ANTI-THYMOCYTE GLOBULIN (ATG) TREATMENT FOR APLASTIC ANAEMIA (ADULTS)

INDICATION
ATG is indicated for patients who are not eligible for sibling donor BMT. This includes:

- Patients with non-severe aplastic anaemia who are dependent on red cell and/or platelet transfusions.
- Patients with severe aplastic anaemia (SAA) or very SAA who are > 30-45 years of age.
- Patients with SAA or very SAA disease who lack an HLA-compatible sibling donor.
- Protocol may be used in selected patients with hypoplastic marrow conditions.

Patients with severe AA who are < 40 years old and have a HLA identical sibling donor, should be treated with allogenic bone marrow transplantation as soon as possible after diagnosis.

INVESTIGATIONS

- Full blood count, reticulocyte count and blood film
- Bone marrow aspirate and trephine biopsy, including cytogenetics
- Peripheral blood cytogenetics to exclude Fanconi's anaemia if < 35 years old
- LFTs, Hep A, Hep B, Hep C, EBV, CMV
- Vitamin B12 and folate
- Autoantibody screen
- Ham test or FACS for CD55 and CD59 to exclude paroxysmal nocturnal haemoglobinuria (PNH)
- Urine haemosiderin if Ham test positive or CD55, CD59 deficiency
- Chest X-ray
- Hickman line prior to therapy.
- Drugs with rare association causing aplastic anaemia: A careful drug history should be obtained detailing all drug exposure for a period of 6 months and ending 1 month prior to presentation. All suspected drugs should be discontinued and the patient should not be re-challenged with the drugs at a later stage. Report adverse drug reaction to Committee on Safety of Medicines.
- Assessment prior to starting ATG
  - Exclude active infection
  - Chest XRay
  - ECG (for patients > 60 years, consider ECHO)
- Assessment of platelet transfusional requirements
- TFTs

It is important to ensure an adequate platelet increment after platelet transfusions, because ATG results in a fall in the platelet count and can precipitate. If refractory to random donor platelets, postpone ATG treatment until further investigated. If HLA antibodies, arrange adequate supply of HLA matched platelets to cover course of ATG.

Irradiated platelet transfusions are not currently indicated for ATG treatment. We are not aware of any reported cases of transfusion-associated GVHD after ATG therapy for AA.
Summary

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Key: Abx: Antibiotics/antifungals, ATG preceded by (P) Platelets, (C) Chlorphenamine, and (M) Methylprednisolone. Pred: Prednisolone, CSA: Ciclosporin A.

DRUG REGIMEN

Test dose Day 0 - 24 hours prior to actual start of treatment. Thymoglobuline - Rabbit ATG (Genzyme®) 2.5 mg (1/10th of a vial) diluted in 100 ml of N/Saline given intravenously over 1 hour. The test dose must be supervised by a doctor with Adrenaline, Chlorphenamine and Hydrocortisone available and drawn up beforehand. A severe reaction or anaphylaxis to the test dose is an absolute contraindication to proceeding with treatment.

NB: Always give ATG through a central line, or an antecubital fossa line with distal end in central vein. Severe thrombophlebitis may occur if ATG is administered via a peripheral vein. To avoid inadvertent administration of particulate matter from reconstitution, it is recommended that Thymoglobuline is administered through a 0.22 µm in-line filter.

Treatment doses days 1 to 5

- Each morning during ATG treatment proton-pump inhibitor and continue until Prednisolone discontinued.
- 1 hour before each daily dose of ATG Chlorphenamine 10 mg iv.
- 30 mins before each daily dose of ATG Methylprednisolone 2 mg/kg/day iv as 30 min infusion.
- ATG 1.5 vials/10 kg body wt/day = 3.75 mg/kg/day for rabbit ATG in 250-500 ml sodium chloride 0.9% and infuse over 18 hours. If tolerated, subsequent doses can be given over 12-18 hours. ATG should be administered within 18 hours of being made up.
- Platelets (one random donor pack or one apheresis pack or one HLA matched pack) should be given to maintain count > 30 x 10⁹/L, but should not be given concurrently with ATG administration because of the anti-platelet activity of ATG.
- Ciclosporin see APPENDIX from day 1.
- If possible, avoid giving more than one unit of blood each day of the 5 days of ATG, to (a) help reduce the risk of fluid overload, and (b) help ensure that the administration of ATG each day starts in the morning.

General and Nursing points

BCSH guidelines recommend that patients stay as inpatients for 2 weeks post-ATG. TVCN Leukaemia Group suggest discharge home is safe if prompt readmission possible.
Concurrent therapy

- Ciprofloxacin 500 mg 12 hourly - start 24 - 48 hours before ATG treatment and continue throughout.
- Chlorhexidine mouthwash 10 ml 6 hourly.
- Fluconazole 50 mg daily (anti-fungal prophylaxis).
- Aciclovir 200 mg tds.
- Tranexamic acid 1g tds, if required.
- Norethisterone 5 mg tds to control menorrhagia.
- No indication for PCP prophylaxis - not aware of any reported case of pneumocystis after ATG treatment given for AA.
- Proton-pump inhibitor.

Prophylactic antibiotics and oral antifungals for all patients, prophylaxis should continue for a minimum of 4 weeks, but consider continuing if the patient has severe aplastic anaemia (esp. if neutrophils < 0.2 x 10^9/L). Serious infection can occur in patients with severe aplastic anaemia soon after discharged from hospital following ATG therapy, particularly in the first few weeks after discharge.

Immediate side effects (during administration of ATG):

- Lymphopenia, neutropenia and thrombocytopenia.
- Fevers and rigors (tend to be worse on the first day and diminish with subsequent doses of ATG).
- Rash, pruritis, urticaria.
- Fluid retention occurs commonly. Acute pulmonary oedema and cardiac failure can develop rapidly if left untreated. Fluid retention needs very close monitoring and early treatment with Furosemide.
- Hypotension or hypertension.
- Elevation of serum transaminases occur commonly.
- Cardiac arrhythmias may occur: bradycardia or tachycardias.
- Chest pain, loin pain, back pain occasionally.
- Nausea, vomiting, diarrhoea may sometimes occur.
- Positive direct antiglobulin test and difficulty with cross matching blood due to the presence of anti-red cell antibodies in ATG.
- Anaphylaxis.
- Other rare reported side effects are acute haemolysis, massive pulmonary haemorrhage and adult respiratory distress syndrome, acute renal failure and renal impairment.

Late side effects after administration of ATG due to serum sickness:

Onset is 7 to 14 days after starting ATG. If a second course is given, serum sickness can occur earlier.

- Fever, rash (maculopapular or urticarial starting on trunk or extremities).
- Serpiginous palmar-plantar distribution is classical. Rash may become purpuric due to platelet consumption during the time of serum sickness.
- Arthralgia, myalgia, nausea, vomiting, proteinuria (usually mild), rarely splenomegaly and lymphadenopathy.
- Increased platelet transfusion requirements due to platelet consumption.
- Glycosuria and/or hyperglycaemia due to corticosteroids.
Other late side effects of ATG:
- Rarely, worsening of autoimmune thyroid disorders and fibrosing alveolitis, and precipitation of Guillan Barre syndrome.
- AA patients treated with ATG are at increased risk of later clonal disorders such as MDS, AML and PNH, and to a lesser degree, solid tumours.

Very rare side effects:
- Positive direct antiglobulin test (DAGT) +/- haemolysis, massive pulmonary haemorrhage and capillary leak.

Treatment of immediate side effects
- Immediate allergic side effects usually respond to an extra dose of Hydrocortisone and Chlorphenamine. If persistent, give Pethidine 25 mg i.v. Pyrexia during ATG may also be due to infection, so broad spectrum i.v antibiotics (as per departmental protocol for neutropenic patients) must be commenced after obtaining blood cultures and appropriate peripheral swabs.
- Treat fluid retention promptly with intravenous Furosemide and review fluid balance later the same day. If the patient gains more than one kg in weight, or if the amount in is one litre more than the amount out in 24 hours, then give a dose of Furosemide. However, assess clinically first, because if febrile, and increased insensible loss, Furosemide may not be appropriate.
- If patient is hypertensive, treat associated fluid retention as above, and use appropriate anti-hypertensives.
- Anaphylaxis discontinue ATG immediately and treat anaphylaxis appropriately.
- If bleeding occurs during ATG, stop the ATG infusion and give additional platelets. Resume ATG when bleeding resolved. Check coagulation screen if bleeding persists despite adequate platelet increment.

Prevention of serum sickness
- Days 1 to 5: Methylprednisolone 2 mg/kg/day iv as 30 min infusion, 30 min before each dose of ATG.
- Day 6 onwards: Prednisolone 1 mg/kg/day po, halving the dose every 5 days. If serum sickness occurs, it usually responds within 24 - 48 hours to 100 mg Hydrocortisone iv 6 hourly, with continued Prednisolone administration.

Ciclosporin - commenced on the first day of ATG (see APPENDIX for full dose and monitoring information).

G-CSF with ATG and Ciclosporin
The benefits of giving daily G-CSF for 4 months following a course of ATG remain uncertain. Clinical studies to date indicate no advantage using G-CSF in terms of response or survival after ATG and CSA, although neutrophil counts recover more quickly and there is a reduction in the incidence of serious infections. There are some concerns that the use of G-CSF may be associated with an increased risk of MDS and AML.

The EBMT is currently performing a second prospective randomized study of ATG and CSA with or without G-CSF for severe AA. It is recommended that all new patients with severe AA, who do not have an HLA identical sibling, should be entered into this study. The routine use of G-CSF in this manner is not currently recommended outside this multi-centre EBMT study.
Monitoring

• Carefully monitor patient clinically for evidence of bleeding, blood pressure and daily fluid balance:
  o weigh patient twice daily
  o keep fluid balance chart daily
  o 4 hourly temperature, pulse, BP and respirations
  o daily urine test for glucose, FBC, U&Es and LFTs

• Monitor for signs of infection - follow hospital guidelines for neutropenic sepsis. Introduce IV amphotericin or voriconazole early if fevers persist.

Contra-indications

• Severe systemic reaction or anaphylaxis to test dose.
• ATG may exacerbate viral and parasitic infections, so do not give in the presence of active infection.
• There is a theoretical risk of acute haemolysis in patients with haemolytic paroxysmal nocturnal haemoglobinuria (PNH) who are already haemolysing. However, ATG can be given cautiously to patients with a quiescent PNH clone.

Time to response

Response to ATG does not usually begin to occur before 3-4 months, so red cell and platelet transfusions will need to be continued as needed until the peripheral blood counts start to improve. Continue oral prophylactic antibiotics and antifungals while the patient is severely neutropenic.

Repeat courses of ATG

More than one course of the same ATG preparation can be given but the risks of side effects and anaphylaxis are increased, and the onset of serum sickness occurs earlier than after a first course. Always give a test dose before the second course of either preparation of ATG.

A second course of ATG should be commenced if there is no response or relapse after the first course. This should not be given earlier than 3 months after the first course as it usually takes around 3 months before a response is seen.

A third course of ATG may be considered if there has been no response to two courses and a BMT is not an option, or if the patient has relapsed after previous courses.

A test dose must be given prior to each repeat course of ATG.

OXYMETHOLONE: available on a named patient basis and is a useful option for those patients who have failed several courses of ATG and ciclosporin, or in certain patients where standard immunosuppressive treatment may not be possible. Vaccinations: Only use when absolutely necessary - there have been anecdotal reports of vaccination producing bone marrow failure or triggering relapse of AA. Live polio vaccine should be avoided following ATG treatment.
APPENDIX: The use of ciclosporin (CSA) in the treatment of aplastic anaemia

The current standard immunosuppressive regimen for the treatment of AA is the combination of ATG and ciclosporin (CSA), and this applies to very severe, severe and non-severe AA.

Dose

Initial dose of oral ciclosporin (CSA) is 2.5 mg/kg twice daily. Since CSA is lipid soluble, dose is based on actual body weight. for elderly patients, start with lower dose, e.g. 1.25 mg/kg twice daily if > 60 years old and adjust according to renal function, blood pressure and CSA levels.

Trough level: 150 - 250 micrograms/l. Measure initial trough levels on day 3 to 7 after starting Ciclosporin. If level is therapeutic and not toxic, monitor weekly thereafter for one month, and then monthly. Monitor BP, serum electrolytes, renal & liver function.

Side effects

- Nephrotoxicity:
  - Increases in serum creatinine are dose and plasma level related. Additive nephrotoxicity occurs particularly with aminoglycosides, vancomycin and amphotericin B (also with ACE inhibitors, NSAID, quinolones and trimethoprim). Hyperkaemia may occur with long term use of CSA. Increased risk with renal impairment or drugs such as ACE inhibitors and K+ sparing diuretics e.g. amiloride. Avoid high dietary potassium intake. CSA can aggravate hypomagnesaemia in the setting of BMT as in renal transplants.
- Hypertension
- Neurological
- Gastrointestinal tract
- Hepatotoxicity
- Anaphylaxis
- Hypertrichosis

Assessment of patient prior to commencing CSA

Check blood pressure (BP), serum electrolytes, urea, creatinine (U&Es) liver function tests (LFTs). Review current medication patient is taking, and ask about herbal remedies.

Monitoring

Aim to keep trough whole blood CSA level between 150 and 250 µg/l

- Frequency of monitoring
  - Weekly CSA levels until stable (consider twice weekly 1st and 2nd weeks). Levels can then be checked every 2 - 3 weeks. If renal and hepatic function is abnormal, levels should be checked more frequently.
- Sample required
  - 12 hour trough whole blood levels are measured i.e. before the morning dose of CSA.
  - Send 3 ml blood in EDTA with special request form to the analytical unit.
  - Always take sample from a peripheral vein.
  - Never take blood for CSA level from the CSA infusion line of the Hickman catheter, even after thorough flushing of the line, otherwise falsely high levels will be obtained.
• Renal function and other electrolytes
  o The most frequent dose limiting toxicity is renal impairment.
  o Monitor renal function daily and liver function 3 times weekly whilst patient is an in-patient.
  o Monitor serum Ca\(^{2+}\) and Mg\(^{2+}\) weekly.
  o A slow rise in serum creatinine to 120-130 µmol/l is common in the first few weeks of therapy.
  o If the creatinine is > 130 µmol/l, a dose adjustment should be made.
  o If a rapid rise in creatinine occurs, stop CSA for 1-2 doses, monitor renal function and CSA level, make appropriate dose adjustment.

• Blood pressure
  o As CSA can cause hypertension, monitor BP regularly.
  o Antihypertensive therapy may be necessary.

Duration of treatment
For the treatment of AA, CSA is given for a minimum of 6 months and usually much longer. If a response occurs, CSA is continued at full dose until the blood count has stopped rising and has plateaued. CSA is tailed off very slowly often over many months or even longer depending on the FBC. Too rapid dose reduction is associated with a high incidence of relapse of aplastic anaemia. Some patients, however, are CSA dependent and will need a low dose for a long period of time. In these patients it may be impossible to stop the CSA completely.

CSA drug interactions
See data sheet at www.medicines.org.uk

REFERENCE