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COVID-19 and MS disease-modifying therapies

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Abstract

Objective

To address concerns regarding the effect of MS disease-modifying therapies (DMTs) on the expression of coronavirus 2019 (COVID-19).

Methods

Review of the current state of knowledge regarding the viral etiology of COVID-19, mechanisms of injury by SARS-CoV-2 infection, and the effect of individual DMTs on the risk of infection and COVID-19 disease expression.

Results

Although data are limited, MS DMTs do not obviously increase the risk of acquiring symptomatic SARS-CoV-2 infection. The severe morbidity and mortality of SARS-CoV-2 appear to be largely the consequence of an overly robust immune response rather than the consequence of unchecked viral replication. The effects of specific MS DMTs on the immune response that may increase the risk of impaired viral clearance and their potential counterbalancing beneficial effects on the development of COVID-19–associated acute respiratory distress syndrome are reviewed.

Conclusion

Although there is currently insufficient real-world experience to definitively answer the question of the effect of a specific MS DMT on COVID-19, registries presently in nascent form should provide these answers. This review provides an approach to addressing these concerns while the data are being accumulated. Early insights suggest that the risk of infection and associated morbidity of COVID-19 in this population is little different than that of the population at large.

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Glossary

ARDS = acute respiratory distress syndrome; **COVID-19** = coronavirus 2019; **CTL** = cytotoxic T lymphocyte; **DMT** = disease-modifying therapy; **JCV** = JC virus; **NK** = natural killer; **PML** = progressive multifocal leukoencephalopathy; **SARS** = severe acute respiratory syndrome.

The dangers in life are infinite, and among them is safety.[1]
Johann Wolfgang Goethe, German poet, novelist, and scientist (1749–1832)

In the treatment of MS, choosing the appropriate disease-modifying therapy (DMT) requires a balance between the benefits of the agent in suppressing disease activity and preventing progression and the risks associated with its administration, chiefly the potential for infectious disease that arises from the immunosuppressive or immunomodulatory effects. MS DMT use during the current coronavirus 2019 (COVID-19) pandemic has sparked growing concern among patients with MS and physicians alike.

The calculation regarding DMT risk in the face of COVID-19 can be distilled to the following: "risk of active disease consequent to DMT discontinuation relative to the risk of acquiring the infection and the risks of developing more aggressive COVID-19 once infection is acquired while on DMT, particularly the potentially life-threatening acute respiratory distress syndrome (ARDS) requiring ICU care and ventilatory support". Few elements of this equation are truly quantifiable with available data. However, knowledge of clinical prognostic factors and risks for rebound MS activity with DMT discontinuation[2–5] should be considered and melded with insights into COVID-19 pathophysiology and the biology of its causative virus, SARS-CoV-2.

With respect to acquisition of the SARS-CoV-2 virus, the risk to individuals with MS who are not on DMT is likely similar to that of the general population. Viral infection is dependent on exposure, which may be difficult to avoid, as it spreads through communities, especially as carriers may be asymptomatic yet infectious. Whether treatment of patients with MS with a given DMT confers an increased risk of becoming infected with the virus and whether it affects the risk of developing severe COVID-19 complications are currently unknown.

Importantly, severe SARS-CoV-2–mediated disease, including ARDS, appears to be the consequence of a robust and dysregulated immune response rather than an immune-deficient state with unchecked viral replication.[6,7] This observation parallels that noted with the related virus, SARS-CoV-1, in which the severe acute respiratory syndrome (SARS) appeared to be mediated by a massive proinflammatory response in infected lungs with an elaboration of cytokines and chemokines and recruitment of inflammatory cells leading to tissue damage, vascular leakage, and pulmonary fibrosis,[8] in addition to complement activation.[9]

In this review, we attempt to combine the known risk of infectious diseases with the various DMTs and their mechanism of action with emerging knowledge of the virus to provide a framework to address the effect of DMTs on the morbidity and mortality of COVID-19 in treated patients with MS.

Potential risks of COVID-19 to patients with MS

First, as with any infectious disease, there is a theoretical possibility that this pandemic virus may exacerbate MS disease activity[10] regardless of DMT use. Second, many DMTs confer their benefit in MS by limiting aspects of the immune response, which could, in theory, allow for greater viral replication and potentially worse infection.[11] This same DMT effect may actually be beneficial by limiting the overly aggressive immune response occasioned by SARS-CoV-2 infection, which is thought to underlie its severe complications. Third, a substantial number of individuals with MS are older than 60 years, a population with a demonstrated increased risk of severe morbidity and mortality from COVID-19.[12,13] Estimates indicate that up to 14% of persons with MS are aged ≥65 years[14] often with comorbidities, such as cardiac and respiratory disease, that are now known in the general population to magnify the mortality risk of this infection.[13] Whether the increased mortality in older patients with COVID-19 reflects impaired regulation of immune responses and whether this may be accentuated in patients with MS with some immune regulatory deficits remain unknown.

The pathogen for COVID-19, SARS-CoV-2

Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. Coronaviruses are named for their appearance by electron microscopy, resembling a crown created by viral spike peplomers. This group of viruses is a well-known cause of respiratory diseases (e.g., the common cold) as well as SARS and Middle East respiratory syndrome. The coronavirus responsible for COVID-19 appears to have crossed from an animal to humans in the markets of Wuhan, China, where the disease was first recognized toward the end of 2019. The viral genome is 29,903 bases long with 96% homology with bat coronavirus, indicating that it may have originated as a bat virus with an intermediate host in another animal.[15] Like SARS-CoV-1, SARS-CoV-2 uses its spike proteins to attach to

angiotensin-converting enzyme receptor type 2 expressed on cells of the respiratory tract[15] in addition to other tissues, including the brain.[16]

As of April 13, 2020, there were nearly 2,000,000 confirmed COVID-19 infections worldwide, with more than 115,000 deaths and 185 countries of 192 in the world affected.[17] The United States leads the world with more than one half million infected persons.[17] Current estimates of the prevalence of MS in the United States indicate that there are more than 1,000,000 people with MS.[18] To date, to our knowledge, there are no publications of the effect of COVID-19 on MS and none on the effects of DMTs on the course of the COVID-19.

At the time of presentation, COVID-19 is clinically indistinguishable from the flu with fever in up to 90%, cough in approximately 70%, myalgia and fatigue in about 50%,[15] headache in 8%,[15] and diarrhea in less than 5%.[19] Anosmia and ageusia may be heralding manifestations.[20] Symptoms develop after a median incubation period of 4 days.[19] Most patients are diagnosed with pneumonia, and in 1 study from China, mechanical ventilation was required in 6.1% of patients,[19] although rates of ARDS as high as 29% have been reported. A study of 262 confirmed cases revealed that 17.6% had severe disease, whereas 73.3% were assessed as mild, 4.2% nonpneumonic, and 5.0% asymptomatic,[21] although widespread testing would likely reveal far higher numbers of asymptomatic or mildly symptomatic persons. Mortality rates by country have varied greatly,[22] but average about 3%.

Innate and adaptive immune responses to viral infections in general

Both innate and adaptive immune responses are important in blocking viral infection. Viral infection is prevented by type I interferons and natural killer (NK) cells as part of innate immunity. Recognition of viral RNA or DNA by Toll-like receptors located in the endosome activates pathways that lead to the release of type I interferons that inhibit viral replication in both infected and uninfected cells. NK cells, which are released from their baseline inhibited state by the absence of Class I major histocompatibility complex expression, are induced in virally infected cells and are able to kill these infected cells.[23]

With respect to the adaptive immune response to viral infection, there are 2 convergent paths combatting viral infection, namely, immunity generated by antibodies and that of cytotoxic T lymphocytes (CTL) that kill infected cells.[23] Neutralizing antibodies that have developed from prior infection or from vaccination are effective only when the virus remains extracellular before the infection of the cell or at the time of their release. CTLs, typically $CD8^+$ T lymphocytes, are responsible for eliminating viruses that reside within cells by recognizing viral peptides presented by Class I major histocompatibility complex molecules on dendritic cells that are either infected or have phagocytosed infected cells.

DMTs and the SARS-CoV-2 elicited cytokine storm

As morbidity and mortality in COVID-19 seem to be the consequences of an overwhelming immune response triggered by the virus, the immunomodulatory and immunosuppressive effects of some DMTs may actually be beneficial. Using SARS-CoV-1 infection as a model for SARS-CoV-2 infection, the chemokines and cytokines expressed include IL-1β, IL-2, IL-6, IL-10, G-CSF, MCP1, MIP1A, TNFα, and CCL2.[12,24,25] These and other cytokines and chemokines recruit neutrophils and cytotoxic T cells, leading to tissue damage. This immune response leads to permanent pulmonary injury.[26] The effects of DMTs on the expression of these chemokines and cytokines and their ability to block trafficking of inflammatory cells into the lung are largely unknown, but where possible, comment on the effect of each will be included herein.

The potential effects of DMTs on immune responses to SARS-CoV-2 infection

The approved MS DMTs, for the most part, preferentially target the adaptive rather than the innate immune system. Consequently, the innate immune system's interferon type I response to infection and the clearance of viral-infected cells by NK cells are less likely to be affected in the patient with MS, regardless of treatment. It is their effect on adaptive immunity of DMTs that could potentially increase the risks associated with COVID-19. As a novel virus, most humans would not be expected to harbor preexisting antibodies to SARS-CoV-2, and whether antibodies to related coronaviruses cross-react and provide some protection remains uncertain. On the other hand, many DMTs have a potential to reduce the CTL response to viruses, which, in part, explains an increased risk of developing certain infections, e.g., recrudescent herpes infections and progressive multifocal leukoencephalopathy (PML), in patients treated with certain MS DMTs. In this review, the DMTs will be systematically evaluated for l risk of magnifying COVID-19 infection and recommendations made regarding management of patients with MS during this pandemic.

Interferon-β (Avonex, Betaseron, Extavia, Plegridy, and Rebif)

Interferon-βs belong to the type I interferons and should theoretically be protective for COVID-19, given their antiviral properties.[27,28] Interferon-β may be protective against respiratory viruses,[29] and of all the DMTs, interferon-β and glatiramer acetate are associated with the lowest risk of infections.[30] One study in an MS population showed a salutary effect of interferon-β on human herpes virus type 6 compared with control groups.[30,31] Similarly, 1 study found that JC virus (JCV) DNA was detected less frequently in the blood of interferon-β–treated patients[32]; however, another study found no effect of interferons on urinary JCV excretion.[33] On rare

occasions, leukopenia and lymphopenia may occur with interferon-β,[34] which could increase the morbidity of SARS-CoV-2 infection, but in their absence, there is low concern with respect to interferon-β administration in MS during the COVID-19 pandemic.

Following administration for 6 months, interferon-βs downregulate both pro- and anti-inflammatory cytokines.[35] A decrease in several of the cytokines found to be elevated with COVID-19, including IL-1β, IL-6, and TNFα, has been demonstrated within 24–48 hours of injection.[36] It has been demonstrated to prevent cytokine-induced neutrophil infiltration in a stroke model,[37] but the role in lung and other organ injury remains unknown. Together, these effects would suggest that the use of IFN-β need not be a concern in the context of COVID-19 and may even confer some benefits, although direct data are lacking.

Glatiramer acetate (Copaxone and Glatopa)

Glatiramer acetate has been proposed to shift a proinflammatory to an anti-inflammatory responses with respect to both T helper cells (Th1 to Th2)[38] and macrophages (M1 to M2).[39,40] There appears to be no significant deleterious effect on immune surveillance or the defense against infectious disease, and there are no suppressive effects on NK cells, $CD4^+$ or $CD8^+$ lymphocytes.[e1] (links.lww.com/NXI/A258) There is no evidence of enhanced infectious risk during treatment with glatiramer acetate.[30]

The shift from a Th1 (proinflammatory) to a Th2 response with glatiramer acetate[e2] could be beneficial in COVID-19. Furthermore, glatiramer acetate has been shown to block IFNγ-mediated activation of macrophages,[e3] which are thought to be essential for the development of COVID-19 ARDS.[e4]

Dimethyl fumarate (Tecfidera)

The therapeutic mechanisms of action of dimethyl fumarate in MS remain incompletely elucidated and may be mediated by both nuclear factor erythroid-derived 2–related factor (Nrf2)-dependent and independent pathways.[e5] DMF treatment results in a degree of lymphocyte losses ($CD8^+$ T cells more so than $CD4^+$ T cells and memory more than naive T cells and B cells)[e6–e9] and anti-inflammatory modulation of B-cell responses.[e10] Pivotal phase 3 trials with DMF showed little difference in infection risk between active treatment and placebo, although grade 3 lymphopenia (499–200 cells) was observed in 5%–7% of treated patients.[e11,e12] Although there appears to be no association between overall infection and the degree of lymphopenia in DMF-treated patients,[e11], the occurrence of PML with DMF has largely, although not exclusively, occurred with lymphocyte counts below 500 cells/mm^3 sustained for >6 months in JCV antibody index seropositive individuals.[11]

Dimethyl fumarate blocks proinflammatory cytokine production[e13] and can inhibit macrophage function in vitro, thereby suppressing inflammation.[e14] Furthermore, DMF has been demonstrated to ameliorate lung fibrosis in pulmonary arterial hypertension.[e15] Despite the potential of an increased risk of infection, dimethyl fumarate's immune modulatory action is not likely to be harmful and may even be beneficial in the context of COVID-19.

Teriflunomide (Aubagio)

Teriflunomide, an active metabolite of leflunomide, selectively and reversibly inhibits pyrimidine de novo synthesis by blocking the mitochondrial enzyme dihydroorotate dehydrogenase. This inhibition results in a reduced proliferation of activated T and B lymphocytes by interrupting the S phase of the cell cycle.[e16,e17] Clinical trials with teriflunomide in MS reveal a mean decrease of leukocyte counts of about 15% from baseline.[e18–e20] Long-term follow-up of patients on teriflunomide revealed that upper respiratory tract infections and influenza were among the more commonly reported infections;[e21] however, there was no overall increased risk of serious infection or resultant increased morbidity or mortality with teriflunomide compared with placebo.[e22] Despite the decrease in activated lymphocytes and associated mild lymphopenia, infection risk (apart from tuberculosis) appears low, suggesting a limited effect on innate and adaptive immune response to infectious pathogens.[e23] Furthermore, there is evidence that leflunomide and teriflunomide possess antiviral activity for some viruses.[e24–26]

Literature on the effects of teriflunomide on cytokines and activated macrophages is sparse; however, it is the active metabolite of leflunomide, which downregulates IL-1, IL-6, and TNFα from activated macrophages in some tissues.[e27,28] Caution may be warranted as leflunomide-induced interstitial lung disease has been reported,[e29] and there is at least 1 case report of leflunomide initiating a macrophage activation syndrome in a patient with rheumatoid arthritis.[e30]

S1P modulators (fingolimod [Gilenya], siponimod [Mayzent], and ozanimod [Zeposia])

Fingolimod, siponimod, and ozanimod are sphingosine receptor (S1PR) modulators, which limit lymphocyte egress from lymph nodes, thereby preventing recirculation of peripheral lymphocytes thought to limit trafficking of pathologic immune cells to the CNS. All S1PR modulators reduce the total mean circulating lymphocyte count by preferentially sequestering the naive and central memory lymphocytes rather than effector memory T cells.[e31,e32] Phase 3 trials of fingolimod revealed an average reduction of the peripheral lymphocyte count by 73% from baseline within 1 month and conferred an increased risk of mild infections, mainly involving the lower respiratory tract (bronchitis and pneumonia).[e33] In addition, herpes virus infections were more common with fingolimod and siponimod but possibly not ozanimod.[e33–36] The greater concern, although low, regarding infectious diseases with fingolimod has been for certain opportunistic infections including *Cryptococcus*, JCV, varicella zoster, and human papillomavirus. A large register-based cohort study from Sweden with data on 6,421 patients collected over 7 years indicated that the risk of infection

with fingolimod did not appear to be significantly higher than with platform therapies when adjusted for confounders, e.g., age, sex, and disability.[30] There is some concern for increased risk due to SARS-CoV-2 infection with S1P modulator treatment mainly because of sequestration of crucial lymphocyte populations, but also, possibly to a lesser degree, related to effects on pulmonary function[e37] (mild dose-dependent decreases in lung function and exhaled volumes in the first month after therapy initiation). The potential for aggressive rebound of MS activity with cessation of S1P modulator therapy should be balanced against any risk in the face of SARS-CoV-2.

Indeed, blunting of the immune response with an S1P modulator has been considered as a possible treatment of COVID-19–associated ARDS, and a clinical trial has been registered on the NIH website (clinicaltrials.gov/ct2/show/NCT04280588). The authors are aware of at least 1 anecdotal case from Italy that observed unanticipated improvement with fingolimod during COVID-19 and another case in which fingolimod was associated with the more severe COVID-19 ARDS outcome. Recruitment of monocytes and macrophages during inflammation is attributed more to effects through the S1PR3,[e38] raising the possibility that the different S1PR modulators that include the less selective fingolimod and the more (S1PR1 and S1PR5)-selective siponimod and ozanimod may differ in their potential salutary effects in COVID-19.

Cladribine (Mavenclad)

Oral cladribine is a purine nucleoside analog prodrug, which interferes with cellular metabolism, inhibits DNA synthesis and repair, and induces apoptosis preferentially in lymphocytes.[e39] This results in a rapid and persistent reduction in $CD4^+$ and $CD8^+$ T cells with a significant effect also on B cells and more minor and transient effects on innate immune cells such as neutrophils, monocytes, and NK cells.[e39,e40] Lymphopenia (most often mild to moderate) was an expected and common adverse event in both the initial phase III clinical trial and extension study with rare cases of severe neutropenia. One year after the initial dosing of cladribine, ≥grade 2 lymphopenia (<800 cells/μL) prohibited the scheduled retreatment in 8%.[e41] After both cycles of therapy, median absolute lymphocyte counts recover to normal and $CD19^+$ B cells to threshold values by week 84, although often at levels below baseline values.[e42] NK cells are transiently reduced after administration of cladribine.[e43] Overall risk of infection with cladribine was comparable to placebo except for higher rates of reactivated herpes virus infections in patients with grade 3 or 4 lymphopenia.[e44,e45] The incidence of infection was higher in patients with the lowest absolute lymphocyte count.[e44,e45] With respect to other infections, there was 1 fatal case of reactivation of latent tuberculosis in a cladribine-treated patient. Given the substantial and sustained effect on lymphocyte count, there is a theoretical concern for increased SARS-CoV-2 infection with oral cladribine, but the real-world experience suggests that infectious risk is low. The published literature presently precludes meaningful comment on the potential effects of cladribine on the immune mechanisms underlying COVID-19 ARDS.

Natalizumab (Tysabri)

Natalizumab, an α4β1 and α4β7 integrin inhibitor, blocks lymphocyte and other cell binding to the adhesion molecules, VCAM and MAdCAM, respectively. VCAM is chiefly expressed on brain endothelial microvasculature and MAdCAM on gut endothelial microvasculature; hence, natalizumab's beneficial effects on MS and inflammatory bowel disease. The impairment of neuroimmunosurveillance is, in large measure, responsible for the increased risk of PML with natalizumab.[e46,e47] The same effect on neuroimmunosurveillance may contribute to the rare occurrence of other opportunistic infections of the nervous system with natalizumab, chiefly, herpes virus infections.[e48–e54] Systemic opportunistic infections (*Pneumocystis carinii* pneumonia, pulmonary *Mycobacterium avium intracellulare*, and bronchopulmonary aspergillosis) have been observed in patients treated with natalizumab for Crohn disease in combination with other immunosuppressive therapy. Upper respiratory tract infections, bacterial pneumonias, and urinary tract infections have been associated with natalizumab use, although most trials reveal an infection risk no different than with placebo.[e55] A registry-based cohort study[30] found no significant increase in general risk of infection with natalizumab compared with platform therapies. Therefore, we do not believe that there is a significant increased risk of infection with SARS-CoV-2 in patients with MS treated with natalizumab.

Natalizumab has been associated with a marked reduction of inflammatory cytokines and chemokines in the CSF of patients with MS, as expected given the important role of VLA4 in immune cell adhesion to CNS barriers,[e56] Although VCAM expression can be induced in pulmonary endothelial cells stimulated by TNFα,[e57] the predominant adhesion molecules expressed on pulmonary endothelia are ICAM and PeCAM,[e58,e59] suggesting that natalizumab may not be particularly beneficial in preventing ARDS with COVID-19.

Anti-CD20 monoclonal antibodies (ocrelizumab [Ocrevus] and rituximab [Rituxan])

Rituximab[e60] and ocrelizumab[e61,e62] are anti-CD20 monoclonal antibodies that reduce B cells and demonstrate significant efficacy in limiting MS relapses. These monoclonal antibodies reduce proinflammatory B-cell cytokines,[e63] decrease the number of antigen producing cells,[e63] and have an effect on a subset of CD20-expressing $CD4^+$ and $CD8^+$ T cells.[e64,e65] Although anti-CD20 treatment in patients with MS has been shown to reduce memory $CD8^+$ T cells targeting certain myelin epitopes, it had no effect on influenza epitopes.[e66] A significantly higher risk of infection was reported with rituximab compared with the platform therapies in the treatment of MS in Sweden,[30] and reactivation of hepatitis B may occur as reported in patients receiving rituximab for malignancy.[e67] In the phase III clinical trial of ocrelizumab for primary progressive MS, upper respiratory infections were more common (10.9%) with ocrelizumab vs 5.9% in the placebo group.[e68] Death from community-acquired pneumonia and aspiration pneumonia was noted in 1 patient from each

treatment group.[e68] The overall infection rates between ocrelizumab and placebo were fairly similar, 71.4% and 69.9%, respectively.[e68] Similarly, serious infections were not obviously overrepresented in the ocrelizumab group at 6.2% vs 5.9% in the placebo group.[e68] In the 2 phase III trials for relapsing-remitting MS, infection rates were only slightly higher with ocrelizumab compared with interferon β-1a (56.9% vs 54.3%, respectively, and 60.2% vs 52.5%, respectively).[e61]

As expected, ocrelizumab has been demonstrated to partially blunt antibody responses to vaccine including to influenza.[e69] As the SARS-CoV-2 infection is novel, a lessened antibody response would not be, in and of itself, expected to increase the risk of infection, nor would anti-CD20 monoclonal antibody therapy be expected to affect responses of the innate immune system, which are critical for initial viral control. With prolonged use, hypogammaglobulinemia may be observed, but is rarely associated with severe infection.[e70] It is unclear whether there will be an effect of anti-CD20 therapies on infection with SARS-CoV-2, but the lack of an increased risk with influenza is heartening. The effects of the anti-CD20 monoclonal antibodies on macrophage activation and the relevant cytokines for COVID-19–associated ARDS remain unknown.

Alemtuzumab (Lemtrada)

Alemtuzumab is a fully humanized IgG1 directed against CD52 that depletes both T and B lymphocytes by inducing antibody-dependent cellular cytotoxicity and complement dependent cytotoxicity and activating proapoptotic pathways on CD52-expressing cells. Following rapid depletion, recovery of total lymphocyte counts to lower limit of normal range averaged 12.7 months (range of 8.8–18.2 months), with B cells 7.1 months (range of 5.3–9.5 months) and $CD8^+$ and $CD4^+$ T cells 20 and 35 months, respectively.[e71] Treatment results in substantial and prolonged lymphopenia requiring prophylaxis against herpes virus and PCP for 2 months after therapy or until CD4 T-cell counts equal or exceed 200 cells/μL.[e55] As with the anti-CD20 monoclonal antibodies, reactivation of chronic hepatitis B infection may occur. The incidence of infection is highest after the first treatment ranging from 56.1% to 63.2% in the pivotal studies; however, the rate of serious infection was <3%.[e72] Herpes simplex was the most common infection observed, followed by varicella zoster.[e72] In light of the known significant infectious risks with alemtuzumab, we believe that there may be a higher risk of SARS-CoV-2 infection following treatment with alemtuzumab (particularly in the first 2 years following treatment). The effects of alemtuzumab on macrophage activation and the relevant cytokines for COVID-19 ARDS remain unknown.

Conclusion

To date, there are no conclusive data regarding the effect of DMTs on the frequency and course of SARS-CoV-2 including the serious COVID-19 complications including ARDS. As noted on the National Multiple Sclerosis Society website, many individuals and organizations have made recommendations regarding DMTs and COVID-19, which are at times conflicting and may cause confusion.[e73] This review was created to provide some relevant background that may help guide considerations around DMT use during this uncertain time. The accompanying table compiles DMT information including presumed mechanism and duration of action, known effects on innate and adaptive immunity, salient infection risks, and our current assessment of DMT risk on COVID-19 (table). More data are emerging, including through the institution of organized registries,[e74] which should provide greater evidence-based insights moving forward.

Reassuringly, initial anecdotal reports suggest that patients with MS, including those on commonly used DMTs, are at no higher risk of contracting symptomatic SARS-CoV-2 viral infection, nor at a higher risk of severe COVID-19 complications, compared with the population at large. There are theoretical reasons to consider that several MS DMTs might even have a mitigating effect with respect to the development of COVID-19 ARDS.

In general, and in keeping with the Institute for Multiple Sclerosis Research (IMSF) report, we recommend that most patients with MS continue on their DMT, particularly those on platform therapy for whom the risk of SARS-CoV-2 infection and COVID-19 is minimal.[e75] Providers will have to tailor decisions to individual patients, particularly for patients with an increased risk of either acquiring infection (e.g., health care workers) or for the more serious COVID-19 complications (e.g., the elderly, those with relevant medical comorbidities). For those on DMT deemed to be possibly higher risk but with infrequent dosing (alemtuzumab and cladribine), there may be no option except for aggressive risk mitigation strategies such as social isolation and frequent hand washing. For anti-CD20 therapies, there remains an option to delay infusion and monitor B-cell counts. The risks of stopping or delaying DMT must be balanced against the risk of reemergence and even rebound of MS activity after cessation, as has been reported with fingolimod[3,e76] and natalizumab.[4,5,e77]

Challenging decisions will need to be made for patients with newly diagnosed MS and need for DMT initiation, particularly those who appear to have active/aggressive disease. Even without a high index of concern for several of the commonly used DMTS, clinicians should inform patients of the possible risk of initiating these treatments during the COVID-19 pandemic. For those with highly active MS, use of natalizumab can be considered, given its rapid onset of action and relative safety in the short term with respect to infections. For those who are JCV antibody seropositive and thus at an increased risk of PML with prolonged natalizumab use, this strategy should be used merely as a bridge to alternate therapies that are thought to pose higher or uncertain risk with respect to SARS-CoV-2 infection. For patients with slowly progressive disease and little evidence for recent inflammatory activity (clinical relapses or radiographic activity), it is reasonable to consider postponement

Table DMTs and risk of COVID-19

Agent	MOA[e16]	Risk of infectious disease	Potential beneficial effect by limiting immune responses mediating severe COVID-19 complication (e.g., ARDS)	Predicted potential to increase the risk of severe COVID-19 complication (e.g., ARDS)
Interferon β-1a and β-1b	Decreases immune cell activation through IFN receptor binding; decreased trafficking	No increased risk of infection[11]	Downregulation of proinflammatory cytokines[35]	None
Glatiramer acetate	Promotes Th1→Th2 shift; induces suppressor T cells and anti-inflammatory myeloid cells	No increased risk of infection[11]	Shift from Th1 and M1 (proinflammatory) to Th2 and M2 (anti-inflammatory)	None
Dimethyl fumarate	Promotes Th1-Th2 shift; induces mild apoptosis of memory T cells and B cells; neuroprotective effect by upregulation of Nrf2-dependent antioxidant response	Potential risk of PML[11]	Block proinflammatory cytokine production[e13] and inhibit macrophage function[e14]	Probably low
Teriflunomide	Inhibits proliferation of activated T and B lymphocytes by inhibiting DHODH	Potential reactivation of tuberculosis[11]	Downregulation of IL-1, IL-6, and TNFα from activated macrophage[e27,e28]	Probably low
S1P modulators	Prevent lymphocyte egress from lymph nodes by binding S1P receptor	Potential increased risk of some opportunistic infections (PML, *Cryptococcus*, VZV, and HPV); slight increased risk of lower respiratory infections[e33]	Block recruitment of monocytes and macrophages via S1P3 receptor modulation[e38] (only with nonspecific S1P modulator)	Probably low
Cladribine	Sustained reduction of T and B cells by interfering with DNA synthesis and repair	Slight increased risk of herpes infections with grade 3 or 4 lymphopenia[e44,e45]	Uncertain, main effects on lymphocytes	Probably low
Natalizumab	Prevents entry of T cells and others into the brain	Potential risk of PML[11]	Uncertain, probably none	Probably low
Anti-CD20 monoclonal antibodies	Binds CD20 resulting in B-cell cytotoxicity	Potential increased risk of URIs[e68]; reactivation of chronic hepatitis B	Uncertain; main effects on B cells/de novo plasmablasts	Probably low
Alemtuzumab	Depletes B and T cells by binding to CD52	Reactivated herpes infection (HSV and VZV)[e72,e78]; listeria[e79]; HPV[e78]	Uncertain	Probably low except during the first months after infusion[e80]

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus 2019; DHODH = dihydroorotate dehydrogenase; DMT = disease-modifying therapy; HPV = human papillomavirus; PML = progressive multifocal leukoencephalopathy; URI = upper respiratory infection; VZV = varicella zoster virus.

of DMT. Last, it is important to ensure that usual safety monitoring of these DMTs continues to diminish risks (e.g., lymphocyte monitoring) while considering the risk of exposing patients to the health care system for laboratory and radiographic screening.

MS care has become increasingly complex, particularly with the availability of many effective therapies that carry with them additional risks, requiring closer monitoring and risk mitigation strategies. DMT decisions typically require a thoughtful consideration of such risks and benefits, and joint decision making between the patient and the provider is paramount. The unclear effect of DMTs on SARS-CoV-2 infection and the serious COVID-19 complications poses a unique challenge to our field, but practice can be guided by current knowledge of DMTs and emerging data from other parts of the world.

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Rachel Brandstadter, MD	Division of Multiple Sclerosis, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Interpretation of data and drafting and revision of the manuscript

Continued

Appendix *(continued)*

Name	Location	Contribution
Amit Bar-Or, MD	Division of Multiple Sclerosis, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Interpretation of data and drafting and revision of the manuscript

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