Multiple Sclerosis and Related Disorders

The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic.

David Baker[1], Sandra Amor[1,2], Angray S. Kang[1,3], Klaus Schmierer[1,4], Gavin Giovannoni[1,4]

[1]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom,

[2]Pathology Department, VUmc, Amsterdam UMC, Amsterdam, The Netherlands

[3]Centre for Oral Immunobiology and Regenerative Medicine, Institute of Dentistry, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom.

[4]Clinical Board:Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom.

Correspondence. David Baker, BartsMS, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, E1 2AT, United Kingdom. Email david.baker@qmul.ac.uk Tel +44 207882 2485.

ABBREVIATIONS: ACE2 angiotensin converting enzyme two, ARDS acute respiratory distress syndrome, ASC antibody secreting cells, CNS central nervous system, DMT, disease modifying therapies, haematopoietic stem cell therapy (HSCT), IRT immune reconstitution therapies, MS multiple sclerosis, RBD receptor binding domain, RNA ribonucleic acid, SARS Severe acute respiratory syndrome,

ABSTRACT

Background: SARS-CoV-2 viral infection causes COVID-19 that can result in severe acute respiratory distress syndrome (ARDS), which can cause significant mortality, leading to concern that immunosuppressive treatments for multiple sclerosis and other disorders have significant risks for both infection and ARDS.

Objective: To examine the biology that potentially underpins immunity to the SARS-Cov-2 virus and the immunity-induced pathology related to COVID-19 and determine how this impinges on the use of current disease modifying treatments in multiple sclerosis.

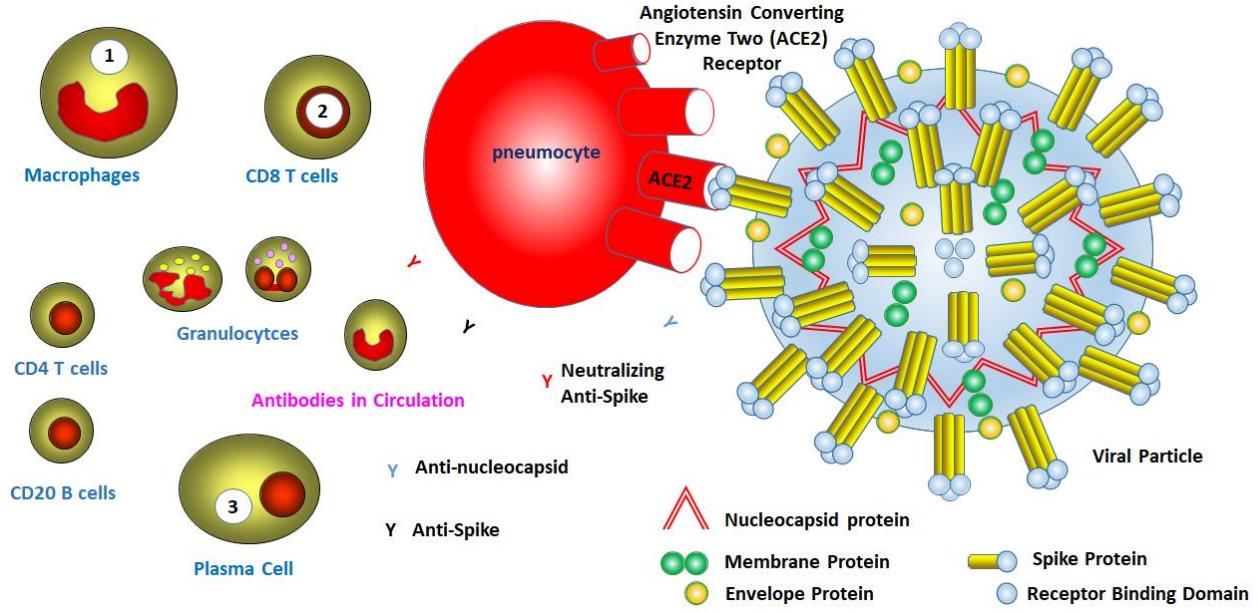
Observations: Although information about the mechanisms of immunity are scant, it appears that monocyte/macrophages and then CD8 T cells are important in eliminating the SARS-CoV-2 virus. This may be facilitated via anti-viral antibody responses that may prevent re-infection. However, viral escape and infection of leucocytes to promote lymphopenia, apparent CD8 T cell exhaustion coupled with a cytokine storm appears to contribute to the damage in ARDS.

Implications: In contrast to ablative haematopoietic stem cell therapy, most multiple-sclerosis-related disease modifying therapies 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. In addition, few block the formation of immature B cells within lymphoid tissue that will provide antibody-mediated protection from (re)infection. However, adjustments to dosing schedules may help de-risk the chance of infection further and reduce the concerns of people with MS being treated during the COVID-19 pandemic.

SARS-Cov-2 and COVID-19 a new pandemic. COVID-19 is the pandemic disease caused by severe acute respiratory syndrome (SARS) coronavirus two (SARS-CoV-2) infection (Zhu et al. 2020a; Zhou et al. 2020). About 80% of people infected with SARS-CoV-2 develop a self-limiting illness, 20% require hospitalisation, largely due to cardiovascular issues and about 5% require critical care and potential ventilatory support (Kimball et al. 2020; Day. 2020). The mortality in those requiring ventilatory support is about 40-50% (Weiss & Murdoch 2020; Zhu et al. 2020b). Death from COVID-19 is associated with older age and comorbidities such as cardiovascular disease, smoking, lung disease, obesity and diabetes (Zhu et al. 2020a; Lippi et al. 2020; Richardson et al. 2020). Mortality in young people and those without comorbidities may be related to excessive viral load (Lui et al 2020a; Chen et al. 2020a). Whilst the typical clinical features requiring self-isolation, and potentially hospitalization are fever, dry cough and shortness of breath related to respiratory tract infection, other symptoms such as headache and gastrointestinal symptoms may go unnoticed or under-appreciated leading to spreading of the virus (Zhu et al. 2020b; Richardson et al. 2020; Huang et al. 2020). People shed infective virus days before symptoms occur and continue to shed virus via the lungs and faeces whilst symptoms develop and resolve, often for more than 7 days after symptom onset (Lauer et al. 2020; Xu et al. 2020a; He et al.2020a).

SARS-CoV-2 is a betacoronavirus closely-related to virus that caused the SARS outbreak in 2002-2004 (Zhou et al.2020). The viral ribonucleic acid (RNA) is bound by the nucleocapsid protein and is encapsulated in a host cell membrane-derived lipid envelope containing the viral spike, envelope and membrane proteins (Chen et al. 2020b, Lu et al. 2020). The spike protein contains the receptor binding domain (RBD), which is important for binding to the angiotensin converting enzyme two (ACE2) cell receptor, and thus key to the cellular target, host range and viral infection (Zhou et al. 2020; Ou et al. 2020; Shi et al. 2020. Figure 1). Viral ACE2 binding is facilitated by host cell, serine proteases such as TMPRSS2 necessary to prime the spike protein (Hoffman et al. 2020; Tai et al. 2020). The ACE2 receptor is expressed on the vasculature and is present in many tissues, such as the kidney, gut, cardiomyocytes and lung epithelia (Hamming et al. 2004; Lukassen et al. 2020). There is very low expression of ACE2 on immune cells, but other co-receptors, including: CD147, proteases and probably lectins, based on similarities with the SARS-CoV virus, may be important in SARS-Cov-2 entry (Letko et al 2020; Yang et al. 2004; Wang et al 2020a; Granberg et al. 2005).

Figure 1. *The protective and destructive immune response against the SARS-CoV-2 virus*.



Immune cells target the SARS-CoV-2 virus that initially involves the innate immune response, which is then supplemented with anti-viral cytotoxic T cell responses and neutralizing and binding antibodies.

Multiple sclerosis in the COVID-19 era. The immune system provides vital defence against viral infections. This has led to concern for people taking immunosuppressive agents, as immune compromised people are particularly vulnerable to infection (Coles et al. 2020; Willis & Robertson 2020; Luna et al. 2020). Infections are more common in people taking DMT and are more frequent with the higher efficacy drugs (Willis & Robertson 2020; Luna et al. 2020). This is consistent with their more potent immunosuppressive activities. Immunosuppressed people have been advised to self-shield and socially distance themselves to avoid infection and will remain a problem, until herd immunity, anti-viral agents or effective vaccines have been developed (Kwok et al. 2020; Stein 2020). Multiple sclerosis (MS) is a major neurological disease that causes disability and can require hospitalisation for uncontrolled disease activity (Compston & Coles 2008). MS is currently managed with immunomodulatory drugs (Pardo & Jones 2017). This has led neurologists to recommend maintaining the *status quo* or curtailing the use of certain disease modifying treatments (DMT) in a pragmatic or non-pragmatic way (Coles et al 2020, Giovannoni et al. 2020; Brownlee et al. 2020. Table 1). It is understandable that a conservative "primum non nocere" (first do not harm) approach was adopted when considering treatments, given the paucity of knowledge surrounding SARS-Cov2 biology when COVID-19 first emerged. However, it is important to recognize the risks of poorly controlled MS may outweigh the perceived risks from COVID-19 (Giovannoni et al. 2020; Brownlee et al. 2020) and an essential goal of MS care must be to limit SARS-COV-2 infection. Therefore, care must be to prevent disease activation and limit the need for hospitalization that could potentially increase the risk of exposure to SARS-CoV-2. This must be balanced by the requirement of hospitalization for infusion treatments and the level of monitoring that each agent requires, that is particularly arduous with alemtuzumab, but minimal with ocrelizumab and glatiramer acetate (Pardo & Jones 2017).

It is important that such recommendations about treatment are made on a rational basis using knowledge of the mode of actions of the various agents and their ability to impact on the functioning of the components of the immune system. This is important as there is no evidence that immunosuppressed people are at increased risk to coronavirus infections (D'Antiga 2020). Therefore, to understand the risks posed to people with MS using DMT, it is crucial to understand the mechanisms of action, the impact of the treatments on infection-risk, vaccination responses and the mechanisms of pathology and immunity to SARS-CoV-2. Although there are gaps in our knowledge, understanding can be gained from the study of SARS-CoV infection, as well as other coronaviruses and lower respiratory tract infections (Channappanavar et al. 2014; Prompetchara et al. 2020; Rokni et al. 2020, Sarzi-Puttini et al. 2020).

Table 1. *Initial recommendations use of MS-related DMT by some European neurological associations*

Summary of SIN/ABN Guidelines						
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	Immunomodulatoy (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 NFKβ
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 and 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. Post immune reconstitution the risk is low.

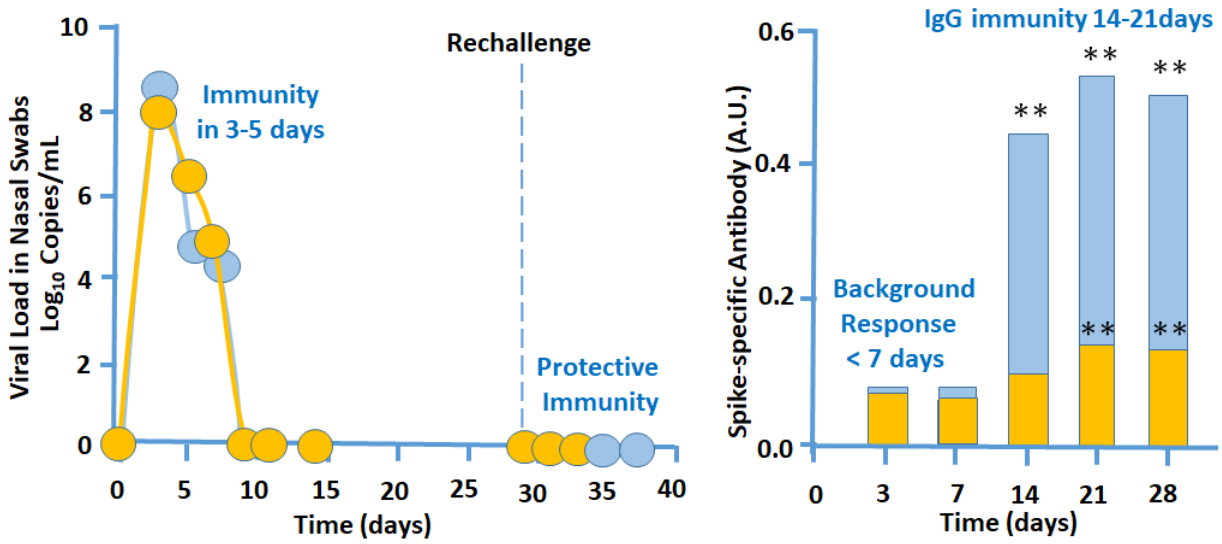
Composite guidelines generated from recommendations to treat MS from the Society of Italian Neurologists (SIN) and the Association of British Neurologists (Coles et al. 2020).

Immune response against SARS-CoV-2 virus. Protection against coronaviruses involves both the innate and adaptive immunity, typical for most viral infections (Yen et al. 2006; Prompetchara et al. 2020). However, consistent with SARS, some influenza infections and COVID-19, it appears to be the immune response and destruction of virally-infected cells and lung epithelial tissue that cause the acute respiratory distress syndromes (ARDS) and the, sometimes fatal, pneumonia (Chen et al. 2020b; Zhang et al. 2020a). It appears that the immune response to SARS-CoV-2 occurs in two phases involving an immune and a tissue, often lung, damaging phase.

Immune Phase. Following infection there is an asymptomatic period of 4-5 days, although some reports indicate this can be up to 3 weeks (Pung et al. 2020, Lauer et al. 2020; Lai et al. 2020), during which time the virus attempts to escape immune surveillance through the inhibition of interferon production and blockade of interferon receptor signalling activity, similar to SARS-CoV (Prompetchara et al. 2020; Chu et al. 2020; O'Brien et al. 2020). There is an early immune

response where the innate and then the adaptive immune response eliminates the virus as seen in non-human primates and by inference in humans (Bao et al. 2020; Thevarajan et al. 2020). Given that the majority of infections are asymptomatic (Kimball et al. 2020; Day 2020) indicates that this is a dominant mechanism in most people with COVID-19. *In vitro* data suggest an early innate response, notably from the alveolar macrophages and/or monocytes that may be recruited from the circulation (Yen et al. 2006; Thevarajan et al. 2020). Histological studies of cancerous lungs of people subsequently positive for COVID19, exhibited significant macrophage activity (Cai et al. 2020; Tian et al. 2020a). Thus, macrophages rather than neutrophils appear to be important as an early defence mechanism in SARS and COVID-19 lesions (Prompetchara et al. 2020; Tian et al. 2020a; Cai et al. 2020). This is probably followed by a CD8 cytotoxic T cell response that is generated within days of infection (Channappanavar et al. 2014; Prompetchara et al. 2020; Thevarajan et al. 2020).

Figure 2. *Removal of the SARS-CoV-2 virus occurs before a significant anti-viral antibody response is generated.*



Rhesus macaques were infected with coronavirus and the viral titre was assessed using nasal swabs. Animals were re-infected one month later. The results show the responses of two individual (blue and orange) monkeys, as seen in two additional monkeys, relating to viral titre and anti-viral antibody response. Adapted from Bao et al. 2020. DoI.org/10.1101/2020.03.13.990226

SARS-CoV-2 may be eliminated before significant blood antibody titres are generated as seen in non-human primate infections and case reports (Figure 2. Thevarajan et al. 2020, Bao et al. 2020; Soresina et al. 2020). These antibody responses are generated around 12 days (IgM) and 14 days (IgG), although this is earlier in some individuals (Zhoa et al. 2020; Okba et al. 2020; Xiang et al. 2020). Antibodies are predominantly generated against the nucleocapsid and spike proteins (Okba et al. 2020, de Assis et al. 2020). Antibodies against the RBD of the spike protein are clearly neutralizing, are able to prevent infection (Okba et al. 2020, Tai et al. 2020; Tian et al. 2020b). These appear to be protective, as evidenced by the use of convalescent sera to protect against severe COVID-19 (Duan et al. 2020; Pei et al. 2020; Shen et al. 2020). People with X-linked agammaglobulinemia have been infected and survived COVID-19 (Soresina et al. 2020). This

further suggests that B cells and immunoglobulin may not be an obligate immune element required for protection against SARS-CoV-2 infection. Although CD8 T cells are important in viral immunity, antibodies will however, be an essential for the vaccination response to prevent primary infection and reinfection. Most infected subjects will develop an immunoglobulin anti-viral response within 1 month (Zhoa et al. 2020, Okba et al. 2020; de Assis et al. 2020). This appears to prevent re-infection as shown in non-human primates (Bao et al. 2020. Figure 2). However, immunity may not be completely protective since people with COVID-19 can rarely present with SARS-CoV-2 re-activation (Ye et al. 2020a; Chen et al. 2020c). However, as the virus may persist in many sites and may not be eliminated at the same rates (Chen et al. 2020d). This may in part explain why viral RNA is detected in faeces when nasopharyngeal swabs become negative (Chen et al. 2020d). There are clearly viral variants (Foster et al. 2020; Yao et al. 2020) and may be important as vaccines will need to target disease-causing pathogenic variants. This data suggests that immunosuppression of macrophage function and probably CD8 activity may limit anti-viral protection, while blunting or inhibition of antibody formation may limit immunity to reinfection.

Destructive Phase. Although most people appear to tolerate COVID-19 a significant number of people experience respiratory distress (Chen et al. 2020e; Zhu et al. 2020b). It has also been suggested that abnormal coagulation, pulmonary embolism, and endothelial dysfunction are other pathologies of severe COVID-19, which could in part be related to virus and inflammation-induced oxidative stress (Fox et al. 2020; Poor et al. 2020). However, severe disease is associated with peripheral blood neutrophilia and notably lymphopenia (Chen et al. 2020e, Lui et al. 2020b, Wang et al. 2020b), where viral load relates to the severity of lymphopenia (Lui et al. 2020c). The lymphopenia could relate to sequestration of cells into the infected tissues as part of the anti-viral response. Post-mortem histology demonstrates significant mononuclear infiltration into the lung and often, but not always, a paucity of natural killer cells and neutrophils, unless associated with secondary infection (Xu et al. 2020b; Fox et al. 2020; Yoa et al.2020; Magro et al. 2020; Aurelio Sonzogni et al. 2020). There is a paucity of B cells and perhaps of relevance is that the lymphocytes are predominantly CD4 T cells (Xu et al. 2020b; Yoa et al. 2020b). Low peripheral blood CD8 T cell numbers are a poor prognostic feature (Du et al. 2020) consistent with a common feature of the COVID-19 lung pathology, where there is a paucity of CD8 T cells (Xu et al. 2020; Yoa et al. 2020; Zhang et al. 2020b). This may reflect senescence and exhaustion of the anti-viral CD8 response (Zheng et al. 2020; Cossarizza et al. 2020). Whether this contributes to severe disease and fatality remains to be established. However, this would be consistent with age being a major poor prognostic feature (Huang et al. 2020). It appears that T cells can be infected via CD147 (Wang et al. 2020c). In addition, infection and expression of envelope protein and Open Reading Frame protein sequestration that has been shown to have an apoptotic effect at least after SARS-CoV infection (Yang et al. 2005). This may play a role in the lymphopenia and immune suppression of the anti-viral response. There is marked atrophy of lymphoid tissues that may contribute to the lymphopenic state (Chen et al. 2020f; Zhang et al. 2020b, Yoa et al.2020). Macrophages may also become infected and can take-up the virus due to expression of CD147, lectins and Toll-like receptors known to recognize SARS-CoV pathogen associated molecular pattern recognition

elements such as single stranded viral RNA or uptake of viral antibody complexes (Wang et al. 2020a; Yang et al. 2004; Li et al 2013; Iwaski & Yang Y 2020). Macrophage activity may contribute to the lymphopenia (Chen et al. 2020f). Macrophage derived cytokines are produced, which lead to cytokines storms associated with worse prognosis (Chen et al. 2020c; Herold et al. 2020; Wen et al. 2020; Wilk et al. 2020). Therefore, agents such as IL-6 receptor and IL-1 blockers used in rheumatoid arthritis, and the case of IL-6R off-label in neuromyelitis optica, are being used to limit severe COVID-19 (Luo et al. 2020). Plasma cell-supporting cytokines such as TNFSF13 may be associated with recovery (Wen et al. 2020), however, the antibody response may contribute to macrophage hyper-activation. As such, severe disease is associated with the highest titres of antibodies (Liu et al. 2019; Zhoa et al. 2020) and antibody-dependent enhancement of disease may occur (Iwaski & Yang Y 2020). There is complement activation and microthrombi that develop, indicative of damage consistent with IgG3 anti-viral responses and IgG antibody-dependent cellular cytotoxicity by macrophages and in some instance neutrophils (Magro et al. 2020; Zhang et al. 2020b). Interestingly, it has been shown that spike-specific antibody may promote IL-8 and CCL2 production that skews macrophage accumulation towards a destructive phenotype (Liu et al 2019). As such in other lower respiratory tract infections antibodies can sometimes have destructive potential (Kim et al. 1969), therefore immunomodulation during periods of lung damage may offer some benefit.

Mechanisms driving multiple sclerosis may be distinct from COVID-19 protection and pathogenesis. Although it is widely considered that CD4, TH17 T cells are the central mediators of MS (Kunkl et al. 2020), all active DMT inhibit memory B cell activity in a hierarchical fashion that reflects their therapeutic activity (Pardo & Jones 2017, Baker et al. 2017, Baker et al. 2018). This could be secondary to inhibition of T cell function (Sabatino et al. 2019a, 2019b). Targeting memory B cell subsets, and possibly CD4, Th17 T cells, is not likely to prevent SARS-Cov-2 elimination by CD8 T cells and the innate immune responses. This may only be relevant with continuous treatments that maintain peripheral B cells in a nadir state and prevent antibody secreting cell (ASC) formation (Sabatino et al. 2019a; Baker et al. 2020a). However, ASC can be generated by germinal centre cells independent of the CD27+, memory B cell pathway (Baker et al. 2018; Hammarlund et al. 2017; Khodadadi et al. 2019). Novel vaccine responses will be generated from the immature/naïve B cell compartments that regenerate most rapidly following B cell depleting therapies (Baker et al. 2017b, Baker et al. 2019, Baker et al. 2020a). Once formed, anti-viral responses will reside within the long-lived plasma cell pool with lymphoid tissue and bone marrow (Khodadadi et al. 2019; Baker et al. 2018). Plasma cells are relatively quiescent (Khodadadi et al. 2019) and thus avoid the action of agents targeting proliferating cells and they also express low levels of CD52, deoxycytidine kinase and CD20 targeted by high-efficacy, depleting DMT (Baker et al. 2020b; Sabatino et al. 2019a, Baker et al. 2019). Furthermore, they reside predominantly in the bone marrow, a site that may not be effectively targeted by depleting antibodies as cell elimination requires entry of antibodies, complement components and effector accessory cells required for depletion (Baker et al. 2018). Thus once formed, plasma cells may not be particularly well targeted by the current DMT, except haematopoietic stem cell therapy

(HSCT) that purges the lymphoid tissues. It will be important to consider how best to deliver a SARS-CoV-2 vaccine in the future (Amanat & Krammer 2020; Chen et al. 2020g). Strategies could be developed for the highly-active agents that accommodate the long-depletion of memory B cells and the more rapid population of naïve cells to allow a vaccination response against SARS-Cov-2 whilst maintaining protection against MS.

Low efficacy MS immunomodulators are unlikely to limit anti-viral immunity. The components of the immune response that drive autoimmunity and control infection use overlapping cellular mechanisms. Therefore, removal of significant immune subsets may have the capacity to reduce anti-viral responses in a manner that reflects their immunosuppressive potential. Low treatment-efficacy agents such as glatiramer acetate, beta interferons and teriflunomide (Table 1) are not associated with significant immunosuppression, notable increased risk of viral infections, nor lack of responsiveness to vaccines (Pardo & Jones 2017; Comi et al. 2019a; Wijnands et al. 2018; Olberg et al. 2018; Hauser et al. 2019). Indeed, interferon beta and teriflunomide may have anti-viral activity that could be beneficial (Hensley et al. 2004; Bilger et al). As such beta interferon has been shown to inhibit SARS-CoV replication and is currently being trialled in COVID-19 (Dahl et al. 2004; Hensley et al. 2004; NCT04350671; NCT04343768). However, these agents have a downside in that they are not that effective in controlling MS disease activity.

Moderate efficacy MS immunomodulators carry higher, but modest infection risks. Dimethyl fumarate is modestly immunosuppressive and targets lymphocytes rather than monocytes (Pardo & Jones 2017; Diebold et al. 2018). Immature/transitional B cells are less affected compared to memory B cell targeting (Mehta et al. 2019). Although plasmablasts and plasma cells can be affected by dimethyl fumarate therapy (Mehta et al. 2019), immunoglobulin levels are not unduly reduced (Diebold et al. 2018). Importantly, vaccine responses in people on dimethyl fumarate were no different to those treated with beta interferons (von Hehm et al. 2017). However, in some individuals persistent lymphopenia has been reported (Mehta et al. 2019; Diebold et al. 2018), notably about 20% of people will exhibit CD8 T cell levels below the lower limit of normal (Mehta et al. 2019). Although this is not generally associated with increased infection rates (Boffa et al. 2020), viral infections, including upper respiratory and lung infections occur with the monomethyl fumarate producing compounds (Pardo & Jones 2017; Diebold et al. 2018; Perini et al. 2018; Fernández et al. 2017; Naismith et al. 2019).

Functional lymphopenia occurs with sphingosine-1-phosphate receptor modulators such as fingolimod (Pardo & Jones 2017; Diebold et al. 2018). This appears to modestly elevate efficacy and infection risks (Pardo & Jones 2017; Kalincik et al. 2019). These agents are reported to sequester lymphocytes within lymphoid tissues and exhibit limited activity on the innate immune response (Kowarik et al. 2012; Pardo & Jones 2017; Thomas et al. 2017; Angerer et al. 2018). Fingolimod targets CD4 more than CD8 T cells and notably the naïve and central memory T cell subsets to retain them in lymphoid tissues where anti-viral responses would be generated

(Kowarik et al. 2012; Angerer et al. 2018; Hjoorth et al. 2020). It also exhibits a more modest decrease in effector memory CD4 and CD8 T cells that will enter inflamed tissues (Angerer et al. 2018). Infections rates are modest (Diebold et al. 2018), but some bacterial and viral, infections such as herpes and varicella, are marginally more common after fingolimod treatment (Calibresi et al. 2014; Pardo & Jones 2017; Diebold et al 2019). There may be subtle differences between fingolimod and the other sphingosine-1-phosphate receptor modulators in terms of infections and adverse effects, however it has a relatively long-half-life compared to other agents, which may be relevant if one wants to stop treatment (Subei et al. 2015; Swallow et al. 2020). A small scale trial of fingolimod has been reported for severe COVID-19 (NCT04280588). Sphingosine-1-phosphate is involved with maintaining the germinal centre and B cell niche (Cinamon et al. 2008) and there may be reduced serum immunoglobulin level following fingolimod treatment (Zoehner et al. 2019) as such vaccine responses are slightly reduced compared to the interferons (Olberg et al. 2018; Signoriello et al. 2020) as occurs with natalizumab (Olberg et al. 2018).

Natalizumab as the preferred high-efficacy agent. Currently natalizumab is perceived to be the high-efficacy treatment of choice (Coles et al. 2020. Table 1). Natalizumab, unlike depleting highly-active DMT, is potentially more rapidly reversible using plasma exchange and is not likely to inhibit migration of immune cells into lymphoid tissues and prevent novel immune responses, and as such has no or limited influence on vaccine antibody responses (Vågberg et al. 2012; Kaufman et al. 2014; Olber et al. 2018). The value of the use of natalizumab may also be enhanced because it is perceived to inhibit T cell migration into the central nervous system (CNS) (Yednock et al.199; Schwab et al. 2015). However, both B cells and importantly monocytes express alpha 4 integrin (CD49d) and thus the antibody directed to CD49d inhibits monocyte binding to vascular cell adhesion molecule one (VCAM-1) (Yednock et al. 1992; Hyduk et al. 2009). Importantly, although natalizumab is used to block migration into the inflamed CNS and gut (Schwab et al. 2015), VCAM-1 is expressed in virally-inflamed lungs (Brodie et al. 1999). Therefore, CD49d is likely involved in mononuclear cell diapedesis into the inflamed lung during SARS-CoV-2 infection (Brodie et al. 1999; Yen et al. 2006). This potential activity is perhaps consistent with increased lung infections in MS following treatment with natalizumab (Polman et al. 2006). Furthermore, that SARS-CoV-2 is neutrotrophic, (Baig et al. 2020; Moriguchi et al. 2020, Helms et al 2020) suggests that a potential risk of natalizumab treatment is that it blocks viral immunosurveillance of the CNS (Hoepner et al. 2014), however this issue is perhaps limited by the extended interval dosing suggested to limit MS activation and reduce the risk of progressive multifocal leukoencephalopathy (Ryerson et al. 2019; Clerico et al. 2020). Thus, whilst natalizumab use could potentially be a risk factor for severe COVID-19, it is likely to limit monocyte and T cell damage to the lung and avoiding severe complications.

High-efficacy depleting agents are not the same and have distinct COVID-19 risks. Based on initial suggestions, immune reconstitution therapies (IRT) were not recommended to be started and ongoing treatment, i.e. additional courses, should be delayed (Table 1. Coles et al. 2020). Autologous HSCT is seen as a high-risk strategy to initiate during the mass-infection stage of

COVID-19 pandemic (Table 1) and will probably remain so until herd immunity (Kwok et al. 2020) develops. Myeloablative HSCT removes both the adaptive and notably the innate immune systems and it is already well recognised that loss of the neutrophils, monocytes and other elements of the innate immune system increases the risk of mortality from infection, and until the innate and adaptive immune response reconstitutes people will be at risk for some time (Storek et al. 2008; Ge et al. 2019; Rush et al. 2019). However, once reconstituted the capacity to generate new immune responses occurs as seen following vaccination against childhood infections, to replace the lost immunity due to the HSCT procedure (Brinkmann et al. 2007, Rush et al. 2019). Therefore, there are clear risks from viral infections until the immune system reconstitutes. It is suggested that current licenced IRT, which both deplete T and B cells (Baker et al. 2017b; Baker et al. 2017c) carry similar risk (Coles et al. 2020). However, this does not accommodate the biologies and as such, oral cladribine is dissimilar to alemtuzumab, in terms of its risk for SARS-CoV-2 infection and appears more similar to ocrelizumab in its immunodepletion profile (Table 2).

Table 2: *High efficacy agents are not the same and oral cladribine is more similar to ocrelizumab than alemtuzumab*

	ALEMTUZUMAB[1]	CLADRIBINE[7]	OCRELIZUMAB[12]
Practicality	INFUSION[1] STEROIDS TO STOP CRS[1]	ORAL TABLETS[8] NO STEROIDS	INFUSION STEROIDS TO STOP CRS
	HOSPITAL VISITS REQUIRED MONITORING FREQUENT[1]	HOSPITAL VISITS NOT REQUIRED MONITORING MINIMAL[8]	HOSPITAL VISIT REQUIRED MONITORING MINIMAL[12]
	DRUG PRESISTANCE ~1 MONTH[1]	DRUG PERSISTANCE 1 DAY[8]	DRUG PERSISTANCE 5-6 MONTHS[12]
Differential Infection Risk	EARLY DELETION MONOCYTE[2-4] NEUTROPHILS IN NORMAL RANGE[3,5]	MONOCYTES IN NORMAL RANGE[9] NEURTROPHILS IN NORMAL RANGE (~10%)[9]	MONOCYTES IN NORMAL RANGE[13] NEUTROPHILS IN NORMAL RANGE[12]
	CD4 DEPLETED (70-90%)[5] CD8 DEPLETED (70-90%)[5] NK CELLS IN NORMAL RANGE (40%)	CD4 IN NORMAL RANGE (40-50%)[9] CD8 IN NORMAL RANGE (30-40%)[9] NK CELLS IN NORMAL RANGE (50%)[9]	CD4 IN NORMAL RANGE (~2%)[13] CD8 IN NORMAL RANGE (6-8%)[13] NK CELLS IN NORAML RANGE (<10%)[13]
Efficacy	IMMATURE B CELL DEPLETED (3-6 MONTHS)[5] MEMORY B CELLS DEPLETED (> 1 YEAR)[5] PLASMA CELLS. LOW CD52[5] EARLY INFECTION RISK[1]	IMMATURE B CELL DEPLETED (6-9 MONTHS)[10] MEMORY B CELLS DEPLETED (>1YEAR)[10] PLASMA CELLS LOW DEOXYCYTODINE KINASE[11] LIMITED INCREASED RISK[8]	IMMATURE B CELLS DEPLETED PERMANENTLY[13,14] MEMORY B CELLS DEPLETE PERMANENTLY[13,14] PLASMA CELLS, NO CD20[12] LIMITED INCREASED RISK[12]
Infection Risk	(EARLY ANTI-VIRAL REQUIRED)	(MAINLY BACTERIAL, INCREASE HERPES)	(MAINLY BACTERIAL, INCREASE HERPES)
	VACCINATION COMPETENT AFTER 6 MONTHS[7]	?	VACCINATION COMPENTENT & BUT BLUNTED[15]

Different characteristics of alemtuzumab, cladribine and ocrelizumab, relevant to efficacy and side-effect potential and their capacity to control MS and exhibit an effective anti-viral immune response. CRS cytokine release syndrome. NK natural killer. 1.Lemtrada® 2019. 2. Thomas et al. 2016, 3. Baker et al. 2017d, 4. Gross et al. 2016, 5. Baker et al. 2017b, 6. Baker et al. 2020b, 7. McCarthy et al. 2013, 8. Mavenclad® 2018, 9. Baker et al. 2017c, 10 Ceroni et al. 2018, 11. Baker et al. 2019, 12. Ocrevus® 2018; 13. Baker et al. 2020a, 14. Fernandez-Verlasco et al. 2019, 15. Stokmaier et al. 2018.

Alemtuzumab. This is a CD52-depleting antibody that induces long-lasting and marked (80-90%) depletion of CD4, CD8 T cells and memory B cells (Table 2. Baker et al. 2017; Akgün et al. 2020). Alemtuzumab induces long-term disease remission if treated sufficiently early after symptom onset (Cohen et al. 2012. Havrdova et al. 2017, He et al. 2020b). Two short cycles of treatment give long-term disease remission. Alemtuzumab treatment cycles are generally given at least 12 months apart, but this interval may be extended up to 18 months, which supports the

important activity of memory B cells as they, and CD4 T cells, can be depleted for at least this time (Tuohy et al. 2015, Havrdova et al. 2017, Akgün et al. 2020). However, alemtuzumab induces transient monocyte depletion and can induce very long-term CD4 and CD8 T cell depletion (Kousin-Ezewu et al. 2014; Thomas et al. 2016, Baker et al. 2017b; Akgün et al. 2020). This influences responses to viral and other infections (Cohen et al. 2012; Wray et al. 2019) and could thus impact on SARS-CoV-2 outcome. Severe lymphopenia increases the risk of infections and pneumonia (Warny et al. 2018). Neutropenia after alemtuzumab can be marked and significant, but is unusual (Baker et al. 2017d). Infection risk is notable following infusion and decreases with time as cellular repopulation occurs (Buonomo et al 2018; Wray et al. 2019). Alemtuzumab has a relatively short half-life and is cleared from the circulation within about a month (Li et al. 2018). Therefore, surviving cells can repopulate in response to infection and given the relatively low dose and delivery over a single week, allows cells escaping elimination to recover. Transitional/immature B cells rapidly repopulate in the relative absence of T cell regulation, possibly related to limited purging of the bone marrow, and can generate anti-drug responses within a month of treatment in 60-83% of people in the virtual absence of peripheral B and T cell (Baker et al. 2017b; Baker et al. 2020b). Therefore, perhaps it may be possible to generate anti-viral responses. As such childhood vaccine responses persist and novel vaccine responses are not notably inhibited with alemtuzumab within 6 months of treatment (McCarthy et al 2013). Thus with time people with MS are likely to be able to generate a SARS-CoV-2 response and respond to vaccination. Although the treatment protocol means that few infusion visits are required (Cohen et al. 2012; Havrdora et al. 2017), the adverse events, notably the secondary autoimmunities that develop in many people with MS (Tuohy et al. 2015; Havrdora et al. 2017) means that intensive monitoring is required, compared to ocrelizumab that required essentially no inter-infusion monitoring (Pardo & Jones 2017).

Ocrelizumab is a CD20-depleting antibody used to treat relapsing and active primary progressive MS (Hauser et al. 2017; Montalban et al. 2017). This depletes peripheral B cells including memory B cells (Fernandez Velasco et al. 2019). Based on a common mechanism of action (Baker et al. 2017a), there is an unanswered question of whether ocrelizumab will behave like alemtuzumab and cladribine and provide long-term disease inhibition from a short-term treatment cycle (Table 2). Even if it acts as an IRT, based on memory B cell depletion and slow repopulation characteristics (Palanichamy et al. 2014; Baker et al. 2018), it may provide some comfort to suggest that delays of 6-12 months may be feasible without MS disease activity reoccurring. The latter is based on information from off-label and phase I/II studies with rituximab in MS (Bar-Or et al. 2008; Juto et al. 2020) and phase II extension trial data of ocrelizumab (Kappos et al. 2012; Baker et al. 2020a). As such retreatment to maintain remission based on repopulation of CD27+ memory B cell population, after 3-4 cycles it seems that doses, at least with rituximab, can be extended to less than once a year (Novi et al. 2019). Given that ocrelizumab exhibits depletion for a longer duration than rituximab suggests similar or better results can be obtained with rituximab (Baker et al. 2020a). Although ocrelizumab can deplete CD8 T cells, this is only a relatively mild steady state depletion of only 6-8% depletion of CD8 cells and 1-2% of CD4 T cells

and has a minor impact on monocytes (Gingele et al. 2018; Baker et al. 2020a). Although infections are generally mild following ocrelizumab treatment (Hauser et al. 2017), some viral infections do occur and can be serious and very rarely life threatening (Hauser et al. 2017; Nicolni et al. 2019). Importantly, this may become a problem with persistent B cell depletion as that which occurs with ocrelizumab (Hauser et al. 2017). In time this can lead to IgM, IgA and IgG hypogammaglobulinemia that will increase infection risk (Tallantrye et al. 2018; Vollmer et al. 2020). However, a delay in repeated cycles may allow immature cells that provide immunity to new infections to partially regenerate, although this process is slow with ocrelizumab (Kappos et al. 2012; Baker et al. 2020a), and improve the vaccination response. Consistent with marked B cell depletion, it is apparent that vaccination responses are blunted when initiated 3 months after infusion however, they are not absent (Stokmaier et al. 2018). As plasma cells do not express CD20, once formed they will not be directly targeted by ocrelizumab (Sabitino et al. 2019a). Ofatumumab is a novel subcutaneous CD20-depleting antibody awaiting licencing following a successful phase III programme (Hauser el al 2019). Ofatumumab dosing shows relatively rapid repopulation of immature B cells compared with slower repopulation with ocrelizumab (Savelieva et al. 2017; Baker et al. 2020a) and thus it remains to be established if the advantage of home injection and reversibility changes the use of anti-CD20 therapies compared to infusions with rituximab and ocrelizumab (Hauser el al. 2017, Hauser et al. 2019). Likewise, the real-life extended dosing experiment with rituximab and ocrelizumab is ongoing (Table 1). If data captured by registries shows maintained efficacy it is likely that the dosing schedule of ocrelizumab will eventually change on grounds of conveniences, safety and cost-effectiveness, although this will need formal testing (Novi et a. 2019; Baker et al. 2020a).

Cladribine. This is an oral small molecule that behaves as an IRT that gives long term-term benefit from short treatment cycles (Giovannoni et al. 2010; Giovannoni et al. 2018). This is a B and T cell depletion agent that is eliminated within one day of treatment (Table 2) (Baker et al. 2017c; Baker et al. 2019; Hermann et al. 2019). Treatment induces depletion via apoptosis rather than cell lysis and thus avoids the need for steroids to manage infusion reactions associated with alemtuzumab and ocrelizumab (Cohen et al. 2012; Hauser et al. 2017). Cladribine can induce comparable long-term memory B cell depletion similar to that observed with alemtuzumab, but without the innate cell and the severe lymphopenia associated with alemtuzumab (Ceronie et al. 2018; Ruggieri et al. 2019). Indeed, the T cell depletion is more modest and CD4 cells are depleted by about 40-50% and CD8 T cells are depleted by 30-40% compared to baseline. In comparison, alemtuzumab results in B and T cell depletion of 80-90% (Baker et al 2017c). As such the T cells generally remain within the lower limit of the normal range as do natural killer cells that show modest depletion (Baker et al. 2017c; Comi et al. 2019b). The CD19+ B cells recover perhaps slower than post-alemtuzumab, as cladribine probably penetrates and acts more in lymphoid tissues, and the dosing schedule of doses being given a month apart targets any rapidly emerging cells (Baker et al. 2017c, Baker et al. 2019). However, B cells probably emerge faster after cladribine compared to ocrelizumab as depleting titres of ocrelizumab remain high for months after infusion (Genovese et al. 2008; Baker et al. 2017c, Baker et al. 2020a). Unfortunately, there

is no information available concerning the influence of vaccination responses of oral cladribine. Although there is an increased risk of viral infections (Giovannoni et al. 2010), these are notably less severe than with alemtuzumab (Pardo & Jones 2017) associated with the milder immunosuppression induced by cladribine. Thus, oral cladribine, behaves like a chemical CD19/CD20 depleter with some additional T cell activity and is perhaps functionally closer to CD20-depleting antibodies than CD52 depleting antibody. It has the advantage that treatment is not continuous. During the time of self-isolation and shielding to prevent COVID-19 agents such as cladribine may have some merit as it is a high efficacy IRT that can be administered at home, with minimal post-dosing monitoring requirements (Table 2).

Preliminary Experience and Personal View of Treatment. As analysis of the mechanisms of action of the different DMT coupled with emerging knowledge of the anti-viral and pathogenic mechanisms in COVID-19, suggest that initial fears relating to immunosuppression in MS, have yet to be realised, supporting that found in the SARS epidemics (D'Antiga 2020; Giovannoni 2020). The pragmatic approach of examining an individual patient's circumstances, their prognostic profile and level of MS disease activity may help guide treatment approaches (Giovannoni et al. 2020; Giovannoni 2020). Although these are early days in the initial infection wave of COVID-19, already a number of people with MS have been infected with SAR-CoV-2 with the majority surviving based on early social media and registry data. Although a few people with MS have died they have tended to be older, with more advanced disease and multiple comorbidities. There are now over 360 people with MS and COVID-19 within Italian COVID MS registry with only 5 reported deaths, with only 2 people being treated with DMT and all having comorbidities associated with poor COVID-19 prognosis in the general population. Thus, there does not yet appear evidence that people with MS are at particular risk of severe COVID-19. As such we suggest that risks should be reviewed (Table 3) and advice regarding the risks associated with individual MS-DMT adjusted. Delays in treatment cycles may provide information on the biology of relapsing MS and, if successful may change prescribing habits in the future as there are risk/cost/benefit advantages of reduced dosing frequency. Thus, it will be interesting to determine whether one returns to the current *status quo* after the COVID-19 pandemic wanes or whether extended interval-dosing remains. Likewise, it will be intriguing to determine if real-life data shows that ocrelizumab exhibits IRT-like characteristics whereby long-term benefit can be seen with only short-term treatment cycle as seen with alemtuzumab and oral cladribine. The positive aspect of this unfortunate human experiment created by the SARS-CoV-2 epidemic, is that it will teach us more about the biology of MS and help inform how best to treat this disease and as safely as possible.

Table 3. *Our opinion of altered risks of different MS DMT for COVID-19.*

Main attributes of licensed MS DMTs in relation to the COVID-19 pandemic												
At risk category	**Rank**	**Class**	**Trade Name**	**Mode of action**	**Efficacy**	**Class**	**Safe to start treatment**	**Advice regarding treatment**	**In the event of COVID-19 infection?**	**Immuosuppression?**	**Response to future SARS-CoV-2 vaccine**	**Attributes and caveats**
Very low	1	Interferon-beta	Betaferon, Avonex, Rebif, Plegridy	Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Moderate	Maintenance immunomodulatory	Yes	Continue	Continue	No	Likely to be intact	Has antiviral properties that may be beneficial in the case of COVID-19
Very low	2	Glatiramer acetate	Copaxone	Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Moderate	Maintenance immunomodulatory	Yes	Continue	Continue	No	Likely to be intact	-
Very low	3	Cladribine / Alemtuzumab / Mitoxantrone / HSCT	see below	Post-immune reconstitution with normal innate and adaptive immunity (lymphocyte count > 1000/mm3)	High / Very high	IRT	N/A	N/A	N/A	No	Likely to be intact	Some patients who may have mitoxantrone or chemotherapy-induced (HSCT) cardiomyopathy may be at increased risk of severe COVID-19
Very low	4	Teriflunomide	Aubagio	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), anti-proliferative	Moderate (1st-line) / Moderate to high (2nd-3rd-line)	Maintenance immunomodulatory	Yes	Continue	Continue	Possible (no well-defined immunosupressive signature)	Likely to be intact	Has antiviral properties that may be beneficial in the case of COVID-19
Low	5	Dimethyl fumarate	Tecfidera	Pleotropic, NRF2 activation, downregulation of NFKβ	Moderate (2nd-3rd-line) / High (1st-line)	Maintenance immunosuppressive	Probably	Continue / Switch if lymphopaenic	Continue	Yes, continous	Likely to be intact	The risk can only be considered low in paients who don't develop a persistent lymphopaenia. Patients with a total lymphocyte count of less than 800/mm3 should be considered be at a higher risk of develping complications from COVID19 infection.
Low	6	Natalizumab (EID / extended interval dosing)	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Yes	Continue	Continue or miss infusion depending on timing	Yes, continous	Likely to be intact	As COVID-19/SARS-CoV-2 is neurotropic natalizumab will potentially prevent viral clearance from the CNS; this risk is likely to be very low on EID or extended interval dosing. I stil have concerns about creating an environment in mucosal surfaces and the gut that may promote prolonged viral shedding; again this risk will be lower with EID.
Low	7	Anti-CD20	Ocrelizumab (Ocrevus), Ofatumumab. Rituximab, Ublituximab	Anti-CD20, B-cell depleter	Very high	Maintenance immunosuppressive	Probably	Risk assessment - continue or suspend dosing	Temporary suspension of dosing depending on timing	Yes, continous	Blunted, particularly to glycoprotein components of a vaccine	Does drop the both CD4+ and CD8+ T-cell populations by up to 20% and this may interact with other factors to affect antiviral responses. Theoretical risk that ocrelizumab and other anti-CD20 therapies may result in prolonged viral shedding.
Intermediate	8	Cladribine	Mavenclad	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, selective T and B cell depletion	High / Very high (highly-active RMS)	IRT (semi-selective)	Probably	Risk assessment - continue or suspend dosing	Temporary suspension of dosing depending on timing	Yes, intermittent	Possibly blunted.	Only reduces the T-cell compartment by ~50% and has less of an impact on the CD8+ population. Provided total lymphocyte counts are above 500/mm3 allowing appropriate antiviral responses should be maintained. Theoretical risk that in the immune depletion phase cladribine may result in prolonged viral shedding.
Intermediate	9	S1P modulators	Fingolimod (Gilenya), Siponimod (Mazent), Ozanimod, Ponesimod	Selective S1P modulator, prevents egress of lymphocytes from lymph nodes	High	Maintenance immunosuppressive	Probably	Continue	Continue or temporary suspension of dosing	Yes, continous	Blunted	Theoretical risk that S1P modulators may result in prolonged viral shedding. Paradoxically S1P modulators may reduce the severity of COVID-19; fingolimod is currently being trialed.
Intermediate	10	Natalizumab (SID / standard interval dosing)	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Yes	Continue, but consider EID	Continue or miss infusion depending on timing	Yes, continous	Likely to be intact	As COVID-19/SARS-CoV-2 is neurotropic natalizumab will prevent viral clearance from the CNS.Intermediate risk; higher theoretical risk on SID. I have that natalizumab will create an environment in mucosal surfaces and the gut that may promote prolonged viral shedding.
High*	11	Mitoxantrone	Novatrone	Immune depleter (topoisomerase inhibitor)	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	Blunted	Theoretical risk that in the immune depletion phase mitoxantrone may result in prolonged viral shedding.
High*	12	Alemtuzumab	Lemtrada	Anti-CD52, non-selective immune depleter	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	Blunted	Theoretical risk that in the immune depletion phase alemtuzumab may result in prolonged viral shedding.
High*	13	HSCT	-	Immune depletion and haemopoietic stem cell reconstitution	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	Blunted	Theoretical risk that in the immune depletion phase HSCT may result in prolonged viral shedding.
*risk refers to acquiring an infection during the immunodepletion phase. Post immune reconstitution the risk is low.												

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