than 307,000 individuals treated with fingolimod [56]. Almost all fingolimod-associated PML cases occurred after more than 2 years of therapy, and the mean age of patients was 54 [60–62]. There have been only isolated reports of PML with alemtuzumab (3 cases, 1 presumed carry-over from natalizumab), cladribine (single case), teriflunomide (single case, likely carry-over related to prior natalizumab therapy), and ocrelizumab (9 cases, all but one of which were confounded by prior natalizumab or fingolimod treatment) [60, 63].

It is recommended to obtain a baseline MRI within 3 months of starting cladribine [21] to exclude asymptomatic PML lesions and to serve as a reference for comparison if patients develop new neurologic symptoms suggestive of PML. This recommendation is logical for other DMTs that have been associated with PML.

Human Immunodeficiency Virus

HIV infects CD4+ lymphocytes and leads to their depletion and a state of acquired immunodeficiency. It is recommended that before starting potent CD4-depleting therapies, such as cladribine and alemtuzumab, patients should undergo HIV testing [21, 32]. It is prudent to screen all patients at risk for HIV (history of sexually transmitted diseases, high-risk sexual contacts, intravenous drug use) before starting other immunomodulatory therapies if they are known to decrease CD4 counts (e.g., fumarates) or are associated with PML (e.g., natalizumab).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Virus

COVID-19, the novel respiratory infection caused by SARS-CoV-2, appears to affect MS patients at a similar rate as the general population [64]. Severe disability [65] and, possibly, anti-CD20 therapy [66–68] increase the risk for COVID-19 complications and death, though likely to a smaller extent than such well-established risk factors for complications as older age, obesity, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes [69]. Patients with risk factors for COVID complications should be counseled on the importance of COVID-19 vaccination and the behavioral modifications that decrease the risk of transmission at the time of the pandemic (e.g. avoiding crowded and poorly ventilated spaces; mask-wearing; social distancing, hand washing). As of March 2021, only mRNA (Moderna, Pfizer-BioNTech) [70, 71] and adenovirus-based (Johnson & Johnson) COVID-19 vaccines have received emergency use authorizations in the USA [72]. These are not live vaccines and can be administered to MS patients on immunosuppressant therapy. The National Multiple Sclerosis Society expert consensus recommendation is to administer COVID-19

vaccines to all MS patients as soon as possible unless otherwise contraindicated [73]. To enhance the effectiveness of vaccination, the guidelines further recommend getting fully vaccinated 2–4 weeks before starting anti-CD20 therapy, S1P modulators, and cladribine [73] and 4 weeks before starting alemtuzumab [73]. For those already on a DMT, the NMSS recommends getting vaccinated 24 weeks or more after the last alemtuzumab dose and 12 weeks after the last ocrelizumab or rituximab dose [73]. If coordination of the suggested DMT scheduling and vaccination is not possible, it is preferable to schedule vaccination regardless, which likely provides at least partial protection against the infection [73].

Mycobacterium Tuberculosis

Mycobacterium tuberculosis (Tb) infection remains among the top 10 causes of death worldwide, with approximately one-quarter of the world's population infected [74]. There are estimated to be 12.4 million individuals in the USA with latent tuberculosis [75]. Tb is a rare complication of MS treatments that impair cell-mediated immunity—alemtuzumab, teriflunomide, and cladribine [41]. In a pivotal trial of alemtuzumab, there were 3 cases of tuberculosis out of 972 treated patients [29]. Teriflunomide and cladribine affect lymphocyte proliferation and have the potential to increase Tb reactivation [41]. In the clinical trial for cladribine, one patient died following the reactivation of latent tuberculosis [10]. Two cases of Tb were reported in clinical trials of teriflunomide [76, 77], but no additional cases were recorded during the long-term follow-up study [78]. Screening for latent tuberculosis is recommended before initiation of alemtuzumab, teriflunomide, and cladribine [21, 32, 79]. Patients with positive tests should be referred to an infectious disease specialist for evaluation and treatment with anti-Tb therapy. [80, 81]. Of note, treatment with DMF may potentially interfere with interferon-gamma release assay (IGRA), leading to false-negative or indeterminate results by decreasing IFN- γ production [82, 83].

Other Infectious Complications Associated with Anti-CD20 Therapies

MS patients treated with rituximab experience a higher rate of common respiratory and urinary infection compared to patients on interferons, glatiramer acetate, fingolimod, and natalizumab [48]. Rituximab is widely used off-label for MS and has a similar mechanism of action as ocrelizumab and ofatumumab, which are both FDA-approved for MS. Ocrelizumab was associated with an increased incidence of upper respiratory infections and nasopharyngitis in phase 3 trials compared to interferon- β or no treatment [46, 84]. The newest anti-

Table 2 Risk mitigation strategies available for commonly used disease-modifying therapies

Key modifiable infectious risks	Screening and patient selection	Vaccination	Prophylaxis	On therapy monitoring	DMT dose and frequency adjustment	Behavioral modifications	Disease-modifying therapy at risk
Hepatitis B	Hep B Core Ab, Hep B S Ag; avoid use in very disabled patients	Hepatitis B vaccination	Concomitant antiviral therapy in those infected with hepatitis B	None, unless there is suspicion for exposure	None	Minimizing risk factors for hepatitis B exposure	Anti-CD20*, cladribine. Reasonable to check with SIPs**, natalizumab, and alemtuzumab.
Hepatitis C	Hep C Ab	None	No established guidelines—recommend expert consultation	None	None	Minimizing risk factors for hepatitis C exposure	Cladribine. Reasonable to check with alemtuzumab
Herpes Viruses	Varicella immunity	Varicella, shingles vaccines are available	None for SIPs. Acyclovir with use of alemtuzumab and cladribine	None	May decrease dose frequency to lessen lymphopenia	None	SIP **, cladribine, alemtuzumab
JC Virus	JC virus antibody titer	None	None	JCV titer monitoring, MRI brain every 6 months	May extend dosing interval, especially in JC seropositive patients	None	Natalizumab
Tuberculosis	Quantiferon Gold	Not required	anti-Tb therapy	None	None	Minimizing exposures to tuberculosis (e.g., travel to endemic regions)	Alemtuzumab, teriflunomide, cladribine
HIV	HIV serologic testing	None available	Anti-retroviral medications, recommend expert consultation, consider use of pre-exposure prophylaxis in those at high risk of HIV infection	None	None	Minimize behavioral risks of HIV exposure	Cladribine, alemtuzumab
Listeria	None	None	Listeria diet, consider cotrimoxazole	None	None	Listeria diet	Alemtuzumab
HPV	Ensure age-appropriate cervical cancer screening.	HPV vaccination available	None	Age-appropriate cervical cancer screening	None	Use of condoms, minimizing number of sexual partners	Alemtuzumab

* includes rituximab, ocrelizumab, and ofatumumab. **includes fingolimod, siponimod, and ozanimod. DMT disease-modifying therapy, HIV human immunodeficiency virus, HPV human papilloma virus

CD20 agent for MS, ofatumumab, was not associated with a higher rate of infections compared to the triflunomide in clinical trials [85], but its long-term profile remains to be determined. Non-ambulatory patients on rituximab had a sixfold higher risk of infection compared to ambulatory patients in a retrospective study [86]. Therefore, caution is advised when prescribing anti-CD20 therapy for significantly disabled individuals, especially as benefits for this patient subset are not well-established. A similar precaution likely applies to ocrelizumab as well.

Long-term rituximab and ocrelizumab use can cause hypogammaglobulinemia [86, 87] and, less commonly, lymphopenia and neutropenia, which are risk factors for severe infections [86, 88–92]. Therefore, baseline blood cell counts with differential and immunoglobulin levels should be checked before starting anti-CD20 therapy and at regular intervals thereafter [19]. In those with serious or recurrent infections in the setting of hypogammaglobulinemia, intravenous immune globulin may be used off-label to reduce infection risk [93, 94]. Another potential strategy to decrease the risk of infection is to extend the interval between infusions [95]. Retrospective data suggest that that stopping anti-CD20 for up to a year does not lead to MS reactivation, as may be the case with natalizumab and S1P modulators, and is associated with a very low risk of disease activity [95].

Other Infectious Complications Associated with Alemtuzumab

Alemtuzumab presents some unique risk mitigation challenges. Up to 5% of women treated with alemtuzumab developed cervical dysplasia [96], a pre-neoplastic condition that is almost invariably associated with human papillomavirus (HPV) infections [97]. Therefore, a recent consensus statement recommends HPV screening [98] and vaccination [99] in women who are starting alemtuzumab [100]. Listeria is another potential complication of alemtuzumab therapy which occurs within 1 month of infusion. It is therefore recommended that patients maintain dietary precautions for listeria [101] from 2 weeks before to at least 1 month after alemtuzumab infusion [102–104]. Alternatively, patients can take listeria antibiotic prophylaxis (cotrimoxazole) for 1 month after the last infusion [103]. There have also been reports of *Pneumocystis jirovecii* (PCP) infection on alemtuzumab [103, 105, 106] during the post-marketing period. Trimethoprim-sulfamethoxazole is used in the setting of alemtuzumab for oncologic conditions for PCP prophylaxis [106, 107], but no formal recommendations for PCP prevention have been put forth in MS.

Vaccinations: General Considerations

Vaccination is a key infection mitigation strategy in the general population and is perhaps more important for people on immunomodulatory and immunosuppressive therapies. Standard vaccine recommendations for healthy adults are summarized elsewhere [108]. Table 1 reviews vaccination timeline as they pertain to MS DMTs and specifies the DMTs for which live or attenuated vaccines are contraindicated. Effectiveness of vaccines appears to be maintained with interferon β , dimethyl fumarate, and natalizumab [109–114] but is reduced in patients on anti-CD20 and S1P modulating therapies [40, 115]. Therefore, if vaccination will not unduly delay treatment, patients should receive vaccinations before starting anti-CD20 and S1P modulators. If patients are already on anti-CD20 and S1P modulators, they should still receive routine vaccinations, as long as they are not live vaccines.

Conclusions

The introduction of newer, more efficacious DMTs into clinical practice has led to better disease control for most people with MS. Because the newer therapies carry specific infectious risks, it is important to understand which strategies can mitigate these risks. In this review, we provide a comprehensive framework for risk mitigation strategies as they apply to the newer MS DMTs. These recommendations are summarized in Table 2. By appropriately screening and selecting patients before starting a DMT; offering vaccinations relevant to specific DMTs; judicious use of antimicrobial prophylaxis in selected patients; implementing laboratory and MRI monitoring while on therapy; adjusting DMT dose and frequency, when appropriate; and educating patients about behavioral modifications that reduce infectious risk, the safety of the newer DMTs will be optimized.

Compliance with Ethical Standards

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Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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