Protocol

Administration of beta interferons in multiple sclerosis (MS)

1 Scope

Treatment of patients with a diagnosis of multiple sclerosis by the MS team at Cambridge University Hospitals.

2 Purpose

To ensure the safe use and monitoring of beta interferons.

3 Introduction

Beta interferons are indicated for treatment of people with active relapsing-remitting multiple sclerosis (but not highly active relapsing-remitting multiple sclerosis or rapidly evolving severe multiple sclerosis) if they have had at least 2 relapses in the previous 2 years.

4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to prescribe and monitor beta interferons.

5 Treatment

5.1 Eligibility and screening

Patients are assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. Risks and benefits of the treatment are discussed. Medications and co-morbidities are documented on EPIC. NICE technology appraisal guidance TA32 "Beta interferon and glatiramer acetate for the treatment of multiple sclerosis" (January 2002) and NHSE Treatment Algorithm (2019) will be followed when assessing eligibility.

Pre-treatment screening occurs in the outpatient clinic setting:

- Screening blood tests are sent as outlined in the Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- Vaccine advice given as per Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- Baseline expanded disability status scale (EDSS)

5.2 Side effects

Common side effects:

- Flu-like syndrome (occurs early): Fever, chills, generalised aches and pains, headache, poor appetite. These symptoms normally occur within 1-2 hours of treatment, may last up to 24 hours (over time the intensity of these symptoms normally decrease and dependent on the dosing schedule). These symptoms commonly respond to NSAIDs.
- Injection site reactions
- Liver abnormalities (normal mild – see figure 1)
- Lowing of blood counts - cytopaenias (see figure 2)
- Difficulty sleeping
- diarrhoea, nausea and vomiting
- Infections
- Changes in menstruation
- Neurological symptoms, mood changes, depression
- Anaemia (see figure 3)

Rare side effects:

- Thrombotic microangiopathy (TMA)
    - A serious side effect (currently only reported with Rebif®). Presents sub-acutely with hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function.

5.3 Cautions and contra-indications

- Balance of benefit vs risk in pregnancy. There is increasing evidence that Betainterferon is unlikely to cause harm and we are therefore happy for it to be continued during pregnancy and also breast feeding.
- Hypersensitivity to natural or recombinant interferon-beta, or to any of the excipients.
- Current severe depression and/or suicidal ideation
- Caution should be used in patients with a history of seizures (uncontrolled)
- Caution should be used in cardiac disease (such as angina, congestive heart failure or arrhythmia) - flu-like syndrome associated with interferon beta-1a therapy may prove stressful to patients with cardiac conditions.
- Caution in severe renal impairment
- Caution in severe hepatic failure
- Caution in severe myelosuppression.

5.4 Selecting a preparation

- Beta interferons are available in a variety of dosing schedules and devices:
    - Avonex® (interferon beta 1a) - Once weekly IM injection
    - Rebif® (interferon beta 1a) - Three times weekly S/C injection
    - Plegridy® (peginterferon beta 1a) - Fortnightly S/C injection
    - Betaferon® (interferon beta 1b) - Alternate day S/C injection

- Extavia® (interferon beta 1b) - Alternate day S/C injection

- Patients will normally see one of the MS nurses on the same day as the neurologist, to discuss product preference (although often other classes of drug will also be discussed).
- Information is provided (MS Trust publication "Disease Modifying Therapies" and website www.msdecisions.org.uk). Patients usually do not make a final decision on the day but ring MS nurses when they have done so.

5.5 Prescription

- When decision is reached to start beta interferon (e.g. when patient rings) the MS nurse/admin passes information to MS team secretary to complete Blueteq form and to forward the prescription for the neurologist of the week to sign.
- Prescriptions are generated on paper prescriptions, an electronic version of which is kept on the network drive.
- Homecare companies supply the medication (these products are not stocked at CUHFT).
- Generally MS nurse sees patient in MS nurse clinic for training and for the patient to self-administer the first dose under supervision although some patients may be able to manage this themselves at home.

5.6 Follow up and monitoring

- **Outpatient appointments** to assess side effects, medication compliance and disease activity:
    - Seen by MS Nurse at 3 months. Follow up thereafter (unless there are problems) is annual.
    - Neurologist and MS nurse alternate annual follow up. Where clinically appropriate some visits can be video/telephone
    - Testing for neutralising antibodies and management: After a minimum of twelve months of treatment blood should be sent for interferon binding antibodies. In practice this might therefore be at the first annual visit (which will be approximately 15 months after starting). These are rechecked once more at next visit. If both are negative or binding antibodies only present in low titre, these are not generally rechecked unless patient relapses (see below). If they are present in moderate or high titre, then the patient is contacted and further appointment arranged to discuss significance and to send confirmatory neutralising antibody assay. Nb, if the patient is going to switch therapy on clinical grounds then there is no need to send neutralising antibody assay, as it will not influence management. If they have high titre neutralising antibodies then they should be switched to an alternative DMT (for instance glatiramer acetate, dimethyl fumarate) or consideration given to stopping disease modifying therapy.

- Patients who have had a relapse, who are not going to be switched to an alternative drug on purely clinical grounds should have binding antibody assay resent, although this would be a rare event given other available DMTs.

- **Blood Monitoring**:
  - FBC, U+Es, LFTs and TSH checked at month 3. If all normal then no further blood monitoring required (other than for antibody testing, or if abnormalities found, see below).

Figure 1. Management of Liver Function Tests

	ALT/Alk Phos	**Bilirubin**	**Management**
Grade 1	>ULN-2.5 times ULN	>ULN-1.5 times ULN	Continue but consider note to GP
Grade 2	2.6-3.5 times ULN	1.6-3 times ULN	Continue but write to GP and patient to request repeat in 1 month. If persistent half dose until LFT improves to Grade 0 or 1
Grade 3	>5.1 times ULN	>3.1 times ULN	Stop treatment

Figure 2. Management of White Blood Cell Counts (WBC)

	WBC	**Management**
Grade 1	3.0-3.9	Continue
Grade 2	2.0-2.9	Continue but write to GP and patient to request repeat in 1 month. If persistent half dose until WBC improves to 0-1
Grade 3+	<2.0	Stop Treatment

Figure 3. Management of Anaemia

	Hb	**Management**
Grade 1	<LLN-10.0g/dl	Continue
Grade 2	8.0-<10.0	Continue but write to GP and patient to request repeat in 1 month. Consider alternative causes (especially iron deficiency). If alternative excluded and persistent half dose until Hb improves to improves to grade 0-1
Grade 3+	<8.0	Stop Treatment

5.7 Stopping criteria

- Development of secondary progression
- EDSS 7.0 i.e. loss of ambulation for greater than 6 months
- Unacceptable adverse effects*

- Allergic reaction to betainterferon*
- Development of neutralising antibodies*
- Persistent failure to keep booked appointments. At the discretion of the clinical team a standard DNA letter will be sent to the patient informing them that further deliveries will cease pending their contacting the department.

*Patients who relapse on treatment may be eligible for alternative DMTs. Patients who develop neutralising antibodies, have allergic reactions or other unacceptable side effects will either need to stop treatment or switch (e.g. glatiramer, dimethyl fumarate) depending on the clinical situation.

6 Monitoring compliance with and the effectiveness of this document

7.1 Process for Monitoring compliance and Effectiveness

- Patients will be assessed every year for continued eligibility for treatment by Consultant Neurologist or MS Specialist Nurse
- Patients will agree before starting treatment, to comply with treatment protocol, keep appointments and contact relevant health professionals in the event of changes in their underlying MS condition or suspected side effects
- On going maintenance of database of patients offered treatment, undergoing treatment and stopping treatment, including reason for stopping treatment, will be kept by the MS Specialist Nurses and Neurology consultants to audit against NICE guidelines

Standards/Key Performance Indicators

- The audit department will request evidence of compliance with NICE guideline.
- Internal checks on safety, compliance and efficacy will be undertaken by MS team.

7 References

Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis *Pract Neurol* doi:10.1136/practneurol-2015-001139 http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139

Clinical Commissioning Policy: disease modifying therapies for patients with multiple sclerosis. NHS England. May 2014. https://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf

National Institute for Health and Care Excellence (2002). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis: https://www.nice.org.uk/guidance/ta32

Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies

https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf

ABN Guidance On The Use Of Disease-Modifying Therapies In Multiple Sclerosis In Response To The COVID19 Pandemic (Date: August 2021, published 26/10/21). https://cdn.ymaws.com/www.theabn.org/resource/collection/6750BAE6-4CBC-4DDB-A684-116E03BFE634/21.10.26_ABN_Guidance_on_DMTs_for_MS_and_COVID-19.pdf

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Document management

Document draft tracking; table will be removed before publication					
Issue	**Author(s)**	**Owner**	**Date**	**Circulation**	**Comments**
Draft 1	John Thorpe		23/8/16		
Draft 2	Lindsey Stockford		10/08/17		
Draft 3	Frances Smith		14/02/18		Formatting updated. LS changes accepted. Hyperlinks included.
Draft 4	John Thorpe		18/09/18		Reviewed

Approved by:	Will Thomas		
Approval date:	November 2021		
JDTC approval:	n/a		
Owning department:	Neurology		
Author(s):	John Thorpe		
Pharmacist:	Frances Smith		
File name:	Betainterferon Protocol version2 Nov 21		
Supersedes:	Version 1, March 2019		
Version number:	2		
Local reference:		Document ID:	101119