Protocol

Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure

1 Scope

Treatment and monitoring of patients with a diagnosis of multiple sclerosis (MS) by the MS team at Cambridge University Hospitals NHS Foundation Trust (CUH).

2 Purpose

To ensure the safe administration and monitoring of disease modifying therapy (DMT) for multiple sclerosis. This document covers treatment and monitoring of MS DMT during the COVID19 pandemic and in the post-pandemic recovery phase.

3 Abbreviations

BP	blood pressure
CCG	clinical commissioning group
CUH	Cambridge University Hospitals NHS Foundation Trust
CXR	chest x-ray
DMT	disease modifying therapy
FBC	full blood count
ID	infectious diseases
IV	intravenous
JCV	John Cunningham virus
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
NICE	National Institute for Health and Care Excellence
OCB	Oligo clonal bands
PCR	polymerase chain reaction
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PRN	as required
STAT	once only
TB	tuberculosis
TFT	thyroid function test
U&E	urea and electrolytes

4 Undertaken by (staff groups)

Consultant neurologists with special interest and expertise in the use of therapy for multiple sclerosis, registered nurses who are competent and trained in the administration of intravenous medication and medical staff with appropriate training and expertise, MS specialist nurses and MS team co-ordinators.

5 Eligibility

Eligible patients are to be assessed only by consultant neurologists who have special interest and expertise in using therapy for multiple sclerosis.

6 Before treatment (new patients, patients switching therapy or patients transferring care to CUH from another centre)

6.1 Prior to attending for first MS DMT clinic appointment

- Where possible new patients will be asked to have screening bloods before attending their clinic appointment. This is to avoid delays in starting DMT if patients require vaccinations.
- The doctor accepting the referral will initiate this by asking the MS administrator to send the letter .MSNEWBLOODS
- Doctor accepting the new patient referral will ask the MS administrator to obtain MRI scans and previous neurologist letters if applicable.

6.2 Pre-treatment screening

At face-to-face assessment clinic appointment:

- Neurologist checks the diagnosis of MS is secure. Consider sending if appropriate aquaporin-4 antibodies, MOG antibodies, ANA etc. EDSS is recorded.
- Prior to starting high potency DMT (such as ocrelizumab) consider an LP to check for OCB (if not done previously). This is not mandatory, however, especially if the history and imaging are typical for MS.

- Risks and benefits of DMT are discussed with neurologist and nurse, and the patient receives an information leaflet from the nurse.
- Screening blood tests (done within two months of treatment if treatment naive) are:
  - **Biochemistry – LFT, U&Es, thyroid function**
  - **Haematology – FBC**
  - **Lymphocyte phenotyping if lymphopaenic**
  - **HIV, hepatitis B and C serology**
  - **Varicella zoster virus IgG.**
    - If negative and the patient is starting immunosuppressive DMT (including dimethyl fumarate) the risks of delaying MS

  - treatment vs risk of not vaccinating need to be considered for individual patients.
  - If delaying DMT is possible advise chicken pox vaccine (live) 2 doses given 1 month apart and completed at least 4-6 weeks before DMT (check individual DMT SmPC).
- **Measles, Mumps and Rubella IgG.**
  - If measles, mumps or rubella IgG are negative and the patient is starting immunosuppressive DMT (including dimethyl fumarate) the risks of delaying MS treatment vs risk of not vaccinating need to be considered for individual patients. If mumps IgG only is negative consider a discussion at the MS MDT and not delaying DMT for MMR vaccination. For patients with highly active MS the risks of delaying treatment and sustaining further relapses are likely to be higher than the very small risk of contracting mumps as an adult. For negative measles and/or rubella IgG give MMR if possible and the delay to starting DMT is not too risky.
  - Women of childbearing age who are not immune to rubella should be offered at least one vaccination with MMR if possible. Maternal rubella infection in pregnancy may result in fetal loss or in congenital rubella syndrome (CRS). A single dose of rubella-containing vaccine as used in the UK confers around 95 to 100% protection against rubella.
  - If delaying DMT is possible advise the MMR vaccine (live vaccine) as per The Green Book:
    - 2 doses given 1 month apart (if the patient has not previously received any doses of MMR)
    - 1 dose is required if the patient has already had 1 dose of MMR in the past
    - The last vaccine dose needs to have been given at least 4-6 weeks before starting immunosuppressive DMT (check individual DMT SmPC).
- **Immunoglobulins (for patients starting ocrelizumab).** If low repeat and if remain low seek advice from Immunology before starting ocrelizumab.
- **TB Quantiferon (ideally for all patients, must be sent in at risk patients and all patients starting cladribine).**
  - If positive request CXR and refer to ID TB clinic (ID team may offer 6 months isoniazid for latent TB to reduce the risk of re-activation).
- **JC virus antibodies** for patients considering starting natalizumab.
- Female patients are advised to be up to date on their smear tests prior to starting alemtuzumab.
- **Baseline ECG is required before alemtuzumab and fingolimod**.
- For fingolimod if patient has diabetes or a history of uveitis seek ophthalmology review, and if IHD or stroke history seek cardiology review

- Weight is required for cladribine.

6.3 Explain before starting treatment that it is the patient's responsibility to comply with blood monitoring and this may involve attending Newmarket road P+R/Addenbrooke's for a blood test. Drug re-prescription may be delayed if bloods are not done. There are no shared care agreements for blood monitoring with GPs (except for alemtuzumab and new alemtuzumab patients should sign up to Ashfield phlebotomy service). If GPs do bloods it is the patient's responsibility to email them to the MS nurse (who will scan it to Media on EPIC). Vulnerable patients e.g. those with mental health/cognitive problems, may need extra clinic visits or support for compliance with blood monitoring. These patients should be identified to the MS co-ordinator and MS nurses for extra help.

6.4 Patients for whom high potency DMT is considered (ocrelizumab, ofatumumab, alemtuzumab and cladribine) or complex patients should be discussed at the MS MDT. Pre-MDT note to be completed by doctor/nurse using smartphrase .MSMDTPREPNOTE.

6.5 **Vaccine advice to all patients:**

- The benefits of vaccination prior to starting DMT needs to be balanced against the risk of new MS activity with delaying DMT for an individual patient.
- See section 6.1 above for advice on MMR and VZV vaccination
- All patients should be advised to have the COVID19 vaccines and follow government guidance on booster and third doses where appropriate. When possible patients should be vaccinated before starting DMTs that are known to reduce vaccine responses.
- Ocrelizumab and fingolimod reduce antibody responses to COVID19 vaccines and other vaccines. Vaccine responses may also be reduced if vaccinated within the first few months alemtuzumab or cladribine. ABN Guidance On The Use Of Disease-Modifying Therapies for Multiple Sclerosis and COVID19 Pandemic will be followed (Date: August 2021, published 26/10/21).
- Annual influenza vaccination (non-live) is advised for all MS patients (not needed prior to starting treatment).
- Pneumococcal vaccination is also recommended, ideally before treatment if starting a DMT that can reduce vaccine response. There are however national shortages and supply issues which may prevent administration.

- Patients may find a copy of the letter .MSVACCINELETTER helpful

6.6 **At the consenting clinic appointment:**

- Doctor or nurse to go through consent process, including sending a letter to the patient with the EPIC smartphrase after the clinic with summary of risks.

- Tecfidera and teriflunomide consent letter is sent by the nurse when a patient has decided to start the treatment

6.7 General information about DMT patient follow-up and monitoring

- GPs should be notified when patients start DMT. For infusions/fingolimod this will be by a discharge summary generated by the nurse as part of their day admission. For other DMTs the consent letter done at the start of treatment is sent to the patient and copied to the GP.
- Clinic follow-up should be tailored to individual patient needs, vulnerable patients (e.g. those with mental health or cognitive problems) without good social support, or those with very active MS, may need more frequent appointments.
- As a **minimum all patients should have an annual clinic review (face-to-face or telephone/virtual) by a member of the MS team, if the patient is stable this should alternate nurse/doctor.** As a minimum all patients should have a face-to-face doctor appointment every 2 years. Patients should have a doctor review sooner if: relapsing, JCV+ on natalizumab (yearly doctor consent required), concern about progression, concern about PML, mental health problems that make remote monitoring difficult etc.
- New patients starting treatment, and those switching treatment may benefit from an MS nurse telephone review at month 3 to check for support and review of side effects and compliance. All patients starting fingolimod need a month 3 nurse appointment to ensure ophthalmology review is done.
- If initial blood monitoring is abnormal then more frequent monitoring may be required
- The responsibility for requesting MRI scans lies with the doctor (except alemtuzumab MRI requested at year 4.5 by nurse). The clinician reviewing natalizumab therapy plans should also check that an MRI is ordered at an appropriate time point based on JCV status.
- Monitoring bloods should be checked at each nurse/doctor appointment. It is the responsibility of the nurse/doctor doing the clinic review to plan with the patient how and when the patient will have their next blood test.
- In between appointments the MS co-ordinator/MS nurses will use the database to help monitor bloods.
- In principle DMT/therapy plans should not be re-prescribed unless the required monitoring bloods have been done, unless there are specific individual circumstance in which case the doctor/nurse will use professional judgement. If the patient was not aware that monitoring bloods were due the doctor/nurse may prescribe a temporary supply until the bloods are available.
- Refer to the individual DMT protocols for blood and MRI monitoring requirements and other additional information e.g. drug washout periods, switching, pregnancy advice:

    - **Alemtuzumab (Lemtrada) protocol**

- Natalizumab (Tysabri) protocol
- Ocrelizumab (Ocrevus) protocol
- **Ofatumumab (Kesimpta) protocol**
- Cladribine (Mavenclad) protocol
- Fingolimod (Gilenya) protocol
- Dimethyl Fumarate (Tecfidera) protocol
- Teriflunomide (Aubagio) protocol
- Interferon-beta (Rebif/Avonex/Plegridy/Betaferon) protocol
- Glatiramer acetate (Brabio/Copaxone) protocol

7 Research opportunities

7.1 Clinic visits are an opportunity to ask patients if they would like to hear more about research opportunities and to record their wishes in the MS grid on the clinic letter. Explain that being interested in research means that the research team can contact them directly about studies but that they are under no obligation to take part. Reassure patients that saying no to research will not in anyway affect their NHS care.

7.2 Encourage all patients to join the MS register UK: https://ukmsregister.org/ and to complete the COVID19 questionnaire on the MS register if they get symptoms.

8 MS DMT and COVID19 infection

8.1 DMTs in pwMS who have active COVID19 infection - follow ABN guidance:

ABN Guidance On The Use Of Disease-Modifying Therapies For Multiple Sclerosis and Covid19 Pandemic Date: August 2021

8.2 Encourage MS patients with COVID19 to complete the COVID19 questionnaire on the MS register.

8.3 During the COVID19 pandemic follow ABN guidance on the use of high dose steroids for a relapse of multiple sclerosis. Steroids probably increase the risk for severe Covid19 disease transiently and the recommendation is to advise self-isolation during treatment for 2 weeks and after treatment.

9 References

ABN Guidance On The Use Of Disease-Modifying Therapies For Multiple Sclerosis and Covid19 Pandemic Date: August 2021
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Owning department:	Neurology		
Author(s):	Claire McCarthy, Consultant Neurologist		
Pharmacist:	Francis Smith, Lead Pharmacist Division D		
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