TERTIARY / QUATERNARY LEVEL ESSENTIAL DRUG LIST
Medication Review Summary

Review date: August 2015

Medication: Anti Thymocyte globulin (ATG)

- Horse ATG
- Rabbit ATG

Indication: Acquired Aplastic Anaemia (AAA)

Context

Severe Acquired Aplastic Anaemia (AAA) is rapidly fatal unless promptly treated. The causes are complex and related to immune modulated mechanisms within the bone marrow. A particular antigen resulting in AAA has not been identified.

Characteristically the bone marrow aspirate and trephine biopsy demonstrate an "empty" marrow space. AAA can overlap with paroxysmal nocturnal haemoglobinuria in up to 40% to 50% of cases. Treatment should be initiated immediately with blood product support and broad spectrum antibiotics. Growth factor support such as filgrastim (G-CSF) or erythropoietin have not been shown to be useful and may lead to overgrowth of abnormal clonal evolution as documented in several clinical trials. Corticosteroids have similarly been shown to be unhelpful and potentially harmful leading to overwhelming fungal infections.[1]

Definitive treatment consists of autograft transplantation where possible or immunosuppressive therapy. Cyclosporin (CSA) used in combination with ATG has become the immunosuppressive therapy standard of care.

Clinical Efficacy

Several large prospective studies conducted from the early 1990's until 2000's demonstrated the efficacy of ATG and CSA in AAA. It is unlikely that new studies of this nature will be conducted in the future. The haematological recovery in many cases was excellent with long-term survivors. The haematological recovery rate ranged from 60% to 70% across studies. The study findings are indicated below:

Table 1: Studies demonstrating the efficacy of ATG and CSA in AAA.

Study	Study type	Intervention	Outcome
Frickenhofen N, et al. N Engl J Med 324: 1297-1304, 1991.[2]	Randomised, multicentre trial	• 41 patients received ATG and cortisone (control group), 43 patients received ATG, CSA and methylprednisolone.	• At 6 months, complete and partial remission was 46% versus 70% respectively
Rosenfeld SJ, et al. Blood 85: 3058-3065, 1995 [3]	Prospective, multicentre study	• 55 patients enrolled in a trial of 4 days of ATG and 6 months of CSA	• 78% responders at one year
Führer M, et al..Klin	Prospective,	• 114 children included	• Overall response

Padiatr 210: 173-179, 1998 [4]	multicentre study	• All patients were treated with a combination of ALG and CSA	rate of 77%
Kojima S et al, Blood 96: 2049-2054, 2000 [5]	Prospective, multicentre study	• 119 children included • ATG and CSA and danazol	• Haematological responses in 71% in severe AAA patients
Bacigalupo A, et al. Blood, 95: 1931-1934, 2000 [6]	Prospective, multicentre study	• 100 patients with severe aplastic anaemia included • Age rage 1 year to 72 • Horse ATG and CSA received as first line therapy	• 77 patients responded (48 complete response, and 29 partial response)

Safety concerns

Safety concerns include hypersensitivity to horse serum, raised liver enzymes, rashes, fever, hypotension, hypoxaemia, septicaemia both bacterial and fungal.

Salvage therapy

Rabbit ATG is more lymphocytic than horse ATG and has been used as salvage therapy for relapsed or refractory AAA. Several retrospective studies comparing horse ATG to rabbit ATG as first-line treatment were inconclusive. A large randomised, controlled, prospective study demonstrated that horse ATG as first-line was superior to rabbit ATG.[7]

Recommendation

Horse ATG is recommended to be used for first-line therapy for severe aplastic anaemia. Rabbit ATG may be used in selected patients with horse serum hypersensitivity or as salvage therapy in relapse or refractory cases of AAA.

NOTE:

- Transplantation is the definitive standard of care.
- AAA must be treated in specialised units.

References

[1] Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blood, 120 : 1185-1196, 2012.

[2] Frickenhofen N, Kaltwasser JP, Schrezenmeier H, et al. Treatment of aplastic anemia with antilymphocyte globulin and methylprednisolone with or without cyclosporine: The German Aplastic Anemia Study Group. N Engl J Med 324: 1297-1304, 1991

[3] Rosenfeld SJ, Kimball J, Vinnig D, Young NS. Intensive immunosuppression with antithymocyte globulin and cyclosporine as treatment for severe acquired aplastic anemia. Blood 85: 3058-3065, 1995

[4] Führer M, Burdach S, Ebell W, et al. Relapse and clonal disease in children with aplastic anemia (AA) after immunosuppressive therapy (IST): the SAA 94 experience. German/Austrial Pediatric Aplastic Anemia Working Group. Klin Padiatr 210: 173-179, 1998

[5] Kojima S, Hibi S, Kosaka Y, et al. Immunosuppressive therapy using antithymocyte globulin, cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with acquired aplastic anemia. Blood 96: 2049-2054, 2000

[6] Bacigalupo A, Bruno B, Saracco P, et al. Antilymphocyte globulin, cyclosporine, prednisolone and granulocyto colony-stimulating factor for severe aplastic anemia: an update of the GITMO/EBMT study on 100 patients. European Group for Blood and Marrow Transplantation (EBMT)working Party on Severe Aplastic Anemia and the Gruppo Italiano Trapianti di Midolio Osseo (GITMO). Blood, 95: 1931-1934, 2000

[7] Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Eng J Med 365: 430-438, 2011