Protocol

Teriflunomide (Aubagio®) 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 (CUH).

2 Purpose

To ensure the safe use and monitoring of teriflunomide (Aubagio®).

3 Introduction

Teriflunomide 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.

4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to prescribe and monitor teriflunomide.

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. Eligibility will be assessed in line with the NICE technology appraisal TA303 Teriflunomide for treating relapsing-remitting multiple sclerosis (2014). Medications and co-morbidities will have been documented on Epic.

If patient decides to proceed with teriflunomide the patient is sent a copy of the consent letter by the MS nurse recording consent discussion, with copy to GP (using smart text .AUBAGIOCONSENT). This is sent prior to attending for the first prescription.

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 blood pressure
- Baseline expanded disability status scale (EDSS)
- Baseline MRI brain scan ordered (optional)
- Pregnancy, breast feeding and importance of contraception whilst on treatment discussed and documented

5.2 Contraindications

- Women who are pregnant
- Women of childbearing age that are not using adequate contraception
- Women who are breast feeding
- Patients with active infection
- Patients with immunodeficiency states (eg AIDS)
- Patients with marrow impairment (eg low blood counts)
- Patients taking anti-neoplastic or immunosuppressive therapies
- Patients with severe renal or severe hepatic impairment
- Patients who are hypersensitive to active drug or excipients
- Patients with marked hypoproteinaemia
- Patient should not receive live vaccines whilst taking teriflunomide

5.3 Dose

The recommended dose is 14mg once daily (orally).

5.4 Side effects

Very common and common

- Headache
- Nausea and diarrhoea (should subside over time)
- Alopecia
- Elevated LFTs
- Rashes and acne
- Neutropenia and anaemia
- Influenza, upper respiratory track infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis
- Increased blood pressure
- Anxiety
- Paraesthesia, Sciatica, Carpal tunnel syndrome
- Palpitations
- Abdominal pain upper, Vomiting, Toothache

- Musculoskeletal pain, Myalgia, Arthralgia
- Pollakiuria
- Menorrhagia
- Pain
- Weight decrease, Neutrophil count decrease, White blood cell count decrease, Blood creatine phosphokinase increased

Uncommon

- Mild thrombocytopenia
- Hyperaesthesia, Neuralgia, Peripheral neuropathy
- Post traumatic pain
- Interstitial lung disease
- Pancreatitis

5.5 Interactions with other medicinal products

- Teriflunomide has the potential to interact with a variety of medicines therefore potential interactions can be checked prior prescribing.
- Teriflunomide is metabolised via cytochrome P450 and thus can have pharmacokinetic interactions with other drugs metabolised via this system (carbamazepine, phenytoin, rifampicin etc.) In particular, levels of teriflunomide can decrease with potent inducers of this system.
- It is recommended that patients receiving teriflunomide are not treated with cholestyramine as this will lead to a rapid decrease in plasma concentration (used to accelerate elimination procedure).
- Teriflunomide can affect medicines metabolised via a variety of systems egCYP2C, CYP1A2 and can affect warfarin (can potential decrease INR).
- Live attenuated vaccines may carry a risk of infections and should therefore be avoided.

5.6 Switching to teriflunomide from other therapies

- Beta interferon or glatiramer acetate: no wash out period is required.
- Fingolimod: at least six weeks is recommended or until lymphocyte count returns to normal or at least 0.8 whichever is the longer.
- Natalizumab: 2-3 months washout is recommended.

5.7 Prescription

- Blueteq to be completed.
- Consultant neurologist prescribes 28 days of treatment on EPIC (Outpatient Pharmacy) with five refills as follows:
    - Epic button top left of screen -> orders only -> enter patient hospital number -> select patient
    - Orders only tab -> ‘problem list’ section -> ensure relapsing remitting multiple sclerosis entered -> add problem to visit

diagnosis by clicking on the icon of a piece of paper with an arrow (next to resolve button)
    - In orders only tab go to 'medication and orders' section -> new order box, put cursor in box and press enter -> brings up preference list browser -> DMTs (OP meds) -> tick box for teriflunomide 14mg tablets -> select
    - Automatically brings up prescriptions
    - Click on teriflunomide 14mg tablets to open and check details are correct as follows:
        - Teriflunomide 14mg tablets
        - Intended use multiple sclerosis
        - Dose 14mg tablets, route oral
        - Frequency once daily
        - Duration 28 days
        - ENTER START DATE
        - Patient instruction 'Take 14 mg ONCE a day with meals for 28 days'
        - Dispense 28 capsule, refill 5
        - Class: Outpatient Pharmacy
        - Accept
        - Sign prescription
    - Then sign visit

MS nurse sees patient in MS nurse clinic to start treatment. Patient given teriflunomide tip sheet for dealing with side effects. Nurse explains that future prescriptions are delivered by Outpatient Pharmacy.

5.8 Follow up and monitoring

- **Outpatient appointments** to assess side effects, drug compliance and disease activity:
    - By MS nurse at month 2, 4, and 8
    - Review by consultant neurologist at month 12
    - After month 12 if stable alternates MS nurse/doctor appointment annually

- **Monitoring**:
    - LFT every four weeks for the first six months and then 4 monthly thereafter.
    - For those with pre-existing liver disease (or taking potentially hepatotoxic drugs) check LFTs every 2 weeks for first six months then every 8 weeks for next 2 years, then regularly thereafter. For ALT elevations between 2- and 3-fold the upper limit of normal, monitoring should be performed weekly. Consider discontinuing teriflunomide if liver enzymes are elevated greater than 3-fold the upper limit of normal (ULN)
    - FBC annually
    - Blood pressure at each visit to nurse or doctor

- Nerve conduction studies will be performed if patient develops clinical features of a peripheral neuropathy

- **Accelerated elimination procedure**:
- If teriflunomide is stopped elimination can take up to two years. If the need for elimination is urgent (for example if patient becomes pregnant) an increased rate of elimination can be achieved by either
- cholestyramine 8g three times a day for 11 days, or cholestyramine 4g three times a day can be used, if higher dose not well tolerated
- alternatively, 50 g of activated powdered charcoal every 12 hours for a period of 11 days
  The level of the drug can be measured and is considered safe when <0.02mg/L

- **Planning a pregnancy**
  - If a patient would like to conceive it is recommended that a drug level below 0.02mg/l is confirmed on two occasions separated by 14 days and that fertilisation does not take place until at least six weeks after the first test (wait time).

Patients should not receive live vaccinations during treatment with teriflunomide.

5.8.1 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 teriflunomide
- Pregnancy and breast feeding
- Persistent failure to keep booked appointments
- Severe infection
- Teriflunomide therapy should be discontinued if liver injury is suspected; consider discontinuing teriflunomide therapy if elevated liver enzymes (greater than 3-fold ULN) are confirmed

For women of child bearing age effective contraception must be continued after stopping teriflunomide. When plasma teriflunomide levels fall below 0.02mg/L (confirmed on a second measurement 14 days later), contraception can be stopped.

6 Monitoring compliance with and the effectiveness of this document

(a) Process for monitoring compliance and effectiveness

- Patients will be assessed 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 healthcare

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.

7 References

Teriflunomide for treating relapsing–remitting multiple sclerosis. NICE technology appraisal guidance [TA303] https://www.nice.org.uk/guidance/ta303

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