

ABN GUIDANCE ON THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS IN RESPONSE TO THE COVID19 PANDEMIC

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AUTHORS: Alasdair Coles and the MS Advisory Group.

CONSULTATIONS: MS Society, MS Trust

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EXECUTIVE SUMMARY

1. All DMTs should be available to people with multiple sclerosis [pwMS] during the SARS CoV2 pandemic, provided that the benefits of treatment outweigh their risks, taking into account the local rate of SARS CoV2 infection, the individual's general health and their exposure to the virus. PwMS should be advised if a DMT might impact on the severity of Covid19 disease or the efficacy of any future SARS-CoV2 vaccine.
2. All people with multiple sclerosis should be encouraged to follow government guidance on measures to prevent SARS CoV2 infection.
3. Consistently, the strongest evidence is for these risk factors for severe Covid19 disease in people with MS: high disability [EDSS>6.0], older age, obesity, male gender, BAME ethnicity, diabetes and cardiorespiratory disease. Physicians should consider these factors when advising a pwMS.
4. Calculating an individual's risk of severe Covid19 disease is complex. Specifically for DMTs, we would anticipate pwMS being advised to strictly self-isolate for at least four weeks after an alemtuzumab administration and for at least two weeks after high-dose steroids. The risk of severe Covid19 disease is increased for many months after ocrelizumab and cladribine; self-isolation for all that time is not appropriate except for individuals with multiple other risk factors.
5. Except in the most extreme phases of the pandemic, where healthcare systems are threatened to be overwhelmed, MS teams should be fully resourced with MS specialist neurologists, nurses and allied health professionals
6. MRI monitoring for JC virus positive patients, treated with natalizumab for more than two years, should continue at all times. Diagnostic scans, and scans influencing treatment decisions, should also continue.
7. When and where the infection risk is high¹, 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. Monitoring should return to recommended SmPC standards as soon as feasible.
8. Interferon beta 1a, interferon beta 1b, glatiramer acetate, teriflunomide and dimethyl fumarate may be used even with high rates of SARS CoV2 infection, because current evidence suggests these drugs do not increase the risk of serious Covid19 disease.
9. Current limited evidence suggests that natalizumab has the lowest risk for severe Covid19 disease, amongst the high-efficacy therapies. Extended interval dosing should be considered.

¹ We do not link our guidance to either the UK government "alert levels" or "tier" system.

10. Fingolimod may be used, noting that the SmPC advises there is an increased risk of viral infections.
11. There is some evidence to suggest that pwMS treated with ocrelizumab are more likely to be hospitalised with Covid19 and to need intensive care. It may be initiated in patients with active relapsing-remitting disease where this risk, taking into account co-morbidities and Covid19 susceptibility, is appropriately balanced by the benefits of the drug. Consideration should be given to delaying ocrelizumab re-treatments.
12. The benefit of using ocrelizumab to treat primary progressive multiple sclerosis may be outweighed by the greater Covid19 risk, as this group are more disabled and are more likely to have comorbidities, as well as the potential compromise to future SARS CoV2 vaccines.
13. There is limited evidence to assess the risk of severe Covid19 disease with cladribine. It may be used in patients with active relapsing-remitting disease where this uncertainty is appropriately balanced by the benefits of the drug.
14. We have not seen sufficient evidence to assess the risk of severe Covid19 disease with alemtuzumab. It should only be started, or retreated, when this significant uncertainty, and the high risk of viral infections in the first month, are appropriately balanced by the benefits of the drug.
15. Autologous haematopoietic stem cell transplantation should only be performed in exceptional cases of relapsing disease that remain highly active despite high-efficacy treatments, and in consultation with the stem cell transplantation team.
16. High dose steroids [for instance for a relapse of MS] probably increase the risk for severe Covid19 disease and we recommend consideration of self-isolation for at least two weeks after steroids.
17. pwMS with mild symptoms of COVID-19 should not stop interferon beta, glatiramer, teriflunomide, dimethyl fumarate or fingolimod, but infusions [and cladribine administration] should be delayed until symptoms resolve.
18. In cases of severe COVID-19 infection, the prescribing team should be consulted, who would normally recommend that oral medication is stopped and infusions delayed, restarting fingolimod and natalizumab treatment if possible within 8 weeks to avoid rebound disease.
19. The effect of DMTS on the risk of SARS CoV2 infection and Covid19 disease remains uncertain and we commend pwMS and MS teams to continue to submit data to registries and research studies, especially the MS Register Covid study [<https://www.ukmsregister.org/Research/COVID19CRF>].

DETAILED GUIDANCE

A. PRINCIPLES OF DMT USE IN PEOPLE WITH MS DURING THE PANDEMIC

1. All DMTs should be available to people with MS [pwMS] during the SARS CoV2 pandemic. For an individual pwMS, the potential benefits of any treatment should outweigh the risks, taking into account: the local rate of SARS CoV2 infection, the individual's general health, their exposure to the virus [e.g. through occupation or caring responsibilities] and the DMT's impact on the risk of serious Covid19 disease and the efficacy of any future SARS CoV2 vaccine.
2. All people with multiple sclerosis should be encouraged to follow government guidance on measures to prevent SARS CoV2 infection.
3. Consistently, the strongest evidence is for these risk factors for severe Covid19 disease in people with MS: high disability [EDSS>6.0], older age, obesity, male gender, BAME ethnicity, diabetes and cardiorespiratory disease. Physicians should consider these factors when advising a pwMS.
4. Calculating an individual's risk of severe Covid19 disease, and so determining who may be "extremely clinically vulnerable" and eligible for "shielding" benefits [when these are available], is uncertain and complex. Examples of risk stratification tools are given in Section F. Specifically for DMTs, we would anticipate pwMS being advised to strictly self-isolate for at least four weeks after an alemtuzumab administration; for at least two weeks after high-dose steroids; and after ocrelizumab and cladribine in individuals with multiple other risk factors.

B. THE MINIMUM MS SERVICE

5. Except in the extreme phases of the pandemic, where healthcare systems are threatened to be overwhelmed, the MS team should be fully resourced with specialist MS neurologists, MS nurses and allied health professionals. It is particularly important that pwMS continue to receive advice and clear communication at all times.

C. ADVICE FOR MINIMUM SAFETY AND DISEASE ACTIVITY MONITORING

6. MRI monitoring for JC virus positive patients, treated with natalizumab for more than two years, should continue at all times. Diagnostic scans, and scans influencing treatment decisions, should also continue.
7. When and where the infection risk is 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. Monitoring should return to recommended SmPC standards as soon as feasible.

	Normal monitoring recommendation	Recommendation when SARS CoV2 infection risk is high
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

C. THE RISK OF COVID-19 IN PEOPLE WITH MS [PWMS] ON DISEASE-MODIFYING THERAPIES [DMTS].

There is more evidence to guide recommendations now [October 2020] than at the time of the last version of this guidance [May 2020], but it is still incomplete. So our guidance should be regarded as provisional. Nonetheless, it is broadly in line with advice from other countries and organisations [summarised in Korsukewitz C et al. Nat Rev Neurol. 2020]. A list of sources is provided at the end of the document.

8. Interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide and dimethyl fumarate may be used with high rates of SARS-CoV2 infection, because these drugs do not significantly increase the risk of serious Covid19 disease.
9. The current limited evidence suggests that natalizumab has the lowest risk for severe Covid19 disease, of the high-efficacy therapies. It should 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. Extended interval dosing [usually after the first year of treatment] may reduce the risk to patients of travelling to clinical sites. 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.

10. Fingolimod may be used, noting that the SmPC advises there is an increased risk of viral infections.
11. There is some evidence to suggest that pwMS treated with ocrelizumab are more likely to be hospitalised with Covid19 and to need intensive care. Ocrelizumab may be initiated cautiously in patients with active relapsing-remitting disease where this risk is appropriately balanced by the benefits of the drug, and the patient is stringent in measures to prevent infection. The risk of severe Covid19 disease is likely to be increased for many months after ocrelizumab and self-isolation for all that time is not appropriate except for individuals with multiple other risk factors. Patients contemplating ocrelizumab should be advised that they may not be able to receive a future SARS CoV2 vaccine if it is a live vaccine, and they may not respond immunologically to a dead or inactivated vaccine. Consideration should be given to delaying ocrelizumab re-treatment. 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 months². Another approach to optimise ocrelizumab retreatment is to emulate the use of rituximab in the management of NMO: to repeat treatment only when CD19+ or CD19+CD27+ lymphocytes have recovered to over 1% of the total lymphocyte population.
12. The benefit of using ocrelizumab to treat primary progressive multiple sclerosis may be outweighed by the greater Covid19 risk, as this group are more disabled and are more likely to have comorbidities, as well as the potential compromise to a future SARS CoV2 vaccine.
13. There is limited evidence to assess the risk of severe Covid19 disease with cladribine. It may be used cautiously in patients with active relapsing disease where this uncertainty is appropriately balanced by the benefits of the drug and the patient is stringent in measures to prevent infection. Any risk of severe Covid19 disease is likely to be increased for months after cladribine, and may be greater in the second year; self-isolation for all that time is not appropriate except for individuals with multiple other risk factors.
14. There is almost no evidence to assess the risk of severe Covid19 disease with alemtuzumab. It should only be started, or retreatment given, when this significant uncertainty, and the high risk of viral infections in the first month after treatment, are appropriately balanced by the benefits of the drug, taking into account co-morbidities and Covid19 susceptibility. We recommend strict self-

² 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

isolation for four weeks after an infusion of alemtuzumab. The second course of alemtuzumab may safely be delayed from 12 to 18 months without concerns for a return of disease activity.

15. Autologous haematopoietic stem cell transplantation is usually a semi-elective procedure for multiple sclerosis and has the highest risk of opportunistic infections. It should only be performed in exceptional cases of relapsing disease that remains highly active despite high-efficacy treatments, and in consultation with the stem cell transplantation teams. We note NICE's recommendation of self-isolation for six months after a transplant.
16. High dose steroids [for instance to treat a relapse of multiple sclerosis] probably increase the risk for severe Covid19 disease transiently and we recommend consideration of self-isolation for two weeks after treatment [MSIF guidelines suggest four weeks].

D. DMTS IN PwMS WITH ACTIVE COVID19 INFECTION

17. pwMS with mild symptoms of COVID-19 should not stop interferon beta, glatiramer, teriflunomide, dimethyl fumarate or fingolimod, but infusions [and cladribine administration] should be delayed until symptoms resolve.
18. 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.

E. RESEARCH

19. The effect of DMTS on the risk of SARS-CoV2 infection and Covid19 disease remains uncertain and we commend pwMS and MS teams to continue to submit data to registries, such as the UK MS Register study of Covid19, and to support studies of Covid19 infection by NHSE, PHE and other statutory, healthcare and research bodies. In particular, we commend the MS Register Covid study: <https://www.ukmsregister.org/Research/COVID19CRF>

F. RISK STRATIFICATION TOOLS

The Association of Local Authority Medical Advisers
<https://alama.org.uk/covid-19-medical-risk-assessment/>

The Renal Association has devised this risk stratification tool:
<https://renal.org/wp-content/uploads/2020/08/COVID-19-RISK-STRATIFICATION-FRAMEWORK-DOCUMENT-7.08.20.pdf>

Ms Society Medical Advisor Statement On risk.
<https://www.mssociety.org.uk/care-and-support/ms-and-coronavirus-care-and-support#higher-risk>

Development of an Objective Risk Stratification Tool to facilitate workplace assessments of healthcare workers when dealing with the CoViD-19 pandemic. <https://www.bma.org.uk/media/2768/bma-covid-19-risk-assessment-tool-july2020.pdf>

G: SOURCES OF INFORMATION

Publications

- 1: Willis MD, Robertson NP. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *J Neurol*. 2020 May;267(5):1567-1569. doi: 10.1007/s00415-020-09822-3. PMID: 32303837; PMCID: PMC7163169.
- 2: Hughes R, et al. COVID-19 in persons with multiple sclerosis treated with ocrelizumab - A pharmacovigilance case series. *Mult Scler Relat Disord*. 2020 Jul;42:102192. doi: 10.1016/j.msard.2020.102192. Epub 2020 May 16. PMID: 32570202; PMCID: PMC7228884.
- 3: Maghzi AH et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. *J Neurol*. 2020 Oct;267(10):2790-2796. doi: 10.1007/s00415-020-09944-8. Epub 2020 Jun 3. PMID: 32494856; PMCID: PMC7268971.
- 4: Louapre C et al, Covisep investigators. Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. *JAMA Neurol*. 2020 Jun 26;77(9):1–10. doi: 10.1001/jamaneurol.2020.2581. Epub ahead of print. PMID: 32589189; PMCID: PMC7320356.
- 5: Korsukewitz C et al. Neurological immunotherapy in the era of COVID-19 - looking for consensus in the literature. *Nat Rev Neurol*. 2020 Sep;16(9):493-505. doi: 10.1038/s41582-020-0385-8. Epub 2020 Jul 8. Erratum in: *Nat Rev Neurol*. 2020 Jul 22;: PMID: 32641860; PMCID: PMC7341707.
- 6: Loonstra FC et al. COVID-19 in multiple sclerosis: The Dutch experience. *Mult Scler*. 2020 Sep;26(10):1256-1260. doi: 10.1177/1352458520942198. Epub 2020 Jul 14. PMID: 32662742; PMCID: PMC7493197.

Unpublished studies

- A manuscript by Sormani et al on the Italian experience
- Presentations at ECTRIMS/ACTRIMS 2020 from the UK MS Register, the COViMS study, MS Data Alliance, Hughes on the Roche database,

Submissions

- Submission from Merck on cladribine: As of 7th September 2020, a total of 85 cases of confirmed (n=38) or suspected (n=47) COVID-19 in multiple sclerosis (MS) patients treated with cladribine have been recorded within the Merck global patient safety database. The majority of these patients had mild to moderate respiratory symptoms and none required mechanical ventilation. No deaths were reported. In a preliminary analysis of available data for 21 patients, the median

time to onset of COVID-19 from last dose of cladribine tablets was 180 days (i.e. approximately 6 months after the last dose).

- A proposal from Dr Basil Sharrack on the use of AHST during Covid.

Guidance

- Advice from the MS International Federation:
<https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/>
- 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
<https://www.encephalitis.info/Blog/coronavirus>

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