Systemic Anti-Cancer Therapy Protocol

ATGAM *(Anti-thymocyte Globulin - Equine*) & Ciclosporin Aplastic Anaemia

PROTOCOL REF: MPHAATGCIHA
(Version No: 1.0)

Approved for use in:

Anti-thymocyte globulin (ATGAM®) and ciclosporin (CSA) is indicated for patients who require treatment for aplastic anaemia (AA) but who are not eligible for sibling donor bone marrow transplant.

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 & >35-50 years of age.
- Patients with SAA / very SAA, who lack a HLA-compatible sibling donor.
- Protocol may be used in selected patients with hypoplastic marrow conditions.

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

Blueteq Registration not required

Dosage:

Drug	Dose	Route	Frequency
ATGAM®	**40mg/Kg**	**IV Infusion**	**Once daily on days 1 to 4 inclusive**
Ciclosporin	**2.5mg/Kg***	**PO capsule**	**Twice daily from day 1. Continue for at least 12 months.**

**Dose adjustments may be made – see page 5*

- Other names for ATGAM® include ATG (Equine), hATG, horse ATG and Anti-thymocyte globulin. Important - Equine anti-thymocyte globulin (i.e. ATGAM®) must be used for these patients and not rabbit ATG.
- Treatment is to prolong survival and provide a rapid (within 3months) and sustained improvement in peripheral blood counts. Treatment is to also restore haematopoiesis.
- Diagnosis of AA should be formally confirmed prior to initiation of therapy.
- Treatment is always given as an inpatient
- For obese patients, the dose of ATGAM® must be calculated using ideal body weight.
- BCSH guidance: The possibility of HLA alloimmunisation and provision of HLA-matched platelets should be considered for patients who are refractory to platelet transfusions, provided other caused for refractoriness are excluded.
- Irradiated blood products must be used when having ATGAM® and after treatment, whilst still taking CSA, until lymphocyte count recovers >1.0 x 10^9/L, or indefinitely.

Inform the Cytotoxic Unit in advance of treatment so that the ATGAM® can be procured.

Administration:

- Patients must be admitted and given this regimen as an inpatient. They should remain inpatients until at least the day after the fourth dose of ATGAM® has been administered, with close monitoring and prompt treatment for serum sickness and other possible complications, should they arise.
- ATGAM® is always given 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 ATGAM® is administered into a peripheral vein.
- The required dose of ATGAM® has already been diluted in the cytotoxic unit and it needs to be infused on the ward using a 0.2micron filter.
- A test dose ***must*** be given on day 1 of each cycle (this is done by administering part of the first infusion bag).
    - The test dose must be supervised by a doctor with adrenaline, chlorphenamine 10mg IV and hydrocortisone 100mg IV drawn up beforehand and ready.
    - Precede the test dose with methylprednisolone and chlorphenamine.
    - Run the infusion through a 0.2micron filter, slowly at 5ml/hour for the first hour

  - A severe systemic reaction of anaphylaxis to the test dose is an absolute contraindication to proceeding with any further ATGAM® treatment.
  - If no reaction has occurred, infuse the remainder of the infusion over 17hours via a 0.2micron filter. It must be administered within 24 hours of manufacture (by the expiry date on the label)
- Infuse the next dose and remaining doses over 18hours, if tolerated.
- Precede each daily dose of ATGAM® with:
  - Platelets (aim to keep platelet count >30 x 10^9/L). ***Do not*** give platelet transfusions during ATGAM® infusion, due to anti-platelet activity of ATGAM®.
  - Methylprednisolone 1mg/Kg IV infusion over 30minutes, start this 30minutes before ATGAM® is started.
  - Chlorphenamine 10mg IV bolus injection.
- If possible, avoid giving more than 2 units of blood each day of the 4 days of the ATGAM® regimen, to help reduce the risk of fluid-overload and to help ensure that the administration of ATGAM® starts in the morning.

Supportive treatments:

Ciclosporin (CSA)

- Neoral® brand, capsules, 2.5mg/Kg twice daily, starting on Day 1 of the regimen.
- For patients on concomitant azole antifungal therapy, reduce the CSA dose to 1.25mg/Kg twice daily. (rounded to nearest achievable dose). *Remember to increase the dose if azole therapy is switched / stopped*.
- For patients >60years old, start with 1.25mg/Kg twice daily and adjust according to renal function, blood pressure and CSA levels
- Continue for a minimum of 12 months, often longer. If a response occurs, Continue 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. 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

- Days 1-4 inclusive: Methylprednisolone 1mg/Kg/day IV infusion over 30minutes, starting 30minutes before ATGAM®.
- From day 5 onwards: Prednisolone 0.5mg/Kg/day oral tablets. Aim to half the dose every 5 days before stopping safely.

Prophylactic medications:

- Ciprofloxacin 500mg twice daily. Review stopping once treatment is complete and the patient is no longer neutropenic.
- Posaconazole 300mg twice daily for 24 hours (loading), followed by 300mg once daily thereafter (If given a non-azole antifungal – be aware of dose changes for CSA). Review stopping once treatment is complete and the patient is no longer at risk of fungal sepsis.
- Aciclovir 400mg twice daily
- Omeprazole 20mg once daily
- Norethisterone 5mg three times a day (pre-menopausal females)
- Note that GCSF is ***NOT*** recommended.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Methylprednisolone **(30mins before ATGAM®)**	**1mg/Kg**	**IV**	Infusion over 30 minutes
	Platelets **(Maintain >30 X 10^9/L)**	**As per platelet count / HLA matched**	**IV**	Infusion over 30 minutes
	Chlorphenamine	**10mg**	**IV**	Bolus injection
	ATGAM® (***TEST DOSE***)	**40mg/Kg**	**IV**	Start infusion at 5ml / hour for 1 hour
	ATGAM® (rest of bag)	**40mg/Kg**	**IV**	Rest of the bag over 17 hours (if not reacted to test dose)
2	Methylprednisolone **(30mins before ATGAM®)**	**1mg/Kg**	**IV**	Infusion over 30 minutes
	Platelets **(Maintain >30 X 10^9/L)**	**As per platelet count / HLA matched**	**IV**	Infusion over 30 minutes
	Chlorphenamine	**10mg**	**IV**	Bolus injection

	ATGAM®	**40mg/Kg**	**IV**	Infusion over 18 hours
3	Methylprednisolone **(30mins before ATGAM®)**	**1mg/Kg**	**IV**	Infusion over 30 minutes
	Platelets **(Maintain >30 X 10^9/L)**	**As per platelet count / HLA matched**	**IV**	Infusion over 30 minutes
	Chlorphenamine	**10mg**	**IV**	Bolus injection
	ATGAM®	**40mg/Kg**	**IV**	Infusion over 18 hours
4	Methylprednisolone **(30mins before ATGAM®)**	**1mg/Kg**	**IV**	Infusion over 30 minutes
	Platelets **(Maintain >30 X 10^9/L)**	**As per platelet count / HLA matched**	**IV**	Infusion over 30 minutes
	Chlorphenamine	**10mg**	**IV**	Bolus injection
	ATGAM®	**40mg/Kg**	**IV**	Infusion over 18 hours
5+	Prednisolone	**0.5mg/Kg**	**PO**	Half the dose every 5 days

Monitoring (see investigations table for more information):

- Ciclosporin: Aim to keep trough ciclosporin level between 100-200micrograms/L (ideally between 150-200micrograms/L to ensure the levels don't become sub-therepeutic). Take the first level on day 2, then twice weekly during inpatient stay. Once discharged, can have weekly levels until stable, then can have them checked every 2-3 weeks thereafter. If renal function is abnormal / deteriorates, check level more frequently.
- U&Es & LFTs: Monitor renal function daily and liver function 3 x week during inpatient stay. Monitor calcium and magnesium weekly. Slow rise in 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 the ciclosporin for 1-2 doses, monitor the renal function and ciclosporin level and make an appropriate dose adjustment.

- Weight: weigh the patient twice daily during ATGAM® days. Keep a strict fluid balance chart daily.
- Observations: four-hourly temperature, pulse, blood pressure, oxygen saturations, respiratory rates during ATGAM® days and once weekly as outpatient.
- Urine tests: daily testing of urine, for glucose.

Dose adjustments:

Dosing in Renal/Hepatic Impairment	
ATGAM®	No data on dose adjustments for renal/hepatic impairment but closely monitor both parameters throughout treatment.
Ciclosporin	No adjustments to begin with but adjust as per level/renal function. A slow rise in creatinine to 120-130 micromol/L is common in the first few weeks of therapy. If the creatinine is >130 micromol/L, adjust the dose. If a rapid rise in creatinine occurs, stop the ciclosporin for 1-2 doses, monitor the renal function / ciclosporin level and adjust the dose.
Dosing in age > 60years	
Ciclosporin	Start with 1.25 mg/kg twice daily and adjust according to renal function, blood pressure, CSA levels
Dosing in Obesity (BMI > 30)	
ATGAM®	Dose based on **Ideal Body Weight (IBW)** IBW calculation Males: IBW = 50Kg +2.3Kg/Inch over 5 feet Females: IBW = 45.5Kg + 2.3Kg/inch over 5 feet

Interactions:

ATGAM®

- No drug interaction tests have been performed on ATGAM®
- Interactions with food / drink are unlikely
- When the dose of corticosteroids or other immunosuppressants is being reduced, some previously masked reactions to ATGAM® may appear. Under these circumstances, observe patients especially carefully during therapy with ATGAM®

Ciclosporin

- Ciclosporin may interact with quite a number of medicines. Ciclosporin may increase or reduce serum levels of other medicines (see their relevant SPCs for further information.)

- Other medicines in turn may reduce or increase levels of ciclosporin, so it is advisable to closely monitor ciclosporin levels during therapy and on the introduction/withdrawal of any new concurrent medication(s).
- Medications that may reduce the concentration of ciclosporin include: orlistat, St. John's Wort, phenytoin and carbamazepine. See ciclosporin SPC for full list / further information.
- Medications that may increase the concentration of ciclosporin include: metoclopramide, oral contraception, high dose methylprednisolone, allopurinol, protease inhibitors, imatinib, colchicine, macrolide antibiotics, verapamil, amiodarone, diltiazem and azole antifungals. See ciclosporin SPC for full list and further information

Main toxicities:

Contraindications

- Severe systemic reaction to the test dose
- Viral and parasitic infections – ATGAM® may exacerbate them. Do not give ATGAM® in the presence of active infection

Adverse Drug Reactions

Immediate (during ATGAM® administration) – *see overleaf for treatment*

- Lymphopenia, neutropenia, thrombocytopenia.
- Fevers, rigors (worse on first day, diminishes with subsequent ATGAM® 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 ATGAM®
- 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

1. serum sickness (associated with ATGAM® administration)
    - Typically 7-14 days after starting ATGAM® if a second course of ATGAM® 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

2. Others:
    - Rarely, worsening of autoimmune thyroid disorders and fibrosing alveolitis, and precipitation of Guillan Barre syndrome.
    - AA patients treated with ATGAM® 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

1. Allergic side effects - usually respond to Hydrocortisone and Chlorphenamine
2. Pyrexia - pyrexia during ATGAM® infusion 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
3. Fluid retention – treat 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
4. Hypertension – if the patient is hypertensive, treat any fluid retention if present, and use appropriate antihypertensive medication to resolve

5. Anaphylaxis - discontinue the ATGAM® immediately and treat the anaphylaxis appropriately
6. Bleeding - if bleeding occurs during ATGAM® infusion, stop the ATGAM® infusion and give additional platelets. Resume ATGAM® infusion when bleeding resolved. Check coagulation screen if bleeding persists despite adequate platelet increment

Please refer to the relevant SPC for more information on toxicities.

Investigations and monitoring:

	Pre-admission	Day 1	Day 2	Day 3	Day 4	Day 5	Ongoing
Informed Consent	X						
Clinical Assessment	X	X	X	X	X		Exclude active infection, AA confirm diagnosis
SACT Assessment (including toxicity assessment and PS)		X	X	X	X		
TFTs	X						Prior to commencing cycle
Chest X-ray	X						
ECG	X						For patients > 60years old, consider echo
FBC	X	X	X	X	X	X	Daily
Platelet transfusional status	X	X*	X*	X*	X*		Ensure adequate platelet increment after platelet transfusion as ATGAM® will cause a precipitous fall in platelet count. If refractory to random donor platelets, **postpone ATGAM® treatment** until further investigated; if HLA antibodies required, arrange adequate supply of HLA matched platelets to cover the cycle *if platelet count is less than 30
CIclosporin level			X				Inpatient – day 2, then twice weekly Outpatient – weekly until stable then every 2-3 weeks Renal impairment – more frequently
Renal function / U&Es	X	X	X	X	X	X	Inpatient - daily
LFTs	X	X		X		X	Inpatient – 3 times a week
Serum Ca2+ & Mg2+	X	X					Weekly
Blood Pressure	X	X	X	X	X	X	Inpatient – Daily Ourpatient – each clinic appointment
Height	X	X					
Weight	X	X	X	X	X	X	Prior to every cycle then **TWICE daily** during ATGAM®
Pregnancy test	X						If clinically indicated

Response to treatment

Response to ATGAM® doesn't 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 antimicrobials whilst the patient is severely neutropenic.

Repeat courses of ATGAM®

More than one course can be given, but the risks of side effects and anaphylaxis are increased, and the onset of serum sickness occurs earlier than after the first course.

- Eltrombopag: eltrombopag is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pre-treated and are unsuitable for haematopoietic stem cell transplantation. It is often a better option to administer eltrombopag if ATGAM® is ineffective although this is **not** routinely funded by the NHS. Completion of an Individual Funding Request (IFR) would be necessary.
- Second course of ATGAM®: If there is no response or relapse after the first course of ATGAM®. This should not begin earlier than 3 months after the first course, as it usually takes around 3 months before a response to previous course is seen.
- Third course of ATGAM®: If there has been no response to two courses and a bone marrow transplant is not an option, or if the patient has relapsed after previous courses. This is rarely appropriate.

Always give a test dose before each cycle of ATGAM® (on day 1)

Vaccines

Only give vaccines when absolutely necessary. There have been anecdotal reports of vaccinations producing bone marrow failure or triggering relapse of AA. Live polio vaccine should be avoided following ATGAM® 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
3. Protocol for the treatment of Aplastic Anaemia with Anti-thymocyte Globulin (ATG) and ciclosporin (CSA). Dr Ed Watson, Jon Barrett, Dr. Andy Peniket, October 2019. Thames Valley Strategic Clinical Network.
4. EMC, Neoral soft gelatin capsules, Novartis Pharmaceuticals UK Ltd, Last updated 10th March 2020. Available at: https://www.medicines.org.uk/emc/medicine/1307 Accessed 10/6/20