Protocol

Dimethyl fumarate (Tecfidera®) treatment of relapsing-remitting multiple sclerosis (MS)

1 Scope

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

2 Purpose

To ensure the safe use and monitoring of dimethyl fumarate (Tecfidera®).

3 Introduction

Tecfidera is 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 two clinically significant relapses in the previous two years, or
- during the covid pandemic, have had at least one clinical relapse in the previous 12 months
- are unable to continue on their current first line therapy due to adverse events

4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to prescribe and monitor dimethyl fumarate.

5 Treatment

5.1 Eligibility and screening

Patients will have been assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. NICE technology appraisal guidance TA320 '[Dimethyl fumarate for treating relapsing-remitting multiple sclerosis]' (2014) will be followed when assessing eligibility. Risks and benefits will have been discussed. Medications and co-morbidities will have been documented on Epic.

A neurologist and MS nurse discuss the benefits and risks of Tecfidera® with the patient. When the patient has decided to start treatment the MS nurse sends a letter recording the discussion to the patient with a copy to GP (using smart text .TECFIDERACONSENT). A Blueteq form is completed.

Pre-treatment screening will have occurred 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)
- Baseline MRI brain scan ordered (should be done within three months of starting treatment) if clinician feels appropriate to allow radiological monitoring of treatment efficacy
- Pregnancy, breast feeding and importance of contraception whilst on treatment discussed and documented

5.2 Caution and contraindications

- Hypersensitivity to active substances
- Severe renal or severe hepatic impairment
- Pre-existing low lymphocyte counts – these require further investigation
- Immunocompromised eg HIV, hepatitis B&C
- Severe active gastrointestinal disease
- Taking anti-neoplastic or immunosuppressive therapies
- Taking nephrotoxic drugs (eg diuretics, NSAIDs or lithium)

5.3 Dosage

The dose is commenced at a lower dose of 120mg twice daily for the first 28 days in order to reduce the incidence of side effects. The dose should then be increased to 240mg twice daily.

5.3.1 Common side effects

- Flushing and feeling hot and/or itchy
- Gastroenteritis
- Gastrointestinal upset (nausea and vomiting, diarrhoea, abdominal pain, indigestion)
- Lymphopenia and leucopenia
- Elevated liver enzymes
- Ketoacidosis and proteinuria

Please note there have been a very small number of cases of progressive multifocal leukoencephalopathy (PML) in patients on dimethyl fumarate who have not previously received natalizumab or other immunosuppression. These

are mostly linked to patients with low lymphocytes counts below 0.5 for 6 months or more.

5.4 Switching to dimethyl fumarate from other therapies

For patients switching from interferon or glatiramer acetate, no wash out period is required prior to starting dimethyl fumarate.

5.5 Switching from dimethyl fumarate to other therapies

If the lymphocyte count is above 1.0, no wash out period is required. In general a lymphocyte count of >0.8 is recommended when starting other MS DMTs. The wash out period required to reach this varies from patient to patient.

5.6 Stopping Tecfidera when planning to conceive

The half- life of Tecfidera is approximately one hour and no circulating Tecfidera is present at 24 hours in the majority of individuals. We advise a one month wash out period given the documented teratogenicity.

5.7 Prescription and supply

- Patient consented to homecare and alert added to patient record.
- MS nurse informs MS team administrator of new starter therapy.
- Blueteq form completed by MS team administrator.
- Initiation homecare prescription (120mg twice daily 28 days, 0 repeats) and registration forms completed.
- Continuation homecare prescription (240mg twice daily, 5 repeats) completed for first six months.
- Continuation homecare prescriptions for patients on treatment > 6 months 240mg twice daily, 2 x 56 supplied, 2 repeats).
- Prescriptions collected by CUH Homecare team for processing.
- Anticipate four week turnaround time from prescription signing to patient receiving treatment.
- Upon registration, the homecare company will contact the patient to arrange delivery.
- A signature is required for delivery.
- If the patient does not consent to homecare, the patient will need to agree to collect treatment from CUH Outpatient Pharmacy.

5.8 Patient counselling

MS nurse reviews patient in MS nurse clinic (may be a remote consultation) to complete the consent process, explain about Homecare and initiate treatment. Patient is given Tecfidera tip sheet for dealing with side effects.

The importance of regular blood tests and clinic appointments will be discussed in clinic.

Patients are advised to take dimethyl fumarate with food in order to improve tolerability with respect to flushing or gastrointestinal adverse events (does not affect exposure significantly).

MS nurse sends Tecfidera smart-text consent letter to patient and GP at the time the nurse asks the doctor (via the MS team administrator) to prescribe the drug.

6 Follow up and monitoring

- **Outpatient appointments** to assess side effects, drug compliance and disease activity:
    - By MS nurse at month 3 and month 12.
    - Seen by consultant neurologist at month 24.
    - After month 12:
        - If the lymphocyte count at month 12 is $<1.0x10^9$/L, the patient should have a monitoring FBC every 3-6 months
        - If the lymphocyte count at month 12 is $\geq 1.0x10^9$/L the patient is seen twelve-monthly, alternating between the MS nurse and consultant.
- **Monitoring**:
    - FBCs checked at month 3 and 9, and then 3-6 monthly depending on the lymphocyte count.
    - LFTs and U&Es at month 3 and then 6 monthly
    - If at any time point the lymphocyte count is $<0.5x10^9$/L the patient should have a repeat FBC after three months. **If the lymphocyte count is sustained <0.5 x10^9/L for six months the patient will be seen by the neurologist and treatment will be stopped**.
    - If the lymphocyte count is very low on a single test (in the region of 0.1 x10^9/L or below) an urgent repeat will be performed and if confirmed treatment stopped.
    - To date there have been a very small number of cases of PML in patients on dimethyl fumarate who have not previously received natalizumab or other immunosuppression. If PML is suspected, an MRI brain should be performed immediately and treatment with dimethyl fumarate should be suspended until PML has been excluded.

6.1 Stopping criteria

- Development of secondary progression
- EDSS 7.0 i.e. loss of ambulation for greater than six months
- Unacceptable adverse effects
- Allergic reaction to dimethyl fumarate
- Pregnancy and breast feeding
- Sustained reduction in lymphocyte count to less than $0.5x10^9$/L for six months

- Persistent failure to keep booked appointments or adhere to blood test monitoring requirements

7 Monitoring compliance with and the effectiveness of this document

(a) Process for monitoring compliance and effectiveness

- Patients will be assessed every twelve months for continued eligibility for treatment by consultant neurologist or MS specialist nurse; this consultation may be remote
- 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
- Ongoing maintenance of database of patients offered treatment, undergoing treatment and stopping treatment, including reason for stopping treatment, will be kept by the MS specialist nurse to audit against NICE guidelines
- The MS team will be vigilant for post marketing safety data.

(b) 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 the MS team.

8 References

National Institute for Health and Care Excellence (2014). Dimethyl fumarate for treating relapsing remitting multiple sclerosis [TA320]. Manchester: NICE. https://www.nice.org.uk/guidance/ta320

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