SARS-CoV-2 and Multiple Sclerosis: Not All Immune Depleting DMTs are Equal or Bad

A major concern during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic[1] is the use of immunosuppressive therapies for the treatment of multiple sclerosis (MS) due to an increased risk of contracting SARS-CoV-2 and more severe disease. The Society of Italian Neurologists (SIN) and the Association of British Neurologists (ABN) MS and Neuroimmunology Advisory Group published guidance for the use of disease modifying treatments (DMTs) in MS (Table 1).[2] However, taking into account less conservative viewpoints,[3] the emerging knowledge of the biology of SARS-CoV-2, and, in particular, the role of the immune mechanisms contributing to the disease, we propose modification of these guidelines because it is not clear that immunosuppression is indeed detrimental in people with MS infected with SARS-CoV-2. Thus, we are proposing a more nuanced approach and that the categories of DMTs should be modified based on scientific principles and the biology of severe coronavirus disease 2019 (COVID-19; Table 2).

The immune mechanisms contributing to severe COVID-19 include viral subversion of innate immunity and infection of macrophages,[4] and, if similar to SARS-CoV-2, may trigger apoptosis of leucocytes leading to lymphopenia.[5] The exact mechanisms are as yet unclear but suppression of innate responses due to modulation of IFN production or receptor signaling, and the apoptotic effects of virally encoded proteins have been proposed.[6] Together, these allow widespread viral infection, excessive monocyte/macrophage activation, and, in severe cases, a cytokine storm triggering severe acute respiratory distress syndrome (ARDS). The viral-specific CD8 T cell responses seem to eliminate SARS-CoV-2, whereas viral specific antibodies are probably more important to prevent reinfection and create long-lasting immunity. A direct role of B cells in the destructive COVID-19 pathology is unlikely because people with X-linked agammaglobulinemia recover from the COVID-19 pneumonia and lymphopenia without need of intensive care or oxygen ventilation.[7] In MS, although a single case, ocrelizumab treatment did not augment or prolong COVID-19 symptoms.[8]

Because many of the MS DMTs have been designed to target the adaptive immune response; and for therapeutic effect most likely need to target the memory B cells,[9] it is unlikely that MS DMTs treatment impact on the innate immune responses, although there is some evidence that fingolmod[10] and alemtuzumab[11] impact on the innate immune system. In addition, DMTs do not substantially limit the antibody responses to SARS-CoV-2 and, thus, do not pose a risk in the development of protective neutralizing antibody responses, however, some DMTs will blunt this.

To avoid "throwing the baby out with the bathwater" we recommend revision of the published guidelines[2] in light of the role of the immune response in controlling SARS-CoV-2 infection (see Table 2), the emerging biology of COVID-19, and accumulating case reports. We propose that although administration of some DMTs should be modified, others may well control the pathogenic immune responses during severe COVID-19. For example, although the original guidelines that suggest anti-CD20 therapies may increase the risk of infection,[12,13] this does not necessarily imply a greater risk of poor outcomes following infection. In addition, most MS-related DMTs do not particularly target the innate immune system and few have any major long-term impact on CD8 T cells to limit protection against COVID-19, perhaps with the exception of alemtuzumab.[14] Importantly, MS DMTs do not generally block immature B cell development, thus allowing antibody production preventing (re)infection, as well as response to vaccines when available. However, we

TABLE 1. SIN and the ABN Guidelines for the DMTs in use for MS during the COVID-19 Pandemic[2]

At risk category	Class	Trade name	Safe to start treatment	On treatment	COVID-19 infection	Mode of action
Low	Interferon-Beta	Betaferon, Avonex, Rebif, Plegridy	Yes	Continue	Stop	Immunomodulatory (not immunosuppressive), pleiotropic immune effects
Low	Glatiramer acetate	Copaxone	Yes	Continue	Stop	Immunomodulatory (not immunosuppressive), pleiotropic immune effects
Low	Teriflunomide	Aubagio	Yes	Continue	Stop	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), antiproliferative
Low	Dimethyl fumarate	Tecfidera	Yes	Continue	Stop	pleiotropic, NRF2 activation, downregulation of nfκβ
Low	Natalizumab	Tysabri	Yes	Continue	Stop	Anti-VLA4, selective adhesion molecule inhibitor
Low	S1P modulators	Fingolimod (Gilenya)	Yes	Continue	Stop	Selective S1P modulator, prevents egress of lymphocytes from lymph nodes
Intermediate	Anti-CD20	Ocrelizumab (Ocrevus)	No (Yes)	Suspend	Delay	Anti-CD20, B-cell depleter
High[aa]	Cladribine	Mavenclad	No	Suspend	Delay	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, selective T and B cell depletion
High[aa]	Alemtuzumab	Lemtrada	No	Suspend	Delay	Anti-CD52, nonselective immune depleter
High[aa]	HSCT	–	No	–	Delay	Non-selective immune depleter

[a]Risk refers to acquiring infection during the immunodepletion phase. With postimmune reconstitution, the risk is low.
ABN = Association of British Neurologists; COVID-19 = coronavirus disease 2019; DMT = disease modifying treatment; MS = multiple sclerosis; SIN = Society of Italian Neurologists.
Modified from Coles et al.[2]

recommend adjustments to dosing schedules to reduce the chance of infection.

Apart from the reactivation of herpes infections, the moderate immunosuppression obtained with most MS DMTs rarely leads to problems dealing with viral infections, even in the case of novel viral infections such as dengue fever.[15] With the notable exception of progressive multifocal leukoencephalopathy (PML) and other rare central nervous system (CNS) viral infections in natalizumab treated patients, which can be de-risked by adopting extended interval dosing,[16] would indicate that the initiation and continuation of DMTs in MS does not pose an additional risk of developing more severe COVID-19 to people with MS. However, immunosuppression to treat COVID-19 has been proposed as a rational therapeutic approach.[17,18] This hypothesis is currently being tested in several trials to evaluate several immunosuppressive therapies for COVID-19, which include fingolimod, an S1P modulator (NCT04280588) and IFNβ

TABLE 2. Proposed Revised Guidelines

At risk category	Class	Trade Name	Safe to start treatment	Advice regarding treatment	COVID-19 infection
Very low	Interferon-beta	Betaferon, Avonex, Rebif, Plegridy	Yes	Continue	Continue
Very low	Glatiramer acetate	Copaxone	Yes	Continue	Continue
Very low	Cladribine/ Alemtuzumab/ Mitoxantrone/HSCT	see below	N/A	N/A	N/A
Very low	Teriflunomide	Aubagio	Yes	Continue	Continue
Low	Dimethyl fumarate	Tecfidera	Probably	Continue/Switch if lymphopenia	Continue
Low	Natalizumab (EID)	Tysabri	Yes	Continue	Continue or miss infusion depending on timing
Low	Anti-CD20	Ocrelizumab (Ocrevus), Ofatumumab, Rituximab, Ublituximab	Probably	Risk assessment - continue or suspend dosing	Temporary suspension of dosing depending on timing
Intermediate	Cladribine	Mavenclad	Probably	Risk assessment - continue or suspend dosing	Temporary suspension of dosing depending on timing
Intermediate	S1P modulators	Fingolimod (Gilenya), Siponimod (Mazent), Ozanimod, Ponesimod	Probably	Continue	Continue or temporary suspension of dosing
Intermediate	Natalizumab (SID)	Tysabri	Yes	Continue, but consider EID	Continue or miss infusion depending on timing
High[aa]	Mitoxantrone	Novatrone	No	Suspend dosing	Suspend dosing
High[aa]	Alemtuzumab	Lemtrada	No	Suspend dosing	Suspend dosing
High[aa]	HSCT	–	No	Suspend dosing	Suspend dosing

[a]Risk refers to acquiring infection during the immunodepletion phase. With postimmune reconstitution, the risk is low.
COVID-19 = coronavirus disease 2019; EID = extended interval dosing; HSCT = hematopoietic stem-cell transplant; N/A = not applicable; SID = standard interval dosing.

(NCT04343768, NCT04350671) that are widely used to treat MS. Although the information is only emerging, we anticipate that knowledge arising from registers collating data on people with MS, DMTs, and their responses to SARS-CoV2 infection (e.g., NCT04354519) will support the hypothesis that moderate immunosuppression induced by the DMT used in MS may protect against the development of severe COVID-19 infection, which is contrary to current opinion.

The accumulating real-world data on the susceptibility of people with MS to develop severe COVID-19 being treated with immunosuppressive therapies will allow us to accept or reject this hypothesis.

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