

# ANTI-THYMOCYTE GLOBULIN (ATG) AND CICLOSPORIN (CSA)

## INDICATION

ATG and CSA is indicated for patients who require treatment for aplastic anaemia (AA) but who are not eligible for sibling donor BMT. This includes (note references to severity are based on the modified Camitta criteria):

- 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 > 35-50 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 ≤ 35 years old and have a HLA identical sibling donor, should be treated with allogenic bone marrow transplantation as soon as possible after diagnosis.*

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## TREATMENT INTENT

- Prolong survival
- Provide a rapid (within 3 months) and sustained improvement in peripheral blood counts
- Restore haematopoiesis

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## PRE-ASSESSMENT

1. ATG should only used by physicians familiar with administering ATG. Medical and nursing teams must be aware of the side effects and how to treat promptly and appropriately.
2. ATG is highly immunosuppressive - only use in centres with at least level 2 facilities. Patients should be nursed in a single or double isolation room, as an inpatient.
3. **Risk of transfusion-associated GvHD following treatment with ATG is unclear, therefore irradiated blood components are currently recommended. It is not known how long the use of irradiated products**

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**should be continued, but it may be reasonable to continue while patients are still taking CSA following ATG therapy.**

4. Patients over 60 years of age should be carefully assessed medically beforehand to determine whether they are fit enough to tolerate ATG treatment.
5. It is recommended that the haematologist responsible for the patient should contact a centre/specialist with expertise in AA beforehand to discuss the management plan (and possibly review the bone marrow slides).
6. Whenever possible, patients are entered into ongoing National or European (EBMT) prospective clinical trials.
7. For further written information relating to diagnosis and management of AA the Nov 2015 revised BCSH guidelines are recommended.
8. For Ciclosporin - check blood pressure, serum electrolytes, urea, creatinine (U&Es), liver function tests. Review current medication including herbal remedies
9. Obtain written consent.

## INVESTIGATIONS

*To confirm diagnosis of AA*

- Full blood count, reticulocyte count and blood film
- Bone marrow aspirate and trephine biopsy, including cytogenetics
- Peripheral blood chromosomal breakage analysis to exclude Fanconi's anaemia if < 50 years old (or regardless of age if transplant candidate or sibling of FA patient)
- FACS for CD55 and CD59 to exclude paroxysmal nocturnal haemoglobinuria (PNH) Vitamin B12 and folate
- LFTs, Hep A, Hep B, Hep C, EBV, CMV, HIV, Parvovirus B19
- Autoantibody screen – ANA and anti-dsDNA
- Chest X-ray
- Consider Abdominal US scan to exclude splenomegaly
- 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.
- Myeloid mutation panel

*Assessment prior to commencing ATG and CSA*

- Exclude active infection
- TFTs

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- Chest X-ray
- ECG (for patients > 60 years, consider echo)
- CVC insertion prior to commencing therapy
- Inform NHSBT of need for irradiated products
- Assessment of platelet transfusional requirements
  - It is important to ensure an adequate platelet increment after platelet transfusion, because ATG will trigger a (precipitous) fall in platelet count.
  - **If refractory to random donor platelets, postpone ATG treatment** until further investigated; if HLA antibodies required, arrange adequate supply of HLA matched platelets to cover course of ATG.

Summary

	Day											
Drug	1	2	3	4	5	6	7	8	9	10	11	12
IV Methylprednisolone <i>To reduce reaction to ATG</i>	*	*	*	*								
Platelets <i>To keep above 20 - 30</i>	*	*	*	*								
Chlorphenamine <i>To reduce reaction to ATG</i>	*	*	*	*								
<b>Equine</b> ATG <i>To treat AA</i>	*	*	*	*								
Ciclosporin <i>To treat AA</i>	*	*	*	*	*	*	*	*	*	*	*	*
Prednisolone <i>To prevent serum sickness</i>					*	*	*	*	*	<i>Aim to halve dose every 5 days</i>		
Ciprofloxacin <i>To prevent bacterial infection</i>	*	*	*	*	*	*	*	*	*	<i>Continue prophylaxis for at least 4 weeks</i>		
Voriconazole <i>To prevent fungal infection</i>	*	*	*	*	*	*	*	*	*			
Aciclovir <i>To prevent viral infection</i>	*	*	*	*	*	*	*	*	*			
Omeprazole <i>To counter steroid</i>	*	*	*	*	*	*	*	*	*	*	*	*
Norethisterone <i>For pre-menopausal women</i>	*	*	*	*	*	*	*	*	*	*	*	*

## DRUG REGIMEN

**NOTE THAT EQUINE ATG MUST BE USED (be aware that rabbit ATG is also available but it not as effective in the therapy of aplastic anaemia)**

Anti-Thymocyte Globulin [Equine] IV infusion **40mg/kg/day on day 1- 4 (for 4 days).**

Allow 5 working days to acquire stock of Equine ATG from manufacturer.

For obese patients, the dose must be calculated according to ideal body weight.

## ADMINISTRATION

- Patients must be admitted as an inpatient
- Patients should remain an inpatient until at least the day after the fourth dose of ATG has been administered, with close monitoring and prompt treatment for serum sickness and other possible complications
- Always give ATG via a central line, or a PICC line in the antecubital fossa line with its distal end in a central vein. Severe thrombophlebitis may occur if ATG is administered via a peripheral vein
- Each 5ml ampoule contains 250 mg of horse gammaglobulin; dilute the required dose (40mg/kg) in 1000 ml sodium chloride 0.9% (concentration should not exceed 4mg/ml) and infuse via a 0.2 micron in-line filter
- A test dose must always be given on day 1 of ATG. To do this:
  - The test dose must be supervised by a doctor with Adrenaline, Chlorphenamine 10mg IV and Hydrocortisone 100mg IV drawn up beforehand
  - Precede the test dose with Methylprednisolone and Chlorphenamine.
  - Run the infusion slowly at 5ml/hr for the first hour of the infusion.
  - A severe systemic reaction or anaphylaxis to the test dose is an absolute contraindication to proceeding with ATG treatment
  - Infuse the remainder of the infusion over 12-18 hours via a 0.2 micron in-line filter. It should be administered within 24 hours of being made up.
- Infuse the first full dose over 18 hours. If tolerated, subsequent doses can be given over 12 hours
- Precede each daily dose of ATG with:
  - Platelets (one random donor pack or one apheresis pack or one HLA matched pack), aiming to keep platelet > 30 x 10<sup>9</sup>/l. Do not give platelet transfusions during the ATG infusion, because of the anti-platelet activity of ATG.
  - Methylprednisolone 1mg/kg IV infusion over 30 minutes, start 30minutes before each dose of ATG.
  - Chlorphenamine 10 mg IV
- If possible, avoid giving more than two units of blood each day of the 4 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

## MONITORING

Carefully monitor patient clinically for evidence of bleeding, infection, fluid retention, hypo- or hypertension:

- Weigh patient twice daily
  - Keep strict fluid balance chart daily
  - Four-hourly temperature, pulse, BP, oxygen saturations, respiratory rate
  - Daily urine test for glucose
- Daily FBC, U&Es and LFTs

## CONCURRENT MEDICATIONS

- Ciclosporin (Capimune®) po 2.5 mg/kg twice daily starting on Day 1 ATG. For patients > 60 yrs old, start with 1.25 mg/kg twice daily and adjust according to renal function, blood pressure, CSA levels.
  - Monitoring on CSA
    - Aim to keep trough Ciclosporin level 200-300 micrograms/L
    - Measured from Day + 2, then twice weekly during inpatient stay
    - Weekly levels as outpatient until stable. Then check every 2-3 weeks, unless renal and hepatic function is abnormal - check more frequently
    - Monitor renal function daily and liver function 3 times weekly during inpatient stay
    - Serum Ca<sup>2+</sup> and Mg<sup>2+</sup> weekly
    - Slow rise in serum creatinine to 120-130 micromol/l is common in the first few weeks of therapy: if the creatinine is > 130 micromol/l a dose adjustment should be made; if a rapid rise in creatinine occurs, stop Ciclosporin for 1-2 doses, monitor renal function and Ciclosporin level, make appropriate dose adjustment
    - Monitor BP regularly - antihypertensive therapy may be necessary
    - Drug interaction – consult Pharmacy
  - Duration of CSA
    - Continue Ciclosporin for a minimum of 12 months, often longer.
    - If a response occurs, Ciclosporin is continued at full dose until blood count has stopped rising and has plateaued. **Continue for a further 12 months, followed by a slow taper of around 25mg every 2-3 months.**
    - Too rapid dose reduction is associated with a high incidence of relapse of aplastic anaemia. Some patients are Ciclosporin dependent, needing a low dose for a long period - in these patients it may be impossible to stop the Ciclosporin completely
- Prevention of serum sickness
  - Day 1 - 4: Methylprednisolone 1mg/kg/day IV infusion over 30 minutes, start 30 minutes before each dose of ATG.
  - Day 5 onwards: Prednisolone 0.5mg/kg/day po from Day 5 and subsequently aim to half the dose every 5 days
- Prophylaxis medications
  - Ciprofloxacin po 500mg 12 hourly

- Chlorhexidine 0.2% mouthwash 10ml 6 hourly
- Voriconazole\* po (body weight >40kg) loading dose 400mg 12 hourly for 2 doses then maintenance 200mg bd (\* reduce dose of Ciclosporin (Capimune®) to half normal dose i.e. 2.5mg/kg daily) OR Liposomal Amphotericin (Ambisome®) 2mg/kg on Monday/Wednesday/ Friday
- Aciclovir po 200mg 8 hourly
- *Continue prophylaxis for a minimum of 4 weeks, longer if very severe AA with ANC < 0.2 x 10<sup>9</sup>/l*
- Omeprazole po 20mg daily
- Norethisterone po 5mg 8 hourly for pre-menopausal females
- GCSF is NOT recommended

## CONTRA-INDICATIONS

- Severe systemic reaction to test dose.
- ATG may exacerbate viral and parasitic infections - do not give ATG in the presence of active infection

## WARNINGS AND SPECIAL PRECAUTIONS / ADVERSE REACTIONS / REGIMEN SPECIFIC COMPLICATIONS

### Immediate - during ATG administration:

- Lymphopenia, neutropenia, thrombocytopenia.
- Fevers, rigors (worse on first day, diminishes with subsequent ATG doses)
- Rash, pruritis, urticaria.
- Fluid retention common. Acute pulmonary oedema and cardiac failure can develop rapidly if left untreated. Fluid retention needs very close monitoring and early treatment with Furosemide. It is usually multi-factorial in origin, for example, diluent, blood and platelet transfusions, corticosteroids, chronic anaemia.
- Hypotension, hypertension.
- Elevated serum transaminases common
- Bradycardia, tachycardias
- Chest pain, loin pain, back pain occasional
- Nausea, vomiting, diarrhoea sometimes occur
- Positive direct antiglobulin test and difficulty with cross matching blood due to presence of anti-red cell antibodies in ATG
- Phlebitis can occur when administered via a peripheral vein
- Anaphylaxis
- Rare reported side effects : acute haemolysis, massive pulmonary haemorrhage, adult respiratory distress syndrome, acute renal failure and renal impairment.

### Late side effects - serum sickness (associated with ATG administration)

Typically 7-14 days after starting ATG. If a second course of ATG is given, serum sickness may occur earlier.

- Fever, rash (maculopapular / urticarial starting on trunk / 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

### TREATMENT OF IMMEDIATE SIDE EFFECTS

- **Allergic** side effects usually respond to a dose of Hydrocortisone and Chlorphenamine. If persistent, give Pethidine 25mg IV.
- **Pyrexia** during ATG may also be due to infection, so broad spectrum IV antibiotics (as per departmental protocol for neutropenic patients) must be commenced after obtaining blood cultures
- Treat **fluid retention** promptly with Furosemide, reviewing fluid balance later the same day. If the patient gains > 1kg, or if input is 1L more than output in 24 hours, 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 any fluid retention if present, and use appropriate anti-hypertensive
- For **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



## 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. It is often a better option to administer Eltrombopag if ATG is ineffective although this is not routinely funded by the NHS. IFR necessary.

Always give a test dose before the second course of ATG.

**A second course** of ATG can 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. This is rarely appropriate.

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

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.

## REFERENCES

1. Killick, S. B., *et al.* and the British Society for Standards in Haematology (2016), Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*, 172: 187-207.
2. Protocol for the treatment of Aplastic Anaemia with Horse Anti-Thymocyte Globulin (hATG, ATGAM®). Professor J Marsh, and Dr A Kulasekararaj. June 2012. King's College Hospital NHS Trust

## REVIEW

Name	Revision	Date	Version	Review date
Dr Ed Watson, Jon Barrett, Dr Andy Peniket	New protocol	Mar 2018	4	Mar 2020
Jon Barrett	Protocol update	Oct 2018	4	Oct 2020
Jon Barrett Haematology Pharmacist. NSSG Myeloid Group	Annual Protocol meeting	Oct 2019	4.1	October 2021

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