Protocol

Natalizumab (Tysabri®) 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 administration of natalizumab (Tysabri®) on a specified neurology infusion bay, clinic or ward.

3 Abbreviations

BP	blood pressure
CCG	clinical commissioning group
FBC	full blood count
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
PCR	polymerase chain reaction
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PRN	as required
STAT	once only
TFT	thyroid function test
U&E	urea and electrolytes

4 Undertaken by (staff groups)

Consultant neurologist with special interest and expertise in the use of therapy for multiple sclerosis, registered nurses, and medical staff with appropriate training and expertise.

5 Clinical equipment list

For natalizumab infusion:

IV infusion pump
Equipment for use of IV medication (access and giving set etc)

For natalizumab SC injections:
None required – pre-filled syringes used.

For both:
Equipment to manage anaphylaxis
Access to MRI scanning
Natalizumab IV monograph

6 Treatment

6.1 Eligibility

Patients will have been assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. NICE technology appraisal guidance TA127 Natalizumab for the treatment of highly active relapsing-remitting multiple sclerosis (2007) will be followed when assessing eligibility.

Eligible patients are to be assessed only by consultant neurologists who have special interest and expertise in using therapy for multiple sclerosis. Natalizumab is indicated in patients with very active relapse remitting MS.

- This is described as having had two disabling relapses in one year plus evidence of disease activity on a recent MRI.

NHS England has further clarified criteria for treatment with natalizumab as follows:
Has had two disabling relapses in the past year, **and** meets one of:
a) One or more gadolinium-enhancing lesions on MRI
b) Increase in T2 lesions compared with previous MRI
c) Comparator MRI is unavailable or gadolinium-enhancement is unreliable as patient treated with steroids around the time of scan

And meets one of:

a) No previous disease modifying therapy (DMT)
b) Receiving first line therapy and does not meet stopping criteria

In addition, during the COVID19 pandemic NHSE have advised that natalizumab can be used in people with MS with highly active disease (one significant relapse within last 12 months on a first line disease modifying therapy).

Patients falling outside NICE eligibility criteria, but in whom it is clinically appropriate to treat, e.g. patients under 18 years of age, will require funding through an exceptional circumstances agreement with the relevant CCG. The agreement to treat beyond protocol may be sought by a consultant neurologist.

6.2 Contraindications and cautions

- Hypersensitivity to natalizumab or to any of the excipients listed
- Progressive multifocal leukoencephalopathy (PML)
- Patients with increased risk for opportunistic infections, including patients' immunosuppressed by disease or medication.
- Taking other disease modifying therapies
- Active malignancies, except for cutaneous basal cell carcinoma
- Significantly abnormal liver function tests (LFTs)
- Herpes encephalitis or meningitis
- Unexplained abnormalities in recent full blood count (FBC)
- Pregnant or breast feeding
- Patients unable to consent to treatment should not be prescribed Tysabri

6.3 Pre-screening

Risks and benefits are to be discussed with the patient, with particular mention of risks of PML. Further risks to be specifically discussed include risk of infusion related reactions and deranged LFTs, with a small risk of significant liver injury. This conversation must be documented by consultant neurologist.

The patient should be signposted to the MS Decisions website (www.mstrust.org.uk) for information about natalizumab and alternative DMTs in order to allow a balanced decision with informed consent.

- 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.

- Abnormal LFT results are to be investigated by appropriate specialist.
- Baseline MRI brain scan (within three months).
- Baseline EDSS recorded.

6.4 Side effects

Common side effects

- Infections eg urinary tract infections, nasopharyngitis
- Rigors
- Urticaria
- Headache
- Dizziness
- Nausea, vomiting
- Joint pain

- Fever
- Fatigue

Less common side effects

- Allergic infusion reactions during infusion
- Serious infections (eg herpes simplex or varicella zoster)
- Spontaneous liver injury have been reported
- Progressive multifocal leukoencephalopathy (PML). PML is caused by the JC virus, probability of developing PML increases according to JCV serology and duration of treatment.

6.5 Dose

Intravenous treatment: 300mg intravenously every four weeks for the first 12 months of treatment. After 12 months, reduce dose frequency to six weekly for all patients.

Subcutaneous treatment: 300mg subcutaneously every four weeks.

Note that for the duration of the Covid Pandemic, the frequency will be reduced to six weekly from the outset of treatment for intravenous therapy only, unless clinically this is felt by the MDT to be inappropriate.

6.6 Prescribing

- The Blueteq form should be completed.
- An intravenous therapy plan or subcutaneous therapy plan should be completed on Epic (check allergy status prior to prescribing). This should include:
    - Paracetamol 1g PO four times a day, if required
    - Chlorphenamine 10mg IV if required for hypersensitivity reaction
    - Natalizumab 300mg IV given over 1 hour in 100ml NaCl 0.9% or natalizumab 150mg SC x 2 given (no more than 30 minutes apart).

Confirm resources are available for managing hypersensitivity reactions (i.e. appropriate staffing level and equipment to manage anaphylaxis).

6.7 Consent

Consent to be treated obtained by the neurologist in clinic and a smartphrase letter will be sent to the patient and their GP.

MS specialist nurse will give to the patient contact details (email and telephone) of relevant healthcare professionals and guidance on whom to contact in the event of patient concerns about changes in MS.

Patients should be re-consented annually at a consultant (If JC positive) or nurse visit (where JCV negative) with a discussion about benefits and risks of treatment.

6.8 Supply and initiation arrangements

Infusion Unit Coordinator will make an appointment and inform patient of date to come to infusion unit for treatment.

Infusion nurses will liaise with pharmacy regarding natalizumab dispensing.

The pharmacist will release natalizumab from the therapy plan and communicate with inpatient pharmacy to dispense.

7 Infusion monitoring

7.1 First infusion

- Health and wellbeing is to be established. Infusion staff to ask the patient the pre-infusion questions specified on the therapy plan:
    - Has there been any significant change in walking, mental function, balance/ co-ordination, upper limbs and vision?
    - Has the patient had any infections?
    - Could the patient be pregnant?

  Any concerns arising to be discussed with consultant neurologist or neurology specialist registrar. If there is the possibility that the patient might be pregnant, treatment should be discussed with the MS Team.

- Natalizumab diluted in 100ml sodium chloride 0.9% as per IV drug monograph by an appropriately trained infusion nurse.
- Infusion to be administered over one hour. Pre-, peri- and post-administration monitoring of vital observations. For the first infusion monitor every 15 minutes during infusion, and for one hour after the infusion has finished.
- Infusion rate can be slowed if patient displays signs of discomfort eg headache, raised temperature. Symptomatic relief may be administered as per Epic therapy plan.
- IV competent nurse to record administration on Epic.
- Patients must stay under observation on the unit for at least one hour after end of first ten infusions, and may leave when well enough to do so thereafter.
- If an adverse reaction indicating hypersensitivity occurs, (eg rash, tightening of throat, vomiting) stop infusion, manage acute symptoms as per Addenbrooke's protocol for anaphylaxis; contact on-call neurology specialist registrar to review patient. Consultant neurologist should be informed by registrar. If hypersensitivity is confirmed, no further treatment will be given.

- The next infusion appointment should then be given to the patient (infusion unit staff to arrange).
- Patient to be reminded by infusion nurse of advice given on patient information leaflet of common side effects and whom to contact if concerned.

7.2 Second infusion

As for first infusion, but in addition:

- If patient presents at or prior to infusion appointment with new or worsening symptoms, contact neurologist or neurology specialist registrar, by bleep, suspend treatment pending investigation. The consultant or registrar will exclude PML and treat confirmed MS relapse as per NICE guidelines.

All hypersensitivity reactions and adverse events to be reported to Biogen Idec by the neurologist or MS nurse.

7.3 Third and subsequent infusions

The previous monitoring parameters should be met however if patient has been well throughout previous infusions, vital observations can be monitored less frequently, e.g. before and after infusion only.

7.4 Patients that fail to attend the infusions

In view of the risks to patient of rebound relapse beyond six weeks after the last infusion.

- If the patient calls to say they cannot attend for a scheduled infusion, an appointment should be rebooked as soon as possible up to a maximum of 8 weeks, but if this is outside the four or six weekly scheduling, the infusion staff should inform the MS Team via add-tr.msnurses@nhs.net and document the reason on EPIC.
- If the patient does not attend for infusion, the infusion team should inform the MS Team on the day the infusion has been missed via add-tr.msnurses@nhs.net. In the first instance, the infusion team should attempt to contact the patient to understand when they did not attend and reschedule as soon as possible – to be documented in EPIC.
- If the patient cannot be contacted with five working days, the infusion team must inform the MS Team via the email above, who will alert the GP surgery and will write a letter to the patient requesting they make contact.

8 Subcutaneous Administration

Natalizumab 150mg pre-filled syringe x 2 administered by subcutaneous injection for total dose of 300mg.

- Treatment naïve patients must have post-dose observations for 1 hour for the first six doses.
- After the first six doses, post-dose observations can be stopped if the patient has been well without any post-dose concerns.
- Patients who have previously been treated on intravenous natalizumab (for a minimum of six doses) are not required to stay for the 1 hour post-dose observations.
- Treatment is administered every four weeks.
- Data for extended interval dosing of six weekly is not currently supported.
- Patients should be advised that the safety profile for natalizumab administered subcutaneously is the same as for natalizumab administered intravenously, except that some 4% of people experience injection site pain with the SC injections.

9 Monitoring visits and follow up

Patients are to be monitored regularly, in a clinic setting, by consultant neurologist or MS specialist nurse depending on JCV titre:

- Low titre or JCV negative patients: consultant review annually (nurse led review in between consultant appointments).
- Medium and high titre patients:
    - First year of treatment, nurse appointment at six months, consultant appointment at 1 year
    - Thereafter, alternate nurse and consultant appointment three monthly
    - Note that for the duration of the COVID19 Pandemic;
        - For JCV negative patients, review will be annual (nurse alternating with consultant).
        - For JCV positive patients, review will be six monthly (nurse alternating with consultant).

- FBCs and LFTs will be monitored at each monitoring visit.
- Measurement of disease progression, EDSS, rate of relapse, health and wellbeing.
- Suspicion of PML or other adverse effects to be investigated and may include MRI and JC virus serology.
- Patients will be advised of any changes to management which may occur with post marketing experience eg increased frequency of MRI, breaks in treatment.
- Beyond 18 months of treatment, JCV serology will be checked at least every six months for those patients who are JCV serology negative or low (<0.9), or medium (>0.9, <1.5) titre positive. A single high titre (>1.5) JCV serology result means no further testing of JCV serology is required, since the patient will be presumed to be high titre positive indefinitely. Nurses should alert the doctor if a JCV negative patient becomes positive or if conversion from low/medium titre to high.

MRI monitoring:

- All patients on natalizumab should have a full MRI brain scan annually.
- For JCV serology negative patients, an annual brain MRI will be performed.
- Abbreviated MRI (DWI and FLAIR) for patients with a higher risk of PML beyond six months.
    - Low titre patients JCV serology positive: six monthly beyond month twelve.
    - Medium titre patients JCV serology positive: increase to six monthly beyond month twelve (four monthly if continuing to have four weekly infusions).
    - High titre patients JCV serology positive: six monthly beyond month twelve provided infusion frequency reduced to six weekly (three monthly if continuing to have four weekly infusions)

- A limited MRI protocol should be used for PML monitoring. A non contrast MRI with DWI and FLAIR should be requested.
- At least annually, review of risk versus benefit will be discussed, with an individual risk of PML provided to the patient in writing, as part of re-consent.
- Responsibility for arranging the following interval MRI will sit with the Consultant who receives the latest MRI result
- At each review, discussion of alternative treatment options.
- If the patient has confirmed disease progression over at least two monitoring visits, treatment should be discontinued as per the NICE TA127.
- Once the patient has been established on four-weekly natalizumab infusions for one year the infusion frequency will be reduced to six weekly.

10 Additional notes for administration of natalizumab in ward setting

The same process and therapy plan should be followed as for treatment in the infusion bay.

Natalizumab may only be administered on a specialist adult neurology ward.

11 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 (as per NICE guidelines) 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.

- 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 prescription of natalizumab to be sensitive to pre and 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.

12 References

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