

ABN GUIDANCE ON THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS IN RESPONSE TO THE COVID 19 PANDEMIC

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SCOPE: This guidance applies to the recovery phase of the COVID 19 pandemic and any future resurgence. We appreciate the risk of becoming infected with SARS-CoV2 will vary over time and between regions.

DATE OF REVIEW: 01 November 2020

EXECUTIVE SUMMARY

1. The risk of SARS-CoV2 infection will vary over time and geographically. In this document, "very high risk" of SARS-CoV2 infection is equivalent to level 4 and 5 of the UK threat alert system, "high risk" to 3 and "low risk" is level 1 and 2.
2. Except in the most extreme phases [level 5] of the pandemic, where healthcare systems are threatened to be overwhelmed, the MS team should be fully resourced with MS nurses and allied health professionals
3. MRI monitoring for JC virus positive patients, treated with natalizumab for more than two years, should continue at all times. Routine monitoring and diagnostic scans should continue up to threat levels 4 and 5.
4. When and where the infection risk is very high, the increased pressures on healthcare services, and the increased risk to patients of travelling to clinical sites, means extended interval safety blood monitoring may be necessary and desirable. Monitoring should return to recommended SmPC standards as soon as possible.
5. The effect of DMTs on the risk of SARS-CoV2 infection and COVID 19 disease remains uncertain and we commend pwMS and MS teams to continue to submit data to the UK MS Register study of COVID 19. We recommend that patients are counselled on the effect of a DMT on their individualised risk of COVID 19 disease, taking into account its duration of action; any comorbidities; and also the DMT's impact on the efficacy of any future SARS-CoV2 vaccine. Patients should be informed if their treatment choice requires shielding [especially cladribine and alemtuzumab].
6. Interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide and dimethyl fumarate may be used when and where rates of SARS-CoV2 infection are very high, because these drugs do not significantly increase the risk of infection of serious COVID 19 disease
7. Natalizumab may be used when and where rates of SARS-CoV2 infection are very high, provided it may be administered in a setting with minimal risks of SARS-CoV2 infection, and where the individual's risk of PML is acceptable, given previous immunosuppressant drug history, duration of previous exposure to natalizumab etc.
8. Fingolimod may be used cautiously at very high rates of SARS-CoV2 infection, noting that the SmPC advises there is an increased risk of viral infections.
9. Ocrelizumab may be started cautiously in patients with active relapsing-remitting disease when and where the rate of SARS-CoV2 infection is very high, provided it may be administered in a setting with minimal risks of SARS-CoV2 infection. Similarly ocrelizumab re-treatment for relapsing-remitting disease may be continued at very high rates of SARS-CoV2 infection, but consideration should be given to delaying re-treatment until the infection rate lowers.
10. The use of ocrelizumab in primary progressive multiple sclerosis, where patients are more disabled, are more likely to have comorbidities and the therapeutic gain

is lower, should continue only when the risk of SARS-CoV2 is low, except on a case by case basis.

11. Cladribine should be started cautiously on a case-by-case basis when the risk of SARS-CoV2 is very high. Re-treatment should be delayed until the risk of infection is level 3 or below.
12. Alemtuzumab should only be started, or retreated, when the risk of SARS-CoV2 is low [threat level 1 or 2], except on a case by case basis.
13. Autologous haematopoietic stem cell transplantation should only be performed when and where the risk of SARS-CoV2 infection is low, for patients with unusually high disease activity, and in consultation with the stem cell transplantation teams.
14. pwMS with mild symptoms of COVID-19 should not stop first-line DMTs, but infusions [and cladribine administration] should be delayed until symptoms resolve.
- 15.** In cases of severe COVID-19 infection, the prescribing team should be consulted, who would normally recommend that all injectables and oral medication are stopped and infusions delayed, restarting fingolimod and natalizumab treatment if possible within 8 weeks to avoid rebound disease.

DETAILED GUIDANCE

A. VARIATION IN THE RISK OF SARS-COV2 INFECTION

1. As the pandemic changes, over time and geographically, the risk of becoming infected with SARS-CoV2 also varies. This includes the risk of getting infected by attending a healthcare setting for infusion or blood tests or MRI scans. We anticipate that MS treatment teams will institute different measures of this advice at different times and in different places. Although the risks cannot yet be quantified exactly, we propose that "high risk" of SARS-CoV2 infection is equivalent to level 4 and 5 of the UK threat alert system and "low risk" is level 1 and 2.

B. THE MINIMUM MS TEAM

2. Except in the most extreme phases of the pandemic, where healthcare systems are threatened to be overwhelmed, the MS team should be fully resourced with MS nurses and allied health professionals. In particular, we are concerned that patients may be acquiring disability and morbidity due to lack of access to physiotherapists, continence advisers, psychologists and the many other professionals whose positive impact on pwMS has long been established.

C. ADVICE FOR MINIMUM SAFETY AND DISEASE ACTIVITY MONITORING

3. **MRI monitoring** for JC virus positive patients, treated with natalizumab for more than two years, should continue at all times. Routine monitoring and diagnostic scans should continue up to threat levels 4 and 5.
4. When and where the SARS-CoV2 infection rate is low, we recommend monitoring as per the drug's SmPC. When and where the infection rate is higher, the increased pressures on healthcare services, and the increased risk to patients of travelling to clinical sites, means **blood monitoring with increased intervals** for DMTs may be necessary and desirable. We propose the following as a minimum. Importantly, patients must remain vigilant to symptoms and report any concerns promptly, especially those on alemtuzumab.

	Normal monitoring recommendation	Recommendation until risk of COVID 19 clarified or passed
Interferon Beta	3 months, 6 months, then 6 monthly	3 months after starting then none required
Glatiramer Acetate	None required	None
Teriflunomide	2 weekly for 6 months, then 2 monthly if stable	Monthly for 1st 6 months then 4 monthly if stable
Dimethyl Fumarate	3 monthly	6 monthly if stable and lymphocytes above 0.5
Fingolimod	1,3,6,12 months, then every 6-12 months	6 monthly in first year then 12 monthly if stable
Natalizumab	Every 3 months	6 monthly JCV
Ocrelizumab	Every 6 months	Prior to dosing
Alemtuzumab	Monthly	3 monthly FBC, C&E, LFTs, TFTs

Cladribine	2 months and 6 months after each course, 2 monthly if lymph <0.5	No change to 2 month test Delay 6 month test if 2 month bloods are stable and lymphocytes >0.5
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C. THE RISK OF COVID-19 IN PEOPLE WITH MS [PWMS] ON DISEASE-MODIFYING THERAPIES [DMTS].

The data on which we can make recommendations is currently limited. To date, there is only one published experience of COVID 19 in pwMS on DMTs: on 232 patients from 38 Italian centres. A limitation of this paper is that no patients had received alemtuzumab and only five had taken cladribine. Five of this cohort died, all of whom had comorbidities or an EDSS of 7.0 and only two were on DMTs [dimethyl fumarate or ocrelizumab; Sormani Lancet Neurology April 29, 2020]. We are aware of unpublished data from the UK MS Register, Wales [Prof Robertson, Cardiff, personal communication] and Sweden [Prof Fredrik Piehl, personal communication] which does not indicate that DMTs are a risk factor in COVID 19 infection or its complications, and a publication of immunotherapies in the rheumatology patients that has a similar conclusion [Chen NEJM April 30, 2020]. Anecdotal experience to date within the UK concurs, whilst noting that all centres have stopped giving alemtuzumab or cladribine during March and April 2020, and only a few have been infusing ocrelizumab. We heard of only one COVID 19 death that could not be explained by advanced disability or comorbidities [a patient aged 51 on fingolimod].

Our provisional conclusion is that most DMTs do not confer a significantly increased risk of SARS-CoV2 infection or its complications. In contrast, advanced disability and comorbidities are risks for death due to COVID 19.

Our advice now is:

5. The effect of DMTs on the risk of SARS-CoV2 infection and COVID 19 disease remains uncertain and we commend pwMS and MS teams to continue to submit data to the UK MS Register study of COVID 19. We recommend that patients are counselled on the effect of a DMT on their individualised risk of COVID 19 disease, taking into account any comorbidities; and also the DMT's potential impact on the efficacy of any future SARS-CoV2 vaccine.¹ Drugs with longer duration of effect [eg ocrelizumab, alemtuzumab] may be given at times of low SARS-CoV2 infection rate, but still confer increased risk of infection and COVID 19 disease at a surge of SARS-CoV2 infection months later.

¹ Metze [CNS Neuroscience and Therapeutics 2019 25: 245-254] reports good responses to influenza vaccine with beta-interferon and glatiramer-treated patients, with somewhat reduced immunogenicity for those on fingolimod and natalizumab. Mc Carthy [Neurology. 2013 Sep 3;81(10):872-6] reports good responses to three vaccines after alemtuzumab, provided it is administered over three months from last dose. According to their SmPCs, live vaccines may only be given to alemtuzumab after a delay [we suggest 12 months] or cladribine [when the lymphocyte count has returned to normal].

6. **Interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide and dimethyl fumarate** may be used even at very high rates of SARS-CoV2 infection [level 4 and 5], because these drugs do not seem to significantly increase the risk of infection or serious COVID 19 disease. The risk of SARS-CoV2 infection may be higher in people on **dimethyl fumarate** with prolonged lymphopenia, although the threshold for this has not been defined.
7. **Natalizumab** may be used even at very high rates of SARS-CoV2 infection, because it does not significantly increase the risk of infection or serious COVID 19 disease. However, it should be administered in a setting with minimal risks of SARS-CoV2 infection. In the short term, this is the safest high-efficacy therapy, because there is very little to suggest that SARS-CoV2 is neurotropic.² But this advantage should be weighed against the individual's risk of PML, given previous immunosuppressant drug history, duration of exposure to natalizumab etc. It may be appropriate to consider extended interval dosing. For the period of the coronavirus epidemic, NHSE has agreed to relax the criteria for natalizumab to include patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy [as per its licence]. This allows us to treat patients with one relapse on DMTs, and radiological evidence of disease activity, with natalizumab [for the duration of the epidemic]. In the longer term, the risks of PML may outweigh the potential benefits of natalizumab treatment.
8. **Fingolimod** may be used cautiously at high or rarely at very high rates of SARS-CoV2 infection. Although increased risk of SARS-CoV2 has not been seen to date with fingolimod, the SmPC advises that the risk of influenza is "very common" and herpetic infections are "common".
9. **Ocrelizumab** may be used cautiously at high or rarely at very high rates of SARS-CoV2 infection, although the SmPC advises there is an increased risk of viral infections, which has not been seen to date with SARS-CoV2. It is reasonably safe to start patients with active relapsing-remitting disease on **ocrelizumab**, at any stage in the pandemic, although we recommend caution during times of very high infection rate. It is also reasonably safe to re-treat people with relapsing remitting disease using ocrelizumab. If the risk of SARS-CoV2 infection is very high, it is reasonable to delay re-treatment until the infection rate lowers. The Swedish experience of rituximab, which is very similar to ocrelizumab, is that an infusion will remain effective at controlling MS for longer than 6 months³. Another approach to optimise ocrelizumab retreatment frequency might be to emulate the use of rituximab now common in the management of NMO: to repeat treatment only when CD19+ or CD19+CD27+ lymphocytes have recovered to over 1% of the lymphocyte population.

² We are aware of two published case reports to the contrary, finding SARS-CoV2 in CSF [Moriguchi IJID March 2020] and brain [Mondolfi J Virol March 2020], but take the view of the Encephalitis Society that the risk of encephalitis, if confirmed at all, is very small.

³ Juto A, Fink K, Al Nimer F, Piehl F. Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity. *Mult Scler Relat Disord*. 2019 Oct 24;37:101468. doi: 10.1016/j.msard.2019.101468.[Epub ahead of print] PubMed PMID: 31683231

10. The use of **ocrelizumab** in primary progressive multiple sclerosis, where patients are more disabled, the prevalence of comorbidities are higher and the therapeutic gain is lower, should continue only when the risk of SARS-CoV2 is low.
11. There is very limited experience⁴ of pwMS on **cladribine** becoming infected with SARS-CoV2 and the SmPC warns of herpetic viral infections being “common”. However it may be considered on a case-by-case basis. When and where the rate of SARS-CoV2 infection is very high, the risks of increased infection for three months after cladribine administration, and the advice to shield, may outweigh its benefits.
12. The established risk of serious opportunistic infection in the first three months of **alemtuzumab** mean it is only usually appropriate for threat level 1 or 2 and should be accompanied by shielding. The second course of alemtuzumab may safely be delayed from 12 to 18 months without concerns for a return of disease activity.
13. **Autologous haematopoietic stem cell transplantation** is usually a semi-elective procedure for multiple sclerosis, and has the highest risk of opportunistic infections and so should only be performed when and where the risk of SARS-CoV2 infection is very low [threat level 1] and in consultation with the stem cell transplantation teams.

D. DMTS IN PwMS WITH ACTIVE COVID 19 INFECTION

14. pwMS with mild symptoms of COVID-19 should not stop a first line DMT, but infusions [and cladribine administration] should be delayed until symptoms resolve.
15. In cases of MS with severe COVID-19 infection [for instance requiring admission or ventilation] the prescribing team should be consulted, who would normally recommend that all injectables and oral medication are stopped and infusions delayed, restarting fingolimod and natalizumab treatment if possible within 8 weeks to avoid rebound MS disease activity.

GUIDANCE CONSIDERED:

Advice from the Italian MS Society:

<https://www.aism.it/sites/default/files/ComunicazioneGdSSINSM-Coronavirus.pdf>

European Society for Blood and Bone Marrow Transplantation

<https://www.ebmt.org/ebmt/news/ebmt-recommendation-coronavirus-disease-covid-19>

The Encephalitis Society

⁴ Merck kindly provided data on four patients.

<https://www.encephalitis.info/Blog/coronavirus>