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

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EXECUTIVE SUMMARY

There remains uncertainty regarding current levels of Covid-19 and the level of risk it poses to people with multiple sclerosis (pwMS). Since the previous Association of British Neurologists (ABN) guidance was published in November 2020 there has been a mass Covid-19 vaccination programme with excellent uptake in pwMS and most recently the removal of legally mandated restrictions on 19 July 2021. The following advice has been updated in the light of further data in both pwMS and in other therapy areas.

The main points are:

1. All DMTs should be available to pwMS during the Covid-19 pandemic, provided that the benefits of treatment outweigh their risks. Local rates of infection, the individual's general health and their risk of exposure to the virus should be considered in the DMT choice.
2. Studies to date are reassuring, showing no additional Covid-19 severity risk for pwMS from all disease modifying therapies (DMTs) with the possible exception of anti-CD20 monoclonal antibodies (ocrelizumab and rituximab). Even with this group of DMTs the risk appears small and should be taken in context with the potential benefit of the therapy.
3. In general, pwMS with mild symptoms of COVID-19 should not stop their DMTs. Certain therapies (infusions and cladribine) should be delayed until symptoms resolve. In cases of severe infection, the DMT should be stopped and the prescribing team urgently consulted for further advice.
4. We continue to encourage, all pwMS (unless contraindicated) to have the Covid-19 vaccination when offered. All pwMS should be offered a Covid-19 'booster' vaccine when available.
5. It is possible that some DMT classes: sphingosine receptor modulators (fingolimod and Siponimod) and CD20 agents (ocrelizumab, rituximab and ofatumumab) reduce antibody production following Covid-19 vaccination. This may, but remains unproven, reduce the efficacy of the Covid-19 vaccine. However, this would not increase any risk associated with the vaccine and therefore we would still strongly encourage pwMS on these DMTs to have the vaccine.
6. Some pwMS should be considered as 'Clinically Extremely Vulnerable' based on age (usually over 65), higher disability (EDSS>6 and/or with swallowing or breathing difficulties) and presence of additional significant co-morbidities. Particularly when background rates of Covid-19 infection are high, people who meet these criteria are advised to follow the most up to date government guidance (see section A).
7. 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.
8. 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. RISK OF SEVERE COVID-19 INFECTION IN PEOPLE WITH MS (pwMS)

1. By its nature as a chronic neurological autoimmune disease all pwMS are considered to be more vulnerable to infections. This risk is modified by other factors such as overall general health, concomitant medications and usually age.

2. All pwMS should be encouraged to follow government guidance on measures to prevent Covid-19 infection.

3. Consistently, the strongest evidence for severe Covid-19 disease in pwMS is with any of the following risk factors: higher disability (EDSS>6.0 and/or significant swallowing or breathing difficulties), progressive disease with longer disease duration, older age (usually above the age of 65), obesity, male sex and presence of significant co-morbidities such as diabetes and cardiorespiratory disease. It is likely from population level data that ethnicity and socioeconomic status also impact on the risk to an individual pwMS. Physicians should consider these factors when advising a pwMS.

4. Calculating an individual's risk of severe Covid-19 infection, and so determining who may be "clinically extremely vulnerable (CEV)" should be based on the presence of risk factors as stated in A3. Examples of risk stratification tools are given in Section F and pwMS who may be CEV are advised to consult the most recent government guidance updated: https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19

B. THE USE OF DISEASE MODIFYING THERAPIES (DMTs)

1. There is increasing evidence to guide recommendations particularly with global initiatives collecting Covid-19 outcomes data in pwMS.[1-9]

2. All DMTs should be available to pwMS during the Covid-19 pandemic. For an individual pwMS, the potential benefits of any treatment should outweigh the risks, considering: the local rate of Covid-19 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 Covid-19 disease and the efficacy of a vaccine.

3. NHS England has agreed whilst the effects of the pandemic continue to allow prescribing of: (a) natalizumab in pwMS with highly active disease (one significant relapse within last 12 months on a first line disease modifying therapy [DMT]); (b) dimethyl fumarate following a single clinical relapse in the last 12 months and (c) mavenclad if relapse criteria alone is satisfied and there is no MRI availability to the pwMS directly as a result of the effects of the Covid19 pandemic on local trust capacity.

4. PwMS with mild symptoms of COVID-19 should not stop interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod or siponimod, but cladribine, ofatumumab, ocrelizumab, natalizumab and alemtuzumab should usually be delayed until symptoms resolve.

5. In cases of severe COVID-19 infection, the prescribing team should be consulted. The usual recommendation would be that oral medication is stopped and infusions delayed, restarting fingolimod, siponimod and natalizumab treatment, if possible, within 8 weeks to avoid rebound disease.

6. PwMS should be advised at the time of initiation, and/or subsequent review if a DMT might impact on the severity of Covid-19 infection or if the DMT may affect the Covid-19 vaccine response based on the most up to date evidence.

7. We anticipate the time periods when pwMS are most vulnerable to infection (CEV) to be at least four weeks after an alemtuzumab infusion at least two weeks after high-dose steroids; and in those on anti-CD20 agents (ocrelizumab, rituximab and ofatumumab). There is particular concern regarding individuals with other risk factors (see A3) and/or hypogammaglobulinemia. It is also possible that cladribine, if associated with significant lymphopenia (usually within the first 2-3 months of each course), may also put a pwMS at greater risk of infection.

8. Based on several large studies collecting data in pwMS on or off DMTs and following high dose steroids there reassuringly appears to be no significant increased risk of severe Covid-19 infection associated with all DMTs with the possible exception of CD20 agents (ocrelizumab and rituximab) (refs). We should caution though that this remains an ongoing process and confidence intervals are still relatively large and non-DMT risk factors such as age and co-morbidity can significantly increase risk independent of DMT.

9. Interferon beta 1a, interferon beta 1b, glatiramer acetate, teriflunomide and dimethyl fumarate do not significantly increase the risk of serious Covid-19 disease. It is unclear if any additional risk is conferred by prolonged lymphopenia (<0.6) that may be associated with some of these DMTs and an individual discussion with the pwMS may be required to discuss the risk and benefit of continuing the therapy. Sphingosine receptor modulators (fingolimod and siponimod) routinely cause significant lymphopenia; however, this appears to be confined to circulating counts only and there is currently no evidence this group of drugs is associated with increased risk of more severe Covid-19 infection.

10. During the first phase of the pandemic in 2020, natalizumab was considered to have possibly the lowest risk for severe Covid-19 disease, of the high-efficacy therapies. Its availability has been extended by NHS England (see B3) accordingly. However, as further data has emerged, it is appropriate that all DMTs should be available to pwMS after an appropriate individualised risk and benefit discussion.

11. Ocrelizumab may be initiated cautiously in patients as per current relevant NHS guidelines where Covid-19 risk is appropriately balanced by the benefits of the drug. There is some evidence to suggest that pwMS treated with ocrelizumab are more likely to be hospitalised with Covid-19 and to need intensive care. However, this data is preliminary.

12. The risk of severe Covid-19 disease associated with ocrelizumab may be increased in people if there is a reduction in immunoglobulin levels (especially IgG). Consideration should be given at times of high infection risk to delaying ocrelizumab infusions and/or switching to an alternative therapy particularly if they have other risk factors for severe Covid-19 infection. Similar to the use of rituximab in the management of NMO in Sweden, ocrelizumab infusions could be delayed until CD19+ or CD19+CD27+ lymphocytes have recovered to over 1% of the total lymphocyte population.

13. The evidence to date regarding the risk of severe Covid-19 disease with cladribine is reassuring and therefore it may be used where there has been an appropriate individual risk and benefit discussion. It should be noted that there is an increased risk of lymphopenia for up to 3 months after each course of cladribine and this may be greater in the second year.

14. Studies to date have not shown an increased risk of severe Covid-19 disease with alemtuzumab. However, the data is incomplete and it is known there is a high risk of other viral infections in the first month after treatment. Hence, an appropriately balanced discussion of the benefits of the drug, considering co-morbidities and Covid-19 susceptibility and current Covid-19 infection risk needs to take place before prescribing. Consideration may be given to delay the second course of alemtuzumab, but this risks the potential return of disease activity. A further assessment should take place with the aim of administering the infusion as soon as possible with suitable mitigation strategies to reduce the risk of infection.

15. Autologous haematopoietic stem cell transplantation (AHSCT) is usually a semi-elective procedure for multiple sclerosis and has the highest risk of opportunistic infections. Its use was paused with only 'exceptional cases' considered until recently. Following the reduction in overall Covid-19 infection risk and widespread vaccination, AHSCT is now available again following suitable discussion with stem cell transplantation teams and regional multidisciplinary team agreement, carefully determining the clinical priority with an individualised risk and benefit discussion based on EBMT guidance.[10] Those receiving AHSCT are likely to be most at risk of contracting infections for up to 12 months following the procedure and are highly likely to need to take additional precautions as advised by the transplantation team and depending on regional Covid19 levels at the time.

16. High dose steroids (for instance to treat a relapse of multiple sclerosis) may increase the risk for severe Covid-19 disease transiently.

C. THE COVID-19 VACCINATION

1. We recommend all pwMS to have the Covid-19 vaccination unless there is a medical contraindication. Otherwise, there is a positive benefit versus risk balance in favour of having the vaccine in pwMS. In addition, we would request all pwMS are eligible for future 'booster' vaccines.

2. As a non-live vaccine, there is no risk of reactivation of Covid19 associated with DMT use.

3. PwMS should be advised if a DMT may affect the Covid-19 vaccine response based on the most up to date evidence.

4. In the context of other vaccines some DMTs, notably fingolimod and CD20 therapies (ocrelizumab, rituximab and possibly ofatumumab), could reduce vaccine antibody response (refs). In addition, the timing of Covid-19 vaccine in the context of immune reconstitution DMTs (Cladribine, Alemtuzumab and AHSCT) is likely to affect vaccine response as these DMTs cause transient immune reduction which can reduce vaccine response.

5. For the reasons above, if possible, it is preferrable for a pwMS to be promptly vaccinated prior to starting their DMT (especially ocrelizumab, ofatumumab, fingolimod, siponimod, cladribine, alemtuzumab and AHSCT). If that is not possible then the timing of vaccine administration should be planned to minimise disruption to therapy and achieve maximal vaccine response.

6. From the initial data available[11,12] there is evidence of reduced antibody response to the Covid-19 vaccination in pwMS on fingolimod (sphingosine receptor modulator) and ocrelizumab (CD20

monoclonal antibody) therapy. There is still benefit and safety associated with the vaccine and these DMTs so we would advise pwMS on these DMTs to have the vaccine and any potential booster, but it is possible there may be reduced vaccination protection from the infection.

7. Additional data is required on this issue, and we await the results of further ongoing studies.

D. THE MINIMUM MS SERVICE AND SAFETY MONITORING

1. 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 always receive advice and clear communication.

2. At the earliest opportunity trusts should offer pwMS pre-pandemic MRI scan availability. Where MRI is fully available within a trust, then its use in the management of pwMS should return to pre-pandemic indications. In trusts where availability remains impacted by Covid-19, prioritisation should be given to diagnostic MRI scans, monitoring for JC-virus positive patients treated with natalizumab for more than two years, and MRI scans influencing treatment decisions. A return to full availability of MRI to pwMS should however be prioritised.

3. Currently as Covid-19 infection risk remains, and health services have not yet returned to pre-pandemic capacity extended interval safety blood monitoring may remain necessary depending on regional circumstances (see Table 1). Monitoring, however, 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

Table 1: Recommended minimum extended interval blood safety monitoring for disease modifying therapies. Monitoring should return to normal recommendations as soon as feasible.

E. RESEARCH

1. The effect of DMTS on the risk of Covid-19 infection and 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

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

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

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

4. 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

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