SARS-CoV-2 and Multiple Sclerosis: Not all immune depleting DMTs are equal or bad

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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 current 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 since it is not clear that immunosuppression is indeed detrimental in people with MS infected with SARS-CoV-2. We are thus proposing a more nuanced approach and that the categories of DMTs should be modified based on scientific principles and the biology of severe COVID-19 (Table 2).

The immune mechanisms contributing to severe COVID include viral subversion of innate immunity and infection of macrophages[4], and if similar to SARS CoV, may trigger apoptosis of leucocytes leading to lymphopaenia[5]. The exact mechanisms are as yet unclear but suppression of innate responses due to modulation of IFN production or receptor signalling, 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 appear to eliminate SARS-CoV-2 while 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 since people with X-linked agammaglobulinemia that 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].

Since 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 neutralising antibody responses although 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 (Table 2), the emerging biology of COVID-19, and accumulating MS cases reports. We propose that while administration of some DMTs should be modified, others may well control the pathogenic immune responses during severe COVID-19. For example, whilst in contrast with the original guidelines suggest anti-CD20 therapies may increase the risk of infection[12,13] but 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 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 PML and other rare 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. Indeed 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, a S1P modulator (NCT04280588) and IFN☐ (NCT04343768, NCT04350671) that are already widely used to treat MS. Whilst 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 pwMS to develop severe COVID-19 being treated with immunosuppressive therapies will allow us to accept or reject this hypothesis.

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Table 1. Society of Italian Neurologists (SIN) and the Association of British Neurologists (ABN) guidelines for the DMTs in use for MS during 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), anti-proliferative
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*	Cladribine	Mavenclad	No	Suspend	Delay	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, selective T & B cell depletion
High*	Alemtuzumab	Lemtrada	No	Suspend	Delay	Anti-CD52, non-selective immune depleter
High*	HSCT	-	No	-	Delay	Non-selective immune depleter

*risk refers to acquiring infection during the immunodepletion phase. Postimmune reconstitution the risk is low. Modified from Coles et al 2020[2]

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 lymphopaenic	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*	Mitoxantrone	Novatrone	No	Suspend dosing	Suspend dosing
High*	Alemtuzumab	Lemtrada	No	Suspend dosing	Suspend dosing

| High* | HSCT | - | No | Suspend dosing | Suspend dosing |

EID - Extended interval dosing; SID - standard interval dosing