Protocol

Alemtuzumab (Lemtrada®, Campath) treatment of relapsing-remitting multiple sclerosis

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 and effective use of alemtuzumab

3 Undertaken by

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. Medical staff with appropriate training and expertise, MS Specialist Nurses and MS Support Nurses.

4 Eligibility

Eligible patients are to be assessed only by consultant neurologists who have special interest and expertise in using therapy for multiple sclerosis. This will be in a MS Disease Modifying Therapy clinic. NICE technology appraisal guidance TA312 "Alemtuzumab for treating relapsing-remitting multiple sclerosis" (2014, updated Mar 2020) and NHS England 2019 Algorithm for Disease Modifying Therapies [170079ALG] modified by the EMA guidance of November 2019, will be followed when assessing eligibility.

Patients falling outside NICE eligibility criteria, but in whom it is clinically appropriate to treat, will require funding through an exceptional circumstances agreement. The agreement to treat beyond protocol may be sought by a Consultant Neurologist.

5 Before treatment

5.1 Pre-treatment screening

At assessment clinic appointment:

- Risks and benefits of alemtuzumab are discussed with neurologist and a specialist nurse.

- 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.
- Female patients are advised to be up to date on their smear tests prior to starting Alemtuzumab. *If under the age of 25 years a cervical smear prior to treatment should be considered (as Public Health England National Guidelines March 2016 recommend a smear for women starting cytotoxic drugs for rheumatological disorders).*
- All patients to have a pre-treatment ECG via Addenbrooke's Cardiology Outpatient appointment within 2 months prior to treatment
- Consent should take place in a clinic appointment (at least 24 hours from the assessment visit). The neurologist should go through the consent process, including sending a letter to the patient after the clinic with the alemtuzumab smartphrase summary of risks.

6 Treatment

6.1 Prescribing

After consent has taken place the following is to be completed:

- Clinical Team to request funding from NHS England by Blueteq
- Doctor to prescribe the **EPIC therapy plan** and check that the following is prescribed:
    - Pre-medication:
        - Days 1-3: Methylprednisolone sodium succinate 1000mg over 60minutes, given 60 minutes before alemtuzumab
        - Days 1-5: prior to each dose of alemtuzumab give:
            - Cetirizine 10mg PO 1-2 hours before Alemtuzumab
            - Paracetamol 1g PO 30-60 minutes before Alemtuzumab
    - Dose of alemtuzumab:
        - Initial treatment course: 12 mg/day on 5 consecutive days (60 mg total dose)
        - Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.
        - Alemtuzumab 12mg added to a 100ml of sodium chloride 0.9% infused over 4 hours i.e. at 25ml/hr (to be protected from light), followed by 50ml flush of sodium chloride 0.9% to be infused over 2hours i.e. at 25ml/hr.
    - Prophylaxis medications
        - Aciclovir PO 200mg BD days 1-5, (continued for 1 month on TTO)
        - Co-trimoxazole (Septrin®) 960mg on days 1, 3 and 5 (continued for 1 month on TTO) if no known allergy.
    - As required medication list:
        - Paracetamol 1g PO/IV QDS PRN (max 1g TDS if IV).

        - Chlorphenamine 4mg PO QDS PRN
        - Salbutamol 2.5mg nebulizer
        - In case of anaphylaxis:
            - Chlorphenamine 10mg IV
            - Hydrocortisone 100mg slow IV

    - Take home medication (will appear on the therapy plan).
        - Aciclovir 200mg tablet: Take ONE tablet TWICE daily for one month
        - Co-trimoxazole 960mg tablet: Take ONE tablet three times a week for one month.
        - Chlorphenamine 4mg tablet: Take ONE tablet every SIX hours when required for allergies.
        - Paracetamol 500mg tablet: Take TWO tablets FOUR times a day when required for mild pain
        - Zopiclone 3.75mg tablet: Take ONE tablet ONCE a day AT NIGHT

6.2 Supply and initiation arrangements

- MS Specialist Nurse will undertake responsibility for pre-ordering alemtuzumab for named patient before admission/booking to unit/advising relevant ward managers of intended admission so that staff with appropriate skill level are on duty. Also if required for obtaining written information from patients GP that they agree to shared care guideline.
- MS Specialist will liaise with pharmacy regarding alemtuzumab dispensing.
- The pharmacist will release alemtuzumab from the therapy plan and communicate with Clinical Trials Dispensary to dispense. In addition, the TTO medications will be released from the therapy plan and sent to Inpatient dispensary for preparation.

6.3 Caution and Contraindications

- Hypersensivity to drug/class/component
- HIV
- In pregnancy
- Uncontrolled hypertension
- History of arterial dissection of cervicocephalic arteries
- History of Stroke
- History of angina or myocardial infarction
- Caution if there is an active infection
- Caution in malignancy or history of malignancy
- Caution in thyroid disorder
- Caution with other concomitant autoimmune diseases besides MS
- Caution if the patient is a Hepatitis B virus (HBV) or Hepatitis C virus (HCV) carrier, or has untreated tuberculosis.

6.4 Infection prophylaxis

Alemtuzumab suppresses the immune system and therefore can increase the risk of infections. Alemtuzumab should not be given if there is any possibility of an active viral infection when the infusion is to be given (emerging shingles or varicella are particularly worrying).

Herpes infections
In order to reduce the risk of a herpes infection aciclovir 200mg twice daily is prescribed from the first day of infusion and continued for one month.

Listeria meningitis/septicaemia
Since marketing authorisation, Genzyme Sanofi pharmacovigilance has been informed of 32 cases of Listeria meningitis/septicaemia (approximately 13,000 people have received alemtuzumab). Nearly all infections have occurred in the first month after alemtuzumab. Therefore, this protocol incorporates giving co-trimoxazole 960mg three times a week for one month as outlined in the ABN document 'Guidance on the prevention of Listeria infection after alemtuzumab treatment of multiple sclerosis' May 2017.

If the patient is known to be allergic to co-trimoxazole they should instead have eight days of amoxicillin 1g three times daily to eliminate Listeria colonisation (starting four days before alemtuzumab treatment) followed by the Listeria-free diet for one month after alemtuzumab.

Patients should be informed on discharge that if they develop a rash they should phone the MS specialist nurse. If co-trimoxazole allergy is suspected then co-trimoxazole should be stopped and eight days of amoxicillin 1g three times daily prescribed to eliminate Listeria colonisation followed by the Listeria-free diet for one month after Alemtuzumab.

COVID-19
During the COVID-19 pandemic patients should be advised to self-isolate for 4 weeks following each infusion. The ABN Guidance On The Use Of Disease-Modifying Therapies In Multiple Sclerosis In Response To The COVID19 Pandemic will be followed (Date: August 2021, published 26/10/21).

6.5 Side effects

Infusion-related Side effects:

- Infusion associated reactions including headaches, fever, rashes, nausea, changes in blood pressure and heart rate.
- Infections - respiratory and urinary
- Lymphopaenia
- Musculoskeletal pain
- Elevated LFTs

- Very rarely within 1-3 days of last infusion: haemorrhagic strokes and ischaemic strokes including from cranial arterial dissection; myocardial ischaemia and pulmonary haemorrhages.

The following side effects occur months or years after last infusion of alemtuzumab, are serious however are treatable if detected early. Patients should be aware of the symptoms of these conditions and ensure a blood test is taken monthly.

- Hypothyroidism or hyperthyroidism
- Idiopathic thrombocytopenic purpura (ITP)
- Nephropathies- which can lead renal failure requiring dialysis and/or transplantation if not treated rapidly
- Rarely, autoimmune liver disease and other autoimmune cytopenias.
- Haemophagocytic lymphohistiocytosis,

7 Switching to alemtuzumab from other therapies

When switching disease modifying treatment the following breaks in treatment are required prior to commencing Alemtuzumab:

- **Beta interferon or glatiramer acetate**:
  Start immediately, or after wash-out of 1 month, provided total lymphocyte count normal.

- **Dimethyl Fumarate:** Start immediately or after wash-out of 1 month, provided total lymphocyte count normal

- **Fingolimod:**
  Start when total lymphocyte count has returned to normal or is greater than 0.8. Fingolimod should be stopped approximately 8 weeks prior to the planned alemtuzumab treatment date. FBC and lymphocyte phenotypes should be checked 2 weeks prior alemtuzumab treatment to ensure normalisation of lymphocyte counts.

- **Natalizumab:**
  If JCV negative: wash-out 1-2 months and then as soon as lymphocyte count normal
  JCV positive (any index):
  - Wash-out 2-3 months. MRI with last natalizumab infusion AND repeated before starting alemtuzumab with CSF for JCV DNA prior to starting alemtuzumab.
  - Repeat MRI brain at month 3 after starting alemtuzumab

8 Admission

8.1 Treatment day 1

- Infusion nurse follows the following checklist and steps (also available as EPIC smartphrase .ALEMTUZUMABINFUSIONCHECKLIST)

Checklist and steps to be completed each day for Alemtuzumab (Lemtrada) infusions by infusion nurse
1. Patient arrives to the infusion unit, is correctly identified, admitted on EPIC and given a wristband
2. Infusion nurse checks baseline observations (vital observations: BP, Temp, SpO2, pulse recorded)
3. Urinalysis done: • to exclude urine tract infections [UTI] see step 5 for action on abnormal results • and in all female patients urine pregnancy test done (alemtuzumab not be given if pregnant)
4. Infusion nurse asks patient if they have any symptoms of infection. • A doctor/MS nurse review is not necessary if the patient is well and afebrile • Alemtuzumab should NOT be given if there is any possibility of an active infection including viral infection (emerging shingles or varicella, or cold sores are particularly worrying). • **If patient has symptoms of infection contact the MS team** on 01223 596319 (if no answer email add-tr.msnurses@nhs.net) and contact the on call neurology registrar. • If the patient is well without symptoms of a UTI but has on urine dipstick: ○ Leucocytes and nitrites (without fever or urinary symptoms) urine should be sent to microbiology for microscopy, culture and sensitivity. The infusion can go ahead but the on call neurology registrar should prescribe an antibiotic to cover the possibility of a urine infection (see trust antibiotic policy). ○ Leucocytes 2+ or more and no nitrites (without fever or urinary symptoms) urine should be sent to microbiology for microscopy, culture and sensitivity. The infusion can go ahead but the on call neurology registrar should prescribe an antibiotic to cover the possibility of a urine infection (see trust antibiotic policy). ○ If well, no symptoms and leucocyte 1+ only (nitrite negative) infusion can go ahead and culture not needed. • It is safe to treat patients recovering from a URTI or UTI if the patient appears well, has had appropriate treatment, and is apyrexial.

5. Peripheral cannula to be inserted (to be removed on day 3 and prior to discharge on day 5). Please note that alemtuzumab can be given by central venous line as well.
6. Alemtuzumab should be collected by the infusion nursing staff from Clinical Trials Pharmacy on day 1, for the whole treatment (5 days for initial alemtuzumab course, or 3 days if subsequent infusion course). Alemtuzumab to be stored in locked fridge.
7. Reconstitute and administer the pre-medications and prophylaxis medications followed by alemtuzumab as per EPIC therapy plan and in accordance with IV drug monograph found via here. Pre-medications include IV methylprednisolone (day 1-3 only) over one hour followed by alemtuzumab. • Aciclovir to be given from unit stock aciclovir not TTOs. The co-trimoxazole is to be used from patients TTO pack as this is a complete course. • Alemtuzumab should not be handled by pregnant women or those wishing to become pregnant. • Refer to the ANTT for administering drugs and fluids by intravenous devices procedure. Ensure protective eyewear is worn and use protective (latex or nitrile) gloves. • Alemtuzumab must be protected from sunlight • Please note that the IV flush should be given at the same infusion rate as alemtuzumab, i.e., at 25 mL/hr.
8. Record vital observations before starting the pre-medications and before alemtuzumab. Then assess vital obs every 15 mins for first hour of alemtuzumab, 30 mins for 2nd and 3rd hrs then hourly for length of infusion (4 hours) and two hours after. Vital obs to be measured once just before discharge.
9. Inform neurology on call SpR of any concerning side effects as they occur and manage with PRN medications.
10. Patient waits for two hours after completion of alemtuzumab infusion.
11. TTOs must be given on day 1 by the infusion nursing staff, who should remind patient to take the TTO as prescribed. This includes co-trimoxazole 960mg three times a week for one month (for listeria prevention) and aciclovir 200mg twice daily for one month. These are commenced on the first day of treatment.
12. If well, patient will go home (return next day until completing the cycle) and be advised that an infusion reaction occurs to seek medical attention via A&E, if required. The cannula can be retained for 72 hr, as per Trust's policy.
13. Discharge letter for GP completed daily by unit staff.

8.2 Subsequent Treatment Days

Days 2-5 of cycle one or days 2-3 of cycle two.

Patient returns to unit each day at agreed time and above checklist/steps completed.

9 Discharge

- TTO medications include:
    - Aciclovir 200mg tablet: Take ONE tablet TWICE daily for one month
        - Co-trimoxazole 960mg tablet: Take ONE tablet three times a week for one month (for listeria prevention).
        - Chlorphenamine 4mg tablet: Take ONE tablet every SIX hours when required for allergies.
        - Paracetamol 500mg tablet: Take TWO tablets FOUR times a day when required for mild pain
        - Zopiclone 3.75mg tablet: Take ONE tablet ONCE a day AT NIGHT
- Follow up OPA and relevant shielding letter will have been booked by MS Specialist nurse.
- Discharge letter for GP to be completed by unit staff.
- Contact details of MS Nurses given to patient.

10 Follow up and Monitoring visits:

Clinic visits:

- Month 11 (after cycle one, just prior to cycle two) – Consultant OPA for EDSS bloods and MRI request (scan to be requested for ~ 11 months after cycle two).
- Year 2 (12 months after second treatment) - Nurse OPA (unless scan shows disease activity)
- Year 3 - Consultant OPA (EDSS)
- Year 4 - Nurse OPA (requests MRI at 4.5 years)
- Year 5 - Consultant. Patients can stop regular follow-up at 48 months from their last dose if no MRI/clinical activity. Give a 2 year patient initiated follow-up ‘PIFU’ appointment.

Blood monitoring, to identify thyroid dysfunction, Goodpasture’s and ITP, is for four years after the last dose of alemtuzumab and consists of:

- Monthly FBC, U+E and three monthly Thyroid function (done via Ashfield or at GP practice as agreed by Cambridgeshire and Peterborough CCG via Shared care guideline. Need agreement BEFORE treatment commences, if GP refuses escalate to CCG).
- Thyroid function should be monitored monthly in female patients actively trying to conceive and during pregnancy.
- If unexplained bruising outside of these times for urgent FBC.
- If unexplained illness, for urine microscopy. Note: as a group we have decided NOT to request monthly urine microscopy or urinalysis, because of the high incidence of false positives and the lack of evidence that either of these tests effectively identify Goodpasture’s syndrome. For selected patients, we may give out urine dipstick tests.
- MS team will monitor blood results and compliance

Female patients to remain up to date with smear tests.

Contraception should be used from the first infusion until four months after cycle two (i.e. 16 months after starting treatment) for women and for 4 months after each infusion course for men.

11 Abbreviations

BP	Blood Pressure
FBC	Full Blood Count
LFT	Liver Function Test
TFT	Thyroid Function Test
U+E	Urea and Electrolytes
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NICE	National Institute for Clinical Excellence
PO	By mouth
IV	Intravenously
PRN	As required
Obs	Observations

12 Monitoring the effectiveness of the protocol

(a) Process for Monitoring compliance and Effectiveness:

- 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.
- 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 alemtuzumab 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 Technical Appraisal.
- Internal checks on safety, compliance and efficacy will be undertaken by MS team.

13 References

- Cambridge University Hospital Alemtuzumab monograph (up-dated 05/02/21), http://sharepoint/sites/pharmacy/IV%20Guides/Adult%20IV%20Monographs/Alemtuzumab%20-%20Multiple%20Sclerosis%20only.doc
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- National Institute for Health and Care Excellence (2014, updated March 2020). Alemtuzumab for treating relapsing-remitting multiple sclerosis [TA312]. Manchester: NICE. https://www.nice.org.uk/Guidance/TA312
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- Shared Care Guideline Alemtuzumab for relapsing-remitting multiple sclerosis, C&P CCG https://www.cambridgeshireandpeterboroughccg.nhs.uk/health-professionals/prescribing-information/shared-care-guidelines/
- Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies NHS England Reference: 170079ALG Date Published: 4 September 2018 Gateway reference: 07603 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/09/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-modifying-Therapies.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

14 Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service Equality and Diversity statement.

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Document management

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