ABN GUIDANCE ON THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS IN RESPONSE TO THE THREAT OF A CORONAVIRUS EPIDEMIC

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VESION: 4

AUTHORS:

- Alasdair Coles and the MS Advisory Group, in consultation with
- Dr Ming Lim, on behalf of paediatric MS group
- Prof Gavin Giovannoni, on behalf of MS Academy
- Phillip Anderson for the MS Society
- Rachel Dorsey-Campbell for MS pharmacists
- Malcolm Qualie for NHS England

We have drafted our recommendations in two forms, one suitable for health professionals and another suitable for people with multiple sclerosis.

RECOMMENDATIONS FOR HEALTH PROFESSIONALS

1. It is safe to start or continue **interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide** and **dimethyl fumarate**. They probably all confer a very slight increase risk in viral infections, but usually far less than posed by a return of disease activity. While some argue that the risk of viral infections can be predicted by total lymphocyte count, the literature is not clear, so we do not recommend any change to the current monitoring guidelines for these drugs.

2. We currently view **natalizumab** as safe to use, and the safest high-efficacy therapy, because Covid19 is not a neurotropic virus. [We are aware of the reported case of Covid19 found in CSF[1] but take the view of the Encephalitis Society that the risk of encephalitis, if confirmed at all, is very small. It may be appropriate to consider extended interval dosing to mitigate even this very low risk]. 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. For such individual patients, the increased risk of Covid19 infection and its complications on ocrelizumab and fingolimod need to be balanced against the increased risks accompanying roughly six months of natalizumab infusions: increased attendance at hospitals in the midst of an epidemic and a very marginal increased risk of PML.

3. The risk of acquiring coronavirus infection is probably moderately increased on **fingolimod**. For those already taking it, the risk of rebound disease probably outweighs the risk of infection. For those with disease breakthrough on first-line therapies, fingolimod has the advantage over ocrelizumab of being able to be stopped in the event of a coronavirus infection.

4. Likewise the risk of acquiring coronavirus infection is probably moderately increased after **ocrelizumab**. If a patient needs a high-efficacy drug, and they are not eligible for natalizumab, it is an option to consider. But it will leave a patient with persistently higher risk of infection throughout the anticipated period of the Covid19 epidemic. For those already on ocrelizumab, we recommend delaying further infusions until the risk of coronavirus infection is clarified or has passed. It is clear from the Swedish experience using rituximab, that an infusion of ocrelizumab will remain effective at controlling MS for longer than 6 months[2].

5. The risk of viral infections is significantly higher in the three to six months after **alemtuzumab** and **cladribine**. We recommend these drugs are not started during the coronavirus epidemic; natalizumab and ocrelizumab are safer options for active disease. For those who have already started treatment, we recommend

[1] In all the cases reported so far, there has been one report of putative coronavirus encephalitis http://www.xinhuanet.com/english/2020-03/05/c_138846529.htm

[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

delaying the second round of both treatments until the risk of coronavirus infection has passed. It is safe to increase the gap between the first and second alemtuzumab treatments to 18 months, without a risk of a return of MS activity. The data are less clear for cladribine. If a third round of alemtuzumab is being considered for new disease activity, we recommend using other DMTs or delaying until the epidemic is over.

6. **Autologous 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 be postponed until the covid19 epidemic recedes.

7. **For patients with active covid19 infection**, It is not necessary for people with mild symptoms of COVID-19 to stop their DMT. In cases of MS with severe COVID-19 infection [for instance requiring admission] we recommend pausing all injectables and oral medication, and delaying infusions. The timing of recommencing treatment is not straightforward. The European Society for Blood and Marrow Transplantation recommends that AHSCT should be deferred for at least three months in patients with low-risk disease [by which they mean malignancy] or, in patients with high-risk disease, until the patient is asymptomatic and has three repeated virus PCR negativity at least one week apart. Clearly, for patients who were on fingolimod and natalizumab, there is concern about rebound disease activity 2-4 months after stopping.

8. **Advice for DMT monitoring**. We recognise that the increased pressures on healthcare services, and the increased risk to patients of travelling to clinical sites, means abbreviated blood monitoring 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	None
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

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

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

ABN ADVICE FOR PEOPLE WITH MULTIPLE SCLEROSIS ON DISEASE-MODIFYING THERAPIES

BACKGROUND

1. There is considerable uncertainty about the impact of covid19 coronavirus on the UK. As of 6th March 2020, the government has advised that the risk of widespread infection with covid19 coronavirus in the UK has risen from low to moderate. The Chief Medical Officer has estimated that the likely duration of an epidemic in the UK, if it occurs, is 6 months.

2. Covid19 coronavirus infection is more likely to occur, and more likely to have serious consequences, in people with compromised immune systems. All MS disease-modifying therapies affect the immune system, to varying degrees. So, it is important that all people with MS take simple preventive measures seriously.

3. Covid19 coronavirus infection does not lead to neurological symptoms and should not be mistaken for a relapse of MS.

GENERAL HEALTH ADVICE FOR PEOPLE WITH MULTIPLE SCLEROSIS

- People with MS (pwMS) should follow diligently the advice given to the public on travel, self-isolation and response to potential symptoms of a coronavirus infection. This advice is updated regularly and is available here: https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public

- In summary, anyone with symptoms to suggest Coronavirus should contact 111. Prevention of coronavirus is difficult because people are often asymptomatic when infected, but hand hygiene is important. As the coronavirus is an enveloped virus it is mainly spread via droplets, is not aerosolized, and is most effectively dealt with by frequent handwashing with soap.

- There is no treatment for coronavirus infection and no drug that can be used by immunosuppressed people to prevent infection.

ADVICE FOR PEOPLE CURRENTLY ON A DISEASE MODIFYING TREATMENT

1. Do not change or stop your medication without first speaking to your MS team.

2. If you have an appointment to come to hospital for a review or treatment, and you have cough, high temperature or shortness of breath please **do not** come to the hospital, but contact your MS team for advice.

3. If you are on **interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide, dimethyl fumarate and natalizumab**, please continue to take these drugs. They do not significantly increase the risk of systemic viral infections.

4. If you are on **fingolimod**, please be aware that the risk of viral infections is moderately increased. So you may be more prone to coronavirus infection and its complications. For most people on fingolimod, this risk is outweighed by the effectiveness of fingolimod in controlling their MS. So, we recommend most people continue on fingolimod. It is important not to stop fingolimod without speaking to your MS team, because there is a risk that multiple sclerosis will become active and cause relapses in the weeks after stopping the drug.

5. If you are on **ocrelizumab**, please be aware that the risk of viral infections is moderately increased. So you may be more prone to coronavirus infection. For many people on ocrelizumab, this risk is outweighed by the effectiveness of ocrelizumab in controlling their MS. The MS team may consider delaying a further round of ocrelizumab until the risk of coronavirus infection is clarified or has passed, because it is clear from experience with a similar drug, rituximab, that an infusion of ocrelizumab will remain effective at controlling MS for longer than 6 months.

6. If you have had one round of **cladribine or alemtuzumab**, and are due another round, then you should discuss this further with your MS team. The risk of viral infections is highest in the three to six months after alemtuzumab and cladribine. Therefore it is sensible to delay the second round of treatment until the risk of coronavirus infection has passed. It is safe to increase the gap between the first and second alemtuzumab treatments to 18 months, without a risk of a return of MS activity. The data are less clear for cladribine. If delaying treatment is a concern, it would be reasonable to consider switching to another treatment.

7. If you have had two rounds of treatment with **cladribine or alemtuzumab** and are well, please be aware that the risk of viral infections is slightly increased. There is no need for you to have any further treatment, unless you have symptoms, or signs on an MRI scan, that your multiple sclerosis is becoming active again, in which case, please see [8].

8. If you have had two rounds of treatment with **alemtuzumab** and your MS has become active then you might consider having a further round of treatment. You should discuss this further with your MS team. The risk of viral infections is highest in the three to six months after alemtuzumab and cladribine. For most people, it would be preferable to consider switching to another treatment.

ADVICE FOR PEOPLE STARTING A DISEASE MODIFYING TREATMENT

1. The choice of disease modifying treatment for someone with MS is complex and takes into account many factors. The potential for a period of some months with an increased risk of coronavirus infection should be part of these considerations. Roughly speaking, the more effective MS therapies confer a greater risk of infection, and the potential harm from infection is greater. Nonetheless, for some pwMS the risks of the disease being untreated, or partially treated, are sufficiently high that the more effective therapies are justified.

2. The following disease modifying treatments do not significantly increase the risk of viral infections: **interferon beta 1a, interferon beta 1b, glatiramer,**

teriflunomide and **dimethyl fumarate.** It is important to comply with blood monitoring on these drugs, which ensures that the immune system is not excessively suppressed. Once these drugs are stopped, the immune system recovers over several weeks.

3. **Natalizumab** is a highly effective therapy, with very few side effects in the first six months of treatment. Natalizumab does increase the risk of viral infections in the brain, but Covd19 does not affect the brain. Once stopped, the immune system recovers over several weeks.

4. **Fingolimod** is an effective treatment of MS but causes a moderate increase in the risk of viral infections whilst you take the drug. It is a tablet and, once stopped, the immune system usually recovers in several weeks.

5. **Ocrelizumab** is a highly effective treatment of MS and more effective than fingolimod. After the first two infusions [a fortnight apart], it causes a moderate increase in the risk of viral infections that persists for months. If someone on ocrelizumab gets coronavirus, the drug's effects on the immune system cannot be reversed, so the likelihood of complications from an infection is probably higher than if taking a drug which can be stopped.

6. **Cladribine and alemtuzumab** are highly effective treatments of MS and are given as two rounds of treatment, separated by twelve months. However, there is a very significant risk of viral infections in the three to six months after a round of alemtuzumab and cladribine. Therefore we would advise delaying the start of these treatments until the risk of coronavirus infection has passed. Most people considering these drugs will have active multiple sclerosis and so delaying treatment altogether may not be wise. In which case it would be reasonable to consider starting another treatment.

7. **Haematopoietic stem cell transplantation (HSCT)** is an intense chemotherapy treatment for MS, which carries a very high risk of infections for many weeks. We would recommend postponing this treatment until the risk of coronavirus has receded.

ADVICE FOR PEOPLE ON DMTS WHO HAVE A CORONAVIRUS INFECTION

1. If you have mild symptoms, the NHS advises that you should self-isolate without having to speak to a doctor or nurse.
2. If you are advised to go to your local hospital by any health professional, or go to hospital for any other reason, you should alert you MS team (even if you are not admitted). If you are taking a DMT they may want to discuss pausing or switching your treatment for the time being.

ADVICE ON INNOVATIVE TREATMENTS

1. **Siponimod, ofatumumab** and **rituximab** are not currently available on the NHS, but are available by private prescription in the UK. These will increase the risk of coronavirus infection, and should only be used after careful discussion with the MS team.

2. **Clinical trials of experimental drugs**. We recommend you speak to the trial team about the risk of coronavirus infection.

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