



Potential Risks and Benefits of Multiple Sclerosis Immune Therapies in the COVID-19 Era: Clinical and Immunological Perspectives

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Abstract

Coronavirus SARS-CoV2 has emerged as one of the greatest infectious disease health challenges in a century. Patients with multiple sclerosis (MS) have a particular vulnerability to infections through their use of immunosuppressive disease-modifying therapies (DMTs). Specific DMTs pose particular risk based on their mechanisms of action (MOA). As a result, patients require individualized approaches to starting new treatments and continuation of therapy. Additionally, vaccinations must be considered carefully, and individuals on long-term B cell-depleting therapies may have diminished immune responses to vaccination, based on preserved T cells and diminished but present antibody titers to influenza vaccines. We review the immunology behind these treatments and their impact on COVID-19, as well as the current recommendations for best practices for use of DMTs in patients with MS.

Key Words Multiple sclerosis · SARS-CoV2 · disease-modifying therapy · vaccination · COVID-19 · immunology

Introduction

In November 2019, the world community was exposed to one of the most challenging infectious diseases in a generation—COVID-19 caused by coronavirus SARS-CoV-2 [1]. Patients with multiple sclerosis (MS) were immediately recognized as a vulnerable population due to the unique combination of immunosuppressive therapies they require. Given the high infectivity rates and incidence of SARS-CoV-2, practitioners were suddenly faced with difficult questions about continuation or interruption of therapy. The prevailing concern has been that immunosuppression through DMT usage increases the risk of infection. On the other hand, some of these treatments may be unexpectedly protective by limiting the effects of auto-inflammation and the cytokine storm seen in severe COVID-19 cases.

Clinical Considerations

Treatment Risks

Initial smaller studies suggested neither an increase in risk of infection nor an increased rate of hospitalization for patients with MS [2]. Case reports of small numbers of subjects treated with dimethyl fumarate [3] or teriflunomide [4, 5] described good outcomes and even hypothesized potentially protective roles for these treatments based on their mechanisms of action. Case reports on fingolimod [5–7] and ocrelizumab or rituximab [8–10] initially appeared to be reassuring as well.

However, although overall disease-modifying therapies appear relatively safe in aggregate [2, 11, 12], there may be concerns related to individual strategies based on newer data. For example, patients on B cell-depleting therapies, such as rituximab, ocrelizumab, and alemtuzumab, may not be as adept at developing protective IgM and IgG antibodies [13–15] and are thus at higher risk of infection [11]. Case studies have demonstrated those infected with SARS-CoV-2 while on B cell-depleting therapies can, nevertheless, recover despite the illness, affirming that innate and/or cell-mediated protective mechanisms against the virus remain viable [16–18]. However, more recent worldwide data have indicated an increased risk of serious infections for patients on these therapies [19, 20]. These concerns include higher rates of hospital

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admissions, intensive care unit admissions, and requirements for mechanical ventilation, but not death, possibly more so for rituximab compared to ocrelizumab [21]. These findings did not appear to be affected by the duration of therapy for ocrelizumab in post-marketing data [22]. An excellent article by Baker et al. [23] reviews B cell therapies in greater detail. Furthermore, a large European prospective cohort study (RADAR-CNS) identified a trend for increased risk of SARS-CoV-2 infection in those on alemtuzumab or cladribine, though these agents did not appear to affect infection severity [24].

Currently, studies are underway collecting data on greater numbers of patients with SARS CoV-2 infection. These cohorts are not yet large enough to make specific conclusions for patients with MS. Notably, the MS population is significantly different from the general population in that they are more likely to have comorbid health issues, including those already identified to put people at risk, such as diabetes, cardiopulmonary disease, and obesity [25]. Interestingly, some studies have suggested that those not on MS therapy may be at higher risk of severe illness from SARS CoV-2 [22, 25], though this may be driven by older patients who are less likely to be on treatment or other confounding factors. Furthermore, risks for worse outcomes appear to be not limited only to relapsing MS patients, but also to those with progressive forms of the disease [19].

Despite reasonable concerns, most practitioners generally do not recommend discontinuation of immunomodulatory therapy [26]. The decision to start MS therapy is not made lightly and, therefore, neither is the decision to continue. Patients who self-discontinue, may in certain instances put themselves at risk of disease rebound, namely with natalizumab or fingolimod [26]. In general, the injectable therapies, glatiramer acetate and the beta-interferons, as well as teriflunomide, dimethyl fumarate, and prednisone formulations, are not believed to increase the risk of immunosuppression significantly. Treatments with a mildly elevated risk include fingolimod, natalizumab, ocrelizumab, and rituximab. More careful consideration should be taken for employing higher potency therapies such as cladribine and alemtuzumab [26]. While these may be maintained, they ought not to be initiated during the pandemic. In fact, the risk for viral infection may be higher at the 3- to 6-month timeframe after starting cladribine or alemtuzumab [27].

Several studies have even suggested that immunomodulatory/immunosuppressive therapies may in fact be protective against the hyper-inflammatory phase of SARS-CoV-2 infection by preventing the release of pro-inflammatory cytokines or B cell activity [17] [27]. This may be particularly true for agents such as fingolimod and siponimod, which work through the RhoA/actin pathway and reduce recruitment of macrophages to pulmonary tissue [28].

One must also balance the risk of hospitalization for an MS relapse due to withdrawing therapy with the risk of exposure to SARS-CoV-2 from attending infusion centers or any monitoring required therewith for surveillance [29]. Fortunately, some infusions can be given at patients' homes, and more exceptions or modifications have been allowed during the pandemic by companies offering infusions for treatments traditionally limited to infusion centers. While posing a higher risk, medications with infrequent delivery, such as the B cell-depleting therapies given on average every 6 months, still present a favorable option. Ofatumumab offers a novel alternative for B cell depletion through monthly subcutaneous injections. The need for frequent monitoring with alemtuzumab, an anti-CD52 therapy administered intravenously, on the other hand, may be an excessive burden.

Treatment Modifications

Current strategies among practitioners include extending the time interval between infusion-based treatments when possible [30]. For example, every 4-week dosing of natalizumab can be extended to every 6-week dosing, based on data suggesting decreased risks of developing progressive multifocal leukoencephalopathy but similar rates of efficacy [31, 32]. And the second alemtuzumab treatment, normally given at 12 months, may be delayed up to 18 months [33]. One may consider switching to another disease-modifying therapy instead of proceeding to subsequent rounds of treatment with alemtuzumab or cladribine following induction. Ocrelizumab and rituximab infusions may also be delayed for certain patients based on serial monthly CD20/CD19 counts [34], although this must be weighed against the risk of exposure to SARS-CoV-2 from having more frequent phlebotomies. In many instances, B cell-depleting therapies provide therapeutic immunosuppression far longer than the standard 6 months, potentially as long as 12 months or more.

Corticosteroids are also generally believed to reduce the robustness of the immune response, and increase the chances of developing an infection in individuals on long-term immunosuppressive therapy [35]. However, in cases of severe SARS-CoV-2 infection, notably with an excessive auto-inflammatory response, well-timed and judicious use of low-dose therapy may be beneficial, possibly also in treating individuals with severe respiratory disease requiring oxygen or mechanical ventilation [36–38]. Nevertheless, IVIg and plasma exchange stand as viable alternatives for treatment of an MS relapse to avoid the immunosuppressive effects of steroids.

In terms of the risk of MS therapies during this pandemic from least to most favorable, the following ranking should be considered: alemtuzumab–cladribine–ocrelizumab/rituximab–fingolimod—and then all others [39] (see Table 1). Thakolwiboon et al. [40] summarize recommendations by

European neurological associations based on risk and mechanism of action. In individuals with active COVID-19, it is advised to defer therapy until symptoms abate [40]. This may not be necessary for the platform therapies, namely glatiramer acetate or interferon, especially for the latter which may have protective properties [19]. These speculations remain hypothetical, however, as little confirmatory data is available comparing continued versus deferred therapy during hospitalization.

The Immune Response to SARS-CoV-2

SARS-CoV-2 is an enveloped single-stranded RNA virus capable of infecting cells in several human organs including the lung epithelium, gastrointestinal tract, heart, kidneys, and the central nervous system [41–43]. ACE-2 expressed on the surface of target cells is the binding receptor for the virus spike (S) protein [44, 45]. This binding results in ACE-2 cleavage from cell surfaces by ADAM metallopeptidase domain 17 (ADAM17). Reduction in ACE-2 levels increases angiotensin II levels leading to increased vascular permeability [46]. ADAM17 converts membrane IL-6 receptor to a soluble form (sIL-6Ra), which forms complexes with IL-6, resulting in the activation of STAT3 and the NF- κ B inflammatory pathway [47]. The invading virus then replicates intracellularly and is released and recognized by pattern recognition receptors (PRPs), Toll-like receptors (TLR), and others on dendritic cells resulting in the activation of innate immune responses. Dendritic cells and subsequently infiltrating macrophages [48, 49] release a myriad of proinflammatory molecules including interleukins, type-1 interferon, chemokines, TNF α , TGF β , and free radicals, which while fighting the virus can also overreact, resulting in a cytokine storm and multisystem organ failure (Fig. 1). The adaptive immune response also comes into play. Helper CD4+, cytotoxic CD8+, and NK cells are activated and play a role in limiting the infection [47].

Cytotoxic CD8+ cells directly kill virus-infected cells. Helper CD4+ cells activate B cells to produce anti-viral IgG and IgM which bind to the virus spike protein and along with complement components C1q,r,s and C3b play a role in opsonization and neutralization of the virus. On the other hand, activation of the lectin pathway through the binding of mannose-binding lectin (MBL) to the spike protein ultimately leads to the formation of the membrane attack complex (C5b-9) and tissue damage [50]. Notably, the virus can lead to immunosuppression by killing infected lymphocytes [51].

Chronic Immunomodulation/Immunosuppression and COVID-19

There are nine classes of FDA-approved therapies for MS and three therapies for neuromyelitis optica spectrum disorder (NMOSD) [52] (Table 2). In general, prior to initiating MS therapies, COVID-19 testing is recommended to exclude asymptomatic infection that may become symptomatic upon initiation of immune therapies. For acute MS exacerbations, short-term corticosteroids, IVIg, and plasma exchange are unlikely to increase significantly the risk of infection with SARS-CoV-2 [53]. Low-dose corticosteroid therapy may, in fact, be beneficial in acute respiratory distress syndrome (ARDS) secondary to COVID-19 [54].

In general, MS patients are not at higher risk for contracting COVID-19 as far as the disease itself is concerned, but they could be at higher risk for worse outcomes if exposed to the virus while on immunosuppressive therapy. As with other infections, patients may experience an MS relapse or a pseudo-relapse. COVID-19 course and outcome will also be influenced by the type of MS therapy the patient is receiving, whether the drug is immunomodulatory or immunosuppressive, and whether it has anti-viral effects such as interferon- β (IFN β) and possibly teriflunomide. In general,

Table 1 Stratification of MS disease modifying treatment plans during the COVID-19 pandemic

Medication	Risk	Currently receiving	New start
Interferon β	Lowest	Continue	Yes*
Glatiramer acetate	Lowest	Continue	Yes
Dimethyl or diroximel fumarate	Low	Continue	Yes
Teriflunomide	Low	Continue	Yes
Fingolimod/siponimod/ozanimod	Medium	Continue	Yes
Natalizumab	Medium	Extend to 6-week intervals	Yes
Rituximab/ocrelizumab/ofatumumab	Medium-high	Extend interval based on B cell counts	Yes
Cladribine	High	Delay/switch	No**
Alemtuzumab	High	Delay/switch	No
Hematopoietic stem cell therapy	High	Delay/switch	No

*Yes: treatment can be initiated; **No: postpone treatment

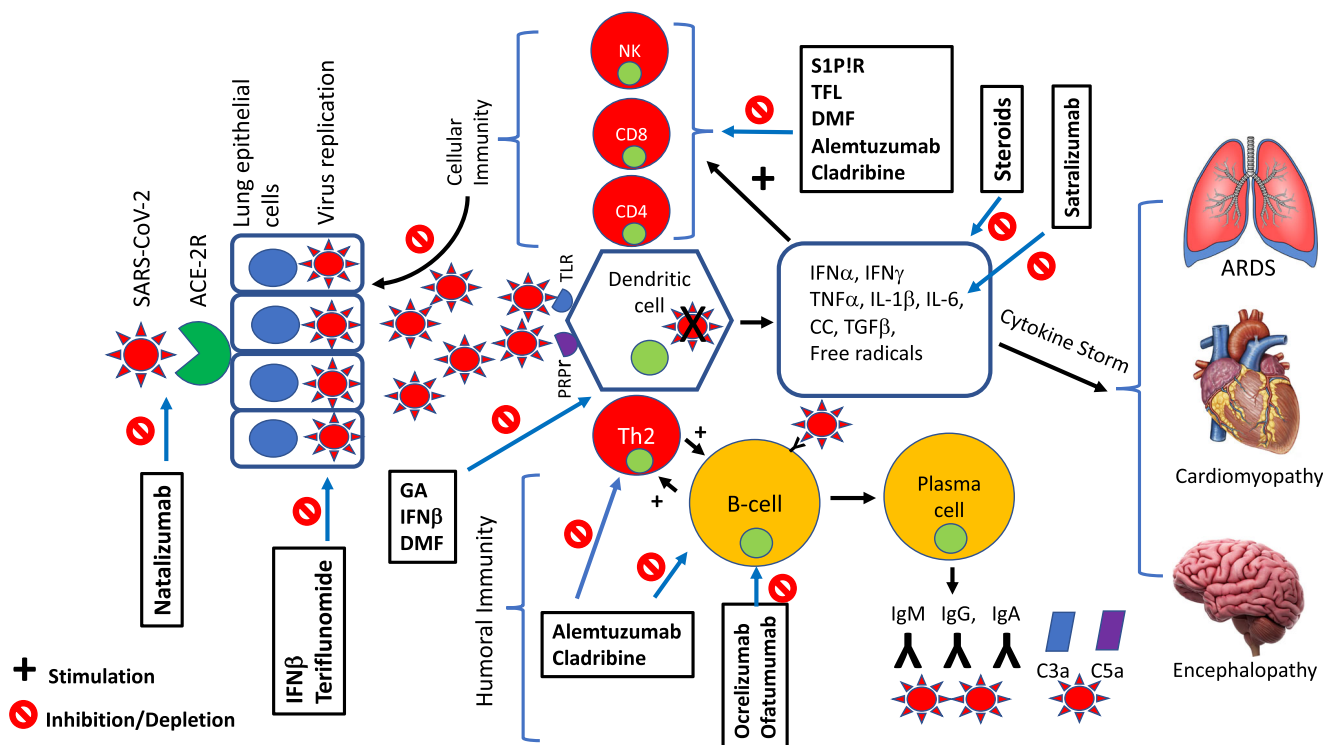


Fig. 1 The immune response to SARS-CoV-2 and potential sites of interaction with MS therapies. The virus binds to the angiotensin-converting enzyme-2 receptor (ACE-2R) on lung epithelial cells allowing cell entry, viral replication, and shedding. It interacts with lung dendritic cells through pattern recognition receptors (PRPs) and Toll-like receptors (TLRs) leading to the upregulation of proinflammatory cytokines, chemokines, and free radicals. An over-reactive immune response results in the "cytokine storm" that leads to the acute respiratory distress syndrome (ARDS), cardiomyopathy, and potentially encephalopathy. Both

cellular (helper T cells, cytotoxic T cells, NK cells, and dendritic cells) and humoral (antibody-producing plasma cells and complement) immune responses are deployed to control the virus. MS therapies can potentially influence the immune response to the infection in beneficial or potentially harmful ways depending on whether the therapy is immunomodulatory (GA, IFNβ, DMF) or immunosuppressive (alemtuzumab, ocrelizumab, ofatumumab, and cladribine). Some may also have anti-viral effects (IFNβ and teriflunomide)

immunomodulatory agents such as IFNβ, glatiramer acetate, and dimethyl fumarate are less likely to affect adversely the course of COVID-19 as long as significant lymphopenia is not present [55]. Conceptually, these three drugs can be beneficial in COVID-19 by modulating different aspects of the immune response to the virus. For example, IFNβ enhances NK cell-mediated cytotoxicity, antibody-dependent cytotoxicity, and phagocytosis [56], and inhibits viral replication [57]. Most concerning are immunosuppressive drugs that deplete T cells, B cells, or both such as alemtuzumab, ocrelizumab, ofatumumab, and cladribine. These agents may weaken cellular and humoral immune responses to the virus by eliminating cytotoxic T cells and antibody-producing plasma cells. Therapy that sequesters lymphocytes in lymphoid tissue such as the sphingosine-1 phosphate receptor (S1P1R) modulator family of drugs (fingolimod and siponimod among others) causes significant leukopenia and may increase the risk for worse outcomes. Therapy-induced lymphopenia can be compounded by the fact that SARS-CoV-2 infects leukocytes triggering apoptosis, which correlates with a worsened disease course [58]. Then again, S1P1R modulation may mitigate acute pulmonary injury through increased endothelial cell

integrity and reduced vascular permeability [59]. Natalizumab, which reduces trafficking of immune cells into the brain, may impair viral clearance from the CNS; this is troubling especially since SARS-CoV-2 may infect the CNS [43]. On the other hand, natalizumab can be beneficial by interfering with virus binding to the ACE-2 receptor. The site of action of MS therapies and their potential interference with the immune response to SARS-CoV-2 are shown in Fig. 1.

Immune Response to Anticipated COVID-19 Vaccines in the Context of MS Therapies

Several vaccines against SARS-CoV-2 are currently in clinical trials, with two approved for use in the USA at the time of this publication [60, 61]. These include the use of recombinant viral vectors as delivery vehicles, attenuated live virus, inactivated virus, and RNA-based vaccines that feature the spike protein of the virus [62]. While live vaccines can conceivably increase the risk of an MS relapse, inactivated vaccines, such as influenza, are generally safe. The two currently approved COVID-19 vaccines do not include the virus itself,

Table 2 Potential impact of MS therapies on COVID-19 clinical course

MS medication	MOA	Potential benefit in COVID-19	Potential adverse effect in COVID-19	References
Interferon β	Immunomodulatory; Anti-viral	Reduced viral replication; inhibition of proinflammatory cytokines	Unknown	[69]
Glatiramer acetate	Enhances Th2 and Treg cells	Counteract proinflammatory responses	Unknown	[70]
Natalizumab	Blocks α 4-integrin on immune cells and trafficking across BBB	May interfere with SARS-CoV-2 host cell entry	Reduced SARS-CoV-2 clearance from the CNS and gut	[71, 72]
S1PR modulators	Traps lymphocytes in lymphoid tissue	Lymphopenia may be beneficial for pneumonia and ARDS	Lymphopenia resulting in reduced viral clearance	[73]
Dimethyl fumarate (DMF)	Nrf2-mediated anti-oxidative stress; cy- tokine modulation	Reduced innate immune response to virus	Lymphopenia-related increased risk of infection and impaired viral clearance	[74]
Teriflunomide	Inhibits de novo pyrimidine synthesis; cytostatic; inhibits viral replication	Anti-viral effect	Lymphopenia-related increased risk of infection and impaired viral clearance	[75]
B cell-depleting agents (anti-CD20)	Decreased antigen presentation, inflammatory cytokines, and antibody production	Unknown	Increased risk of infection and impaired viral clearance	[76, 77]
Cladribine	Purine analogue that results in T and B cells depletion	Unknown	Lymphopenia-related increased risk of infection and impaired viral clearance	[78]
Alemtuzumab (anti-CD52)	T and B cell depletion; enhanced Treg cells	Unknown	Lymphopenia-related increased risk of infection and impaired viral clearance	[79]
Satralizumab (anti-IL6 in NMOSD*)	Inhibition of B cell differentiation and IL-17	Reduced impact of cytokine storm	Unknown	Kleiter, I. et al. MS Virtual 2020
Eculizumab	Complement C5 inhibitor	Reduced tissue damage	Unknown	[80]

ARDS acute respiratory distress syndrome, BBB blood-brain barrier, MOA mechanism of action, NMOSD neuromyelitis optica spectrum disorder, Nrf-2 nuclear factor erythroid 2-related factor-2, S1PR sphingosine-1 phosphate receptor, Treg regulatory T cells

only the instructions to generate a target viral-type protein against which an immune response can be generated [63]. While these vaccines contain no adjuvant, they may hypothetically signal TLR and lipid particles may be immunostimulatory, or be taken up by macrophages in turn releasing pro-inflammatory cytokines. These processes could contribute to the short-term side effects of the vaccine. The safety of the anticipated COVID-19 vaccines remains to be established in vulnerable populations especially those with autoimmune conditions such as MS. With the anticipated development and availability of effective and safe vaccines against COVID-19, the question is how effective the vaccine will be in generating protective immunity in patients on immunomodulatory or immunosuppressive therapies. This is likely to depend on the mechanism of action of the MS therapy and timing of the vaccine relative to the treatment cycle. Based on experience with other vaccines in MS-treated patients, therapies that do not deplete or suppress immune cells are less likely to interfere with vaccine efficacy, whereas those that deplete T cells, B cells, or both could interfere with vaccine efficacy, especially if the timing of the vaccine relative to the treatment cycle is not optimal [64]. For example, in the

case of the B cell-depleting therapy ocrelizumab, which is typically administered on a 6-month interval schedule, it would make sense to administer the vaccine toward the end of the cycle and 1 month before the next cycle. Given the need for a booster injection for the currently approved vaccinations at day 21 or 28 after the first vaccine dose, additional time may be required for plasma cell or memory B cell development in secondary lymphoid organs which would require delaying the ocrelizumab dose by 4–6 weeks [65, 66]. In the case of the newer monthly administered subcutaneous B cell-depleting therapy ofatumumab, vaccinations could be delivered toward the end of the monthly cycle and the next two ofatumumab doses skipped to allow for the booster vaccine to take effect. In certain cases, therapy interruption may be necessary [23]. Serological monitoring of humoral and cellular immune responses to the vaccine would be instructive under such circumstances. The specific choice of therapy may also affect the duration of B cell depletion. Memory B cell repletion can take up to 18 months after discontinuation of ocrelizumab, but up to 11–12 months for rituximab and ofatumumab [23]. Moreover, the presence of worsening IgA and IgM hypogammaglobulinemia with repeated infusions in some

patients may lead to suboptimal serological responses in those individuals on prolonged therapy [67, 68]. Possible solutions may include additional booster vaccinations or utilizing more than one vaccine formulation for patients demonstrating insufficient SARS-CoV-2 post-vaccination antibody responses. Ciotti et al. provide an excellent review of data on vaccination responses to various MS DMTs, identifying potential impairments in all but the interferons [64]. With additional information gleaned from future studies, we hope to gain better insight about the safety profiles specific to each DMT and best strategies for vaccination.

Future Considerations

As MS registries across the world are increasingly recording and reporting on COVID-19 cases, important knowledge will be gained about the demographics and risk factors that affect COVID-19 outcomes in the MS population, which immunomodulatory and immunosuppressive therapies increase the risk of contracting COVID-19, and which therapies are potentially beneficial especially in patients with ARDS. As vaccines against COVID-19 become available, choosing a safe vaccine that does not increase the risk of MS relapses is critical. Additionally, timing vaccine delivery relative to receiving immunosuppressive therapy, and analyzing the humoral and cellular immune responses to the vaccine will inform optimal vaccine delivery.

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