Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

The COVID-19 pandemic and the use of MS disease-modifying therapies

Gavin Giovannoni[a,*], Chris Hawkes[a], Jeannette Lechner-Scott[b], Michael Levy[c], Emmanuelle Waubant[d], Julian Gold[a,e]

[a] Blizard Institute, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London, E1 2AT, UK
[b] School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
[c] NMO Clinic and Research Laboratory, Division of Neuroimmunology & Neuroinfectious Disease, Massachusetts General Hospital, Boston, USA
[d] Department of Neurology, UC San Francisco, San Francisco, California, USA
[e] The Albion Centre, Prince of Wales Hospital, Sydney, New South Wales, Australia

Maria was distraught after reading about the 'potential' epidemic, yet to happen, and the horror stories on Facebook needing reassurance and certainty about what she should do. She requested an urgent appointment to review her treatment plan. Maria was a 26-year-old woman with relapsing multiple sclerosis who had recently experienced brainstem relapse with double vision and ataxia despite treatment with pegylated interferon-beta for the last 18 months. A brain MRI performed one month prior had shown 16 new T2 lesions, four of which were enhancing. One of the enhancing lesions was at the pontomedullary junction and was certainly the cause of her relapse. Treatment was to be escalated to ocrelizumab with the first dose in a week's time. In view of the emerging coronavirus pandemic, she was questioning whether or not she should go ahead with ocrelizumab. This was despite only a handful of confirmed COVID-19 cases in the country and none in her town and region.

If this scenario sounds plausible what should neurologists do? Human coronaviruses are predominantly associated with respiratory tract infections and includes those that cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and now the COVID-19 pandemic.

In an uncertain world, where we do not have a clear evidence-base, you often have to default to scientific principles, rather than using the wisdom of the crowd. Not surprising, with Italy being one of the epicentres of the COVID-19 epidemic, the Italian society of neurology or SIN (Società Italiana di Neurologia) broke cover first producing recommendations on the management of patients with MS during the COVID-19 epidemic (see Box 1). The SIN guidelines provide relatively straightforward, and one could argue arbitrary, advice on how to manage patients with MS in the short-term, but do not address supervision of these patients in the intermediate or long-term especially those with highly active MS. If the public health measures being taken flatten the peak of the epidemic, but extend its tail, the problem of community-acquired SARS-CoV2 infection and COVID-19 may be with us for many months and potentially years. Are the SIN guidelines compatible with the best interests of our patients or a knee-jerk response to an undefined problem that may not be a problem at all?

It is clear that COVID-19 is a pandemic and global health crisis with the potential to kill millions of people, particularly the elderly and people with comorbidities such as hypertension, smoking and lung disease. At present we do not know if people with MS are at increased risk acquring SARS-CoV-2, COVID-19 or developing severe COVID-19. Individuals with MS are not unique in their requirement to be treated with immunosuppressive therapies. We discussed the COVID-19 epidemic with our renal transplant team who informed us that at present they are not taking any specific action about the levels of immunosuppression for their transplant patients during the epidemic. Basic measures are recommended namely: to improve hand and home hygiene, to avoid high-risk travel and unnecessary contacts, to self-isolate if necessary and to reduce contact with the hospital and other medical institutions as much as possible, because they are more likely to be sources of COVID-19. It is business as usual. Nor are they necessarily halting their transplant programme. Their argument is that transplanted kidneys and other transplanted organs are too precious not to protect them with relevant immunosuppressive drugs. Why would we not have the same attitude about the brains and spinal cords of our patients with active multiple sclerosis?

We could argue that solid-organ transplant patients are significantly more immunocompromised than pwMS on disease modifying treatment (DMT). Most transplant patients are on triple immunotherapy, compared to pwMS who are on monotherapy and even then, the level of immunosuppression is generally low. Hence, the mortality/morbidity risk to an individual on a DMT, infected with COVID-19, may be actually quite moderate to low. Another hypothesis being considered is that moderate immunosuppression may prevent severe complications associated with COVID-19 infection. The severe pulmonary complications of COVID-19 infection are consistent with ARDS (acute respiratory distress syndrome) caused by an over-exuberant immune response to the virus (Ramanathan et al., 2020). As a result, several exploratory trials are currently being undertaken in China and elsewhere using immunosuppressants to try and dampen the immune response to the virus. Interestingly, fingolimod, a S1P modulator licensed for MS, is being tested as a treatment for COVID-19 associated ARDS

* Corresponding author.
E-mail address: g.giovannoni@qmul.ac.uk (G. Giovannoni).

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Table 1
Main attributes of licensed MS DMTs in relation to the COVID-19 pandemic

At risk category	Class	Trade name	Mode of action	Efficacy	Class	Safe to start treatment	Advice regarding treatment	In the event of COVID-19 infection?	Immuosuppression?	Attributes and caveats
Very low	Interferon-beta	Betaferon, Avonex, Rebif, Plegridy	Immunomodulatoy (not immunosuppressive), pleitropic immune effects	Moderate	Maintenance immunomodulatoy	Yes	Continue	Continue	No	Has antiviral properties that may be beneficial in the case of COVID-19
Very low	Glatiramer acetate	Copaxone	Immunomodulatoy (not immunosuppressive), pleitropic immune effects	Moderate	Maintenance immunomodulatoy	Yes	Continue	Continue	No	
Very low	Teriflunomide	Aubagio	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), anti-proliferative	Moderate (1st-line) / Moderate to high (2nd-3rd-line)	Maintenance immunomodulatoy	Yes	Continue	Continue	Possible (no well-defined immunosupressive signature)	Has antiviral properties that may be beneficial in the case of COVID-19
Low	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	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	Natalizumab	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Yes	Continue	Continue or miss infusion depending on timing	Yes, continous	Low risk, but theoretical concerns of creating an environment in mucosal surfaces and the gut that may promote prolonged viral shedding. Also risk that as COVID-19/SARS-CoV-2 is neurotropic it may prevent viral clearance from the CNS.
Intermediate	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	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	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	Theoretical risk that ocrelizumab and other anti-CD20 therapies may result in prolonged viral shedding.
Intermediate	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	Theoretical risk that in the immune depletion phase cladribine may result in prolonged viral shedding.

(*continued on next page*)

Table 1 (*continued*)

At risk category	Class	Trade name	Mode of action	Efficacy	Class	Safe to start treatment	Advice regarding treatment	In the event of COVID-19 infection?	Immuosuppression?	Attributes and caveats
High*	Mitoxantrone	Novatrone	Immune depleter (topoisomerase inhibitor)	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	Theoretical risk that in the immune depletion phase mitoxantrone may result in prolonged viral shedding.
High*	Alemtuzumab	Lemtrada	Anti-CD52, non-selective immune depleter	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	Theoretical risk that in the immune depletion phase alemtuzumab may result in prolonged viral shedding.
High*	HSCT	-	Immune depletion and haemopoietic stem cell reconstitution	Very high	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Yes, intermittent	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.

(ClinicalTrials.gov Identifier: NCT04280588). Interferon beta is also being trialled in COVID-19 based on its antiviral properties (ClinicalTrials.gov Identifier: NCT04276688).

Then there is the virology to take into account. SARS-CoV-2, the cause of COVID-19, is a new human pathogen that is likely to have recently crossed species (Andersen et al., 2020). COVID-19 will eventually become endemic and hence pose a seasonal risk to patients on immunosuppressive therapies. As it is a small RNA virus with low fidelity it is likely to mutate rapidly making a one-off vaccine only a partial solution. Vaccines take time to be developed, tested and introduced at a population level. Delaying treatment, de-escalating therapy by switching to immunomodulatory DMTs, such as interferon-beta, glatiramer acetate or teriflunomide, or interrupting dosing of DMTs to wait for a vaccine will delay the adequate treatment of MS, especially as it may take 12–18 months to develop a vaccine. We, therefore, need a pragmatic response on management of the potential threat of COVID-19 in individuals with MS. If patients have active MS they need to be treated based on the clinical evidence at hand and hence may need to be treated with higher efficacy DMTs. This should be implemented in conjunction with appropriate behavioural modifications to reduce or ideally prevent exposure to the virus.

It is essential to consider the potential risk of morbidity and possible mortality for each MS patient, who may be infected with SARS-CoV-2 and develops COVID-19. The individual's risk profile is multifactorial; their DMT and consequent immune response is one of the factors. Other aspects to consider, when assessing a respiratory viral infection include: smoking practices (increased cigarette smoking increases risk); ambulatory status (less mobility increases risk, especially if the patient is in a wheelchair); age (increasing age increases risk); weight (increasing weight impacts on ambulation and respiratory function); underlying respiratory illnesses, such as asthma or COPD. Also, the frequency of necessary attendance at a hospital or healthcare facility for laboratory or MRI testing, but also for infusions may place the patient at a higher risk of exposure. In the context of these factors the health care professionals should weigh the potential risks of SARS-CoV-1 exposure and manage their DMT accordingly. Visits for MS care should preferably be done by telemedicine or phone.

The potential hazards posed by each DMT differ and, rather than imposing a blanket rule, decisions regarding treatment should be individualised (See Table 1) and discussed with patients. For some patients having their MS treated and controlled may be more important than the potential danger of being exposed to and acquiring a more severe COVID-19 infection. Table 1 is our attempt to define the risks associated with the different classes of DMTs in the event of a patient acquiring a COVID-19 infection.

Assuming that antiviral responses are driven mainly by T-cells, in particular CD8+ cytotoxic T-lymphocytes, and natural-killer cells and less so, at least initially, by B-cells, allows one to construct a hierarchy of immunosuppression of DMTs. The highest risk are the immune reconstitution therapies during the depletion phase of the treatment, i.e. haematopoietic stem cell transplantation (HSCT), alemtuzumab (Lemtrada), mitoxantrone (Novantrone) and cladribine (Mavenclad). After immune reconstitution, once the total lymphocyte counts have returned to normal or near normal the risk of severe viral infections are probably no higher than expected for the background population and would be associated with age and other comorbidities. Please note, immune reconstitution takes months to years, so if the patient's last course of treatment was in the previous 6–12 months they may still be immunocompromised. A total lymphocyte count less 1.1×10^9/L or 1100/mm^3 is associated with an increased risk of infection and infection-related mortality (Warny et al., 2018). This risk increases progressively the lower the absolute lymphocyte counts; particularly when the lymphocyte count drops below 800/mm^3 (>50% risk) (Warny et al., 2018). As a rough guide, pwMS with a lymphocyte count above 800/mm^3 (WHO grade 2) are able to deal with viral infections reasonably well provided they have no other comorbidities and are relatively young.

Of the immune reconstitution therapies, cladribine (Mavenclad) is classed as intermediate risk, because it is a relatively poor T-cell depleting agent (Stuve et al., 2019). T-cells are only depleted post-cladribine by an average of 50% with the CD4+ population being more sensitive than the CD8+ population. In the phase 3 CLARITY study, viral infections were uncommon post-cladribine and apart from herpes zoster, infections were no more frequent in cladribine-treated subjects compared to placebo (Cook et al., 2011). When viral infections occurred post-cladribine they tended to be mild or moderate in severity. Similarly, anti-CD20 therapies such as ocrelizumab have a minor impact on T-cell counts and are not associated with severe viral infections (Mayer et al., 2019). In the phase 3 relapsing-remitting and primary progressive trials, infections were slightly more frequent on ocrelizumab compared to comparator arms (interferon-beta-1a or placebo) (Hauser et al., 2017; Montalban et al., 2017). Most of these infections were mild and moderate with the severe infections being bacterial in nature (pneumonia, urinary tract infections and cellulitis). We therefore feel that both cladribine and anti-CD20 therapies are relatively safe to use during the COVID-19 pandemic based on their profiles defined in phase 3 trials.

The sphingosine-1-phosphate (S1P) modulators (fingolimod, siponimod, ozanimod, ponesimod) work by reducing the egress of lymphocytes from secondary lymphoid organs into the circulation (Stepanovska and Huwiler, 2019). The actual degree of lymphopaenia is not associated with their efficacy nor the risk of infection (Francis et al., 2014). Overall infectious complications are relatively low on S1P modulators, with opportunistic infections emerging over time (Epstein et al., 2018; Luna et al., 2019). Importantly, the vast majority of patients on S1P modulators do not have a problem dealing with community acquired viral infections. Patients on fingolimod who are exposed to and acquire exotic viral infections such as dengue fever seem to deal with them without complications (Fragoso et al., 2016a). This is why patients on S1P modulators should be at relatively low risk of complications from COVID-19 infection and why it may be safe to continue these treatments during the epidemic. Fingolimod does however blunt vaccine responses (Kappos et al., 2015) indicating that both the priming and effector arms of the immune system are affected, whether this will impact on COVID-19 outcomes is at present unknown.

Although most neurologists consider natalizumab relatively safe there is a small increased risk of upper respiratory tract infections on this medication (Kapoor et al., 2018; Polman et al., 2006; Rudick et al., 2006) and there are theoretical reasons why it may reduce trafficking of lymphocytes in the lung and mucosa (Woodside and Vanderslice, 2008). It is clear that natalizumab blocks immune surveillance of the CNS, hence a person on natalizumab who develops a COVID-19 encephalitis could be in danger of major complications of this infection. The latter is analogous to PML, which is also a viral encephalitis, and similar to herpes-simplex and varicella -zoster encephalitis resulting from natalizumab exposure (Fine et al., 2013). Coronaviruses are potentially neurotropic and there has been one online case report of a 56-year old Chinese man developing COVID-19 encephalitis. He developed a decreased level of consciousness with a normal CT scan of the brain. Spinal fluid analysis revealed SARS-CoV-2. He subsequently made a recovery and was discharged (Xinhua, 2020). There is also clear evidence from the large Chinese cohort that anosmia may be an early sign of COVID-19 infection, suggesting involvement of the neuraxis.

Another human coronavirus HCoV-OC43, which is generally associated with mild upper respiratory tract infections, has been shown to have neuroinvasive properties. Studies in mice have shown that HCoV-OC43 can infect neurons and cause encephalitis and cause persistent infections in human neural-cell lines (Arbour et al., 1999). There are case reports identifying HCoV-OC43 RNA in the cerebrospinal fluid or brain of children with acute disseminated encephalomyelitis (Yeh et al., 2004) and acute encephalomyelitis (Morfopoulou et al., 2016). Coronaviruses mutate very rapidly and hence may produce neurotropic strains quite quickly. The latter is a potential issue in the context of natalizumab, which creates an immune privileged site that may allow for the selection of these neurotropic mutants. Another aspect that needs to be considered is what happens in the gut. SARS-CoV-2 infects the gastrointestinal tract, with about 3–4% of people with COVID-19 developing diarrhoea (Guan et al., 2020). SARS-CoV-2 is shed in the stool (Holshue et al., 2020). Natalizumab also reduces lymphocyte trafficking to the gut and is a licensed treatment for Crohn's disease (Ghosh et al., 2003). Will patients on natalizumab and other DMTs have increased viral replication in the gut and shedding in the stool? Will patients on natalizumab and other DMTs infected with the virus become superspreaders? Despite these questions the current science indicates that patients on natalizumab should be able to deal with a novel viral infection such as dengue (Fragoso et al., 2016b). Reassuringly, five patients on natalizumab infected with dengue virus cleared the virus without complications similar to those on fingolimod (Fragoso et al., 2016b).

Clearly, any decision to start a DMT during the COVID-19 pandemic will need to be taken carefully and will depend on the state of the COVID-19 pandemic, not only in the particular country concerned, but in the specific area the patient lives and receives therapy. For example, aggressive public health steps to contain the spread of the virus locally may make it relatively safe for a patient to start an immunosuppressive therapy. Our concern is that the COVID-19 pandemic may trigger a large number of neurologists and patients to reconsider treatment strategy and choice of initial DMT and to opt for less effective immunomodulatory DMTs. This change needs to be considered carefully. The COVID-19 pandemic in all likelihood will be short lived and it would be unfair to patients treated during the epidemic to be disadvantaged in the long term regarding the management of their MS. Neurologists have spent an extraordinary amount of time and effort to activate the MS community: to advance the principle that 'time is brain', to treat MS proactively to a target of no evident disease activity (NEDA) and more recently, to flip the pyramid and use higher efficacy treatments first line. These treatment principles are evidence-based and should not be thrown out in the context of a potential, but yet undefined, risk to our patients.

Box 1
Recommendations on the management of Italian MS patients during the COVID-19 epidemics

These are recommendations made by neurologists and infectious diseases specialists whilst we have no evidence-based data at present.

Treatment of MS patients

Given the lack of knowledge or data on the COVID-19 disease course in MS patients receiving DMTs, at present there is no recommendation to stop the different DMTs and therefore expose MS patients to the risk of MS exacerbations. We, therefore, recommend continuing the current DMT specifically with:

- First-line DMTs (beta-interferons, glatiramer acetate, teriflunomide or dimethyl fumarate). These DMTs can be prescribed as usual.
- Fingolimod
- Natalizumab

For 'lymphodepleting' DMTs: Any decisions about these DMTS should be based on individual circumstances.

- Temporarily delay the start of lymphodepleting DMTs such as ocrelizumab, alemtuzumab, rituximab or cladribine.
- Temporarily delay (between 6 and 12 months depending on the DMT) re-dosing of alemtuzumab, ocrelizumab and

cladribine. This decision should be made according to individual factors such as disease severity and activity. For anti-CD2O DMTs it is recommended to delay the next dose even beyond 6 months if CD19+ and CD20+ lymphocyte counts are severely decreased at the time the next dose is due.
- Some special considerations: for patients who have already received the first dose of the first cycle, it is recommended to give the second dose (i.e. complete the first cycle) and 'extra precautions' should be taken.

Patients with confirmed COVID-19 infection: Withhold any first or second-line DMT until clinical resolution and/or approval to continue treatment by an infectious disease specialist. Note: given the potential antiviral activity of beta-interferons, the decision to continue this treatment rests with the treating neurologist.

Symptoms of potential COVID-19 infection: headache, anosmia, fever, dry cough and asthenia.

What to do in the event of COVID-19 symptoms?

Instruct your patients not to attend accident and emergency services to avoid overcrowding and further spreading of the virus. Instruct your patients to call the local emergency number, describe their symptoms and wait for instructions.

Evaluate the temporary withdrawal of current DMT based on the guidelines provided above.

Recommendations for MS patients and healthcare professionals at MS centres:

- If possible, avoid crowded places such as cinemas, theatres, schools, etc.
- In high risk areas, restrict access to MS centres to MS patients only.
- For patients on immunosuppressive infusion therapies, the use of protective surgical-grade masks is recommended.
- If travelling long distances or using public transport is absolutely necessary, it is recommended to use protective masks and hand sanitizing (particularly for patients on fingolimod, alemtuzumab, ocrelizumab, cladribine or rituximab).
- If possible, work from home.
- Good personal hygiene is always important, specifically, it is recommended to wash your hands frequently, ideally in an alcohol-based gel (>60% alcohol).

These recommendations are provided as a guideline only, please always refer to your local government advice. These recommendations are likely to change depending on the evolution of the epidemics.

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