London Cancer
New Drugs Group

North East Treatment
Advisory Group

Anti-thymocyte globulin for first-line treatment of adult aplastic anaemia

NHS North East Treatment Advisory Group appraisal report based on original report by the London and South East Regional Medicines Information service for the London Cancer New Drugs Group
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Summary

- Anti-thymocyte globulin is used as an immunosuppressive therapy in the management of aplastic anaemia by attacking the immune system cells which are believed to be responsible for damaging the bone marrow. It is used primarily for patients who can't have a bone marrow transplant.

- ATG can be sourced from different host animals such as rabbits and horses. Horse ATG was the standard preparation until the product was withdrawn in Europe and replaced with the more potent rabbit ATG. Horse ATG is still available as a licensed medicine in the USA.

- A large randomised controlled study has recently found that patient outcomes including survival were significantly worse with rabbit ATG compared with horse ATG. This was an unexpected outcome and has been replicated in several smaller case series reports.

- Consequently, official guidance and guidelines from respected professional bodies now recommend horse ATG in preference to rabbit ATG in the treatment of aplastic anaemia.

- Horse ATG for use in Europe has to be obtained from specialist importers. A course of treatment using a standard regimen is estimated to cost about £22,000. A course of rabbit ATG using a standard regimen is estimated to cost about £9,500. The cost of horse ATG will be susceptible to cost fluctuations whereas the cost of rabbit ATG is essentially fixed.

- The number of adult patients requiring a course of ATG for aplastic anaemia within NHS North East is estimated at four to six patients per annum.

- The NHS North East Treatment Advisory Group only has a remit to make treatment recommendations for adult patients with aplastic anaemia. The treatment of paediatric patients with aplastic anaemia is covered by the specialised services specifications and is therefore the responsibility of the NHS Commissioning Board.

Introduction

Disease background

Aplastic anaemia (AA) is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin (1). Patients most commonly present with symptoms of anaemia and skin or mucosal haemorrhage or visual disturbance due to retinal haemorrhage. Although most cases are idiopathic, a careful drug and occupational exposure history should be taken. Many drugs and chemicals have been implicated in the aetiology of AA, although reasonable evidence is available only for a few (and even then causality is difficult to definitively establish) (1).

Epidemiology

The incidence of acquired AA in Europe and North America is around 2 per million population per year, and it has a biphasic age distribution, with peaks from 10 to 25 years and > 60 years (1).

Antithymocyte globulin (ATG)

Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes, produced by the purification of sera from appropriately immunised animals and which act by suppressing cell-mediated immunity. This term implies a product raised against all lymphocyte subsets, whereas antithymocyte globulin (ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). In practice both terms tend to be used for antibodies raised against T-cells (2).

ATG has been the standard treatment for AA in patients unsuitable for a stem cell transplant (HSCT) for many years. Studies supporting ATG in AA date back to the early 1980's and show that horse ATG produces a haematopoietic response sufficient to eliminate the need for red cell and platelet transfusions in around half of patients. Almost all of those who respond to treatment do so within six months and the majority within three months. A controlled study published in 1983 showed that horse ATG produced a substantially higher haematological response rate determined by sustained increases in peripheral blood cell counts and decreased transfusion requirements at three months compared with conventional supportive therapy alone. Patients with duration of aplasia longer than nine months may be less likely to respond to ATG than those with disease of shorter duration (7, 8).

It has not been clearly established whether horse ATG therapy prolongs survival in patients with AA, but patients treated with horse ATG and supportive therapy, sometimes combined with bone marrow infusion and androgens, generally have a one-year survival rate of about 60 to 70%; historical data indicate that the one-year survival rate is about 25% in patients receiving conventional supportive therapy alone (7).

The standard ATG preparation used for the treatment of AA in the UK had been horse ATG (Lymphoglobuline®, Genzyme) however this was withdrawn from the market in 2007 and replaced with rabbit ATG (Thymoglobuline®, Genzyme). Rabbit ATG had previously been used mainly for a second course of immunosuppressive therapy (IST) in patients who had relapsed or were refractory to a first course of horse ATG (2, 3). Thymoglobuline® is licensed in the UK for immunosuppression in solid organ transplantation; it is not licensed for the treatment of AA (4).

Another horse ATG preparation (Atgam®, Pfizer) is approved in the US for the treatment of moderate to severe AA in patients who are unsuitable for bone marrow transplantation (5). The recommended dose regimen in AA is 10 to 20 mg/kg/day for 8 to 14 days; additional alternate-day therapy up to a total of 21 doses can be administered. Patients may require prophylactic platelet transfusions to maintain platelets at clinically acceptable levels due to associated thrombocytopenia. Atgam® is not licensed in the UK but it is available on a named patient basis from specialist importers and suppliers (6).

As ATG has been considered a standard treatment for AA for many years this review focuses on evidence which compares horse ATG to rabbit ATG.

Clinical evidence

Evidence for the use of horse ATG as opposed to rabbit ATG for AA is supported primarily by a single large prospective randomised study. (9) Other studies are of lower methodological quality, being retrospective, non-comparative, or smaller, and are therefore not considered separately with the exception of a larger series reported by the European Bone Marrow Transplant (EBMT) Severe Aplastic Anaemia Working Party (SAAWP). (10)

The randomised trial of horse ATG vs. rabbit ATG for first-line treatment of patients with severe AA included 120 consecutive patients (age 2 to 77 years; n = 30 were aged under 18 years) (9). The underpinning hypothesis of the study was that rabbit ATG would result in higher response rates than horse ATG based on its efficacy in the transplant setting even though the majority of formal studies in the 1980's and '90's used horse ATG. Patients were randomised to horse ATG (Atgam® 40 mg/kg/day for four days; n = 60) or rabbit ATG (Thymoglobulin® 3.5 mg/kg/day for five days; n = 60), plus ciclosporin (10 mg/kg/day, or 15 mg/kg/day for children under 12 years, every 12 hours continued for at least six months). There were no significant differences in baseline demographic or clinical characteristics between the groups.

The primary endpoint was haematological response defined as no longer meeting the criteria for AA at six months. After six months treatment response rates (95% confidence interval) were 37% (24 to 49%) with rabbit ATG and 68% (56 to 80%) with horse ATG ($p < 0.001$). The majority of patients who responded did so within three months (responses of 62% vs. 33% respectively, $p = 0.002$). The cumulative incidence of relapse at three years did not differ significantly between groups (28% [9 to 43%] with horse ATG and 11% [0 to 25%] with rabbit ATG). Survival at three years was 96% with horse ATG compared with 76% with rabbit ATG ($p = 0.04$, censored at stem-cell transplant; 94 vs. 70% [$p = 0.008$], uncensored data) (9).

The addendum to the BCSH guidelines on AA issued in 2011 noted that similar results with rabbit ATG were observed in a preliminary analysis of 35 patients in an EBMT group study (3). This was a non-randomised prospective case series of rabbit ATG (Thymoglobulin®) plus ciclosporin for first-line treatment of acquired AA (10). Although the study did not contain a direct comparator group the outcomes of 105 historical matched controls treated with horse ATG plus ciclosporin were included from the EBMT registry. At six months there was a complete response in 3% and a partial response in 37% of patients treated with rabbit ATG. Compared with control patients, the best response rate was 60% for rabbit ATG and 67% for horse ATG. Two-year overall survival rates were 68% and 86% respectively ($p = 0.009$).

The EBMT SAAWP published a commentary in 2011 which discussed the rabbit vs. horse ATG in AA debate (11). It noted that as well as the studies by Scheinberg (9) and Marsh (10), four out of five other studies had also demonstrated poorer outcomes in AA with rabbit ATG compared with horse ATG, with the other study reporting similar results. It concluded that most studies, although mainly of low methodological quality, demonstrated significantly superior response, survival and mortality rates with horse ATG compared with rabbit ATG; only two studies showed equivalent results and none indicated superiority of rabbit over horse ATG (11).

Guidelines

The BCSH published updated guidance on the management of AA in 2009 (1). According to this, the standard specific treatment for a newly diagnosed patient with AA is either allogeneic haemopoietic stem cell transplantation (HSCT) from an HLA identical sibling donor or IST with a combination of ATG and ciclosporin. HSCT is the first-line treatment of choice for newly diagnosed patients with severe disease, who are <40 years and have an appropriate donor; whereas use of IST is recommended for the following patients:

- Non-severe aplastic anaemia who are transfusion-dependent
- Severe or very severe disease who are >40 years old
- Younger patients with severe or very severe disease who do not have an HLA-identical sibling donor

In 2011, an urgent addendum to this guideline was issued by the BCSH AA Writing Committee, following the presentation of study results showing that the use of rabbit ATG was associated with poorer outcomes than horse ATG for first-line treatment of AA (3). As a result the European Blood and Marrow Transplant Severe Aplastic Anaemia Working Party (EBMT SAAWP) wrote to the European Medicines Agency and Pfizer requesting the urgent availability of horse ATG (Atgam®) in Europe made the following recommendation which is supported by the BCSH AA Writing Committee (3):

- Horse ATG (Atgam®) is recommended as first line immunosuppressive therapy for patients ineligible for HLA identical sibling HSCT.
- If horse ATG (Atgam®) is not available it would be reasonable to consider treatment with rabbit ATG even if response rates are lower rather than no treatment at all. At a recent meeting of the EBMT SAAWP a lower dose of rabbit ATG was proposed using 2.5 mg/kg/day for 5 days instead of 3.75 mg/kg/day for 5 days until more data is available.

At this time the availability of horse ATG (Atgam®) was restricted almost exclusively to the US. It is only available in the UK on a named patient basis from specialist importers (6).

Cost analysis

All costs include VAT at 20% unless otherwise indicated.

Atgam® is available on a named patient basis in the UK at a cost of £2,286 per pack of five vials with each vial containing 250 mg (50 mg/mL; 5 mL) (6). For a course of treatment using the standard regimen of 40 mg/kg/day for four days the cost is estimated thus:

- For a patient weighing 70 kg, the daily dose is 2.8 g (12 vials)
- Over four days this will require 48 vials of Atgam®
- 48 vials is estimated to cost about £22,000

Rabbit ATG (Thymoglobuline®) is licensed in the UK for use in the transplant setting; it is not licensed for the treatment of aplastic anaemia. It is available in 25 mg vials, each at a cost of £191 (12). For a course of treatment of 3.5 mg/kg daily for five days the cost is estimated thus:

- For a patient weighing 70 kg, the daily dose is 245 mg (10 vials)
- Over five days this will require 50 vials of Thymoglobuline®
- 50 vials will cost about £9,500

The incremental cost of Atgam® over Thymoglubuline® is about £12,500 per patient per ATG course. This will vary depending on the actual doses used and this in turn will be largely dependent on patient mass, as well as clinical factors.

If the efficacy rates of the direct comparative study (9) are realised in practice, the incremental cost-effectiveness of horse ATG over rabbit ATG can be expressed as about £40,000 per additional responder at six months; £73,500 per relapse prevented at three years; £52,000 per additional survivor at three years. These outcomes are cumulative.

This analysis focuses on drug costs only and does not include costs of admission, stay, monitoring, other drugs, and management of adverse effects amongst other factors. The majority of these costs would be expected to be the same regardless of whether horse or rabbit ATG was being used and therefore the incremental cost difference identified would not be expected to vary substantially.

Most patients would be expected to receive only a single course of ATG. In the randomised study, 13% of patients in the horse ATG group, and 38% of the rabbit ATG group received a second course of immunosuppressive therapy. Non-drug costs arising from this disparity would therefore be a valid consideration. For example, an admission for aplastic anaemia with complications costs £2,684 (up to 20 days), or £653 (up to five days) without complications. (13) Therefore horse ATG could provide substantial off-set costs from a reduction in the use of subsequent immunosuppressive therapies although a large mean cost per patient differential would probably remain.

Points to consider

Immunosuppressive therapy with antithymocyte globulin (ATG), usually in combination with ciclosporin, is established as standard first-line treatment for patients with aplastic anaemia ineligible for HSCT.

Horse ATG (Lymphoglobuline®) was used in the UK for many years but this was withdrawn from the market in 2007 and replaced with rabbit ATG (Thymoglobuline®). However recent clinical evidence has identified substantial and significant differences in efficacy between horse and rabbit ATG in patients with AA. Consequently the British Committee for Standards in Haematology and the European Group for Bone and Marrow Transplantation now specifically recommend horse ATG as first-line ATG in AA in preference to rabbit ATG.

One high quality study and several lower quality studies provide evidence that horse ATG is at least as effective as rabbit ATG in AA, or that it is substantially more effective. No studies indicate that rabbit ATG may be more effective than horse ATG in AA. The events relating to the outcome rates of the randomised study, although statistically significant, do relate to relatively small absolute values. For example, the difference in uncensored mortality rates at three years (6% vs. 30%) corresponds to a difference of 10 deaths between groups, one of which was clearly unrelated to the disease or treatment. The question arises as to whether the randomised study has yielded an atypical or spurious result, however several other reports support these outcomes being real.

ATG, whether horse or rabbit in origin, is a costly therapy. However treatment is limited in duration and can promote patient survival. Horse ATG is currently about £12,500 more costly than rabbit ATG per course although if efficacy outcomes are realised in practice there may be considerable costs to off-set against this from, for example, reduced need for subsequent immunotherapy cycles.

Rabbit ATG (Thymoglobuline®) is a licensed product although it is not licensed for AA. Horse ATG is essentially an unlicensed product when used in the UK. It is only available in the UK on a named patient basis as a US preparation (Atgam®, Pfizer) provided by specialist suppliers or importers. The cost of this product could be subject to considerable price fluctuations as its price is not agreed with the Department of Health and will be subject to exchange rate, delivery and handling costs amongst others, all of which will vary over time.

The NHS North East Treatment Advisory Group only has a remit to make treatment recommendations for adult patients with AA. The treatment of paediatric patients with AA is covered by the specialised services specifications and is therefore the responsibility of the NHS Commissioning Board. Most, if not all, studies reporting on horse and rabbit ATG in AA included a minority of paediatric patients and it has not been possible to distinguish outcomes relating to adult patients only. Therefore it is possible that the efficacy of horse and rabbit ATG in adult patients with AA could be differ significantly to that reported herein.

References

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9. Scheinberg P et al (2011) Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. NEJM; 365(5):430-8

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12. British National Formulary September 2012 edition (accessed online via www.medicinescomplete.com on 19/12/2012)

13. Payment by results indicative tariff for 2013-14. www.dh.gov.uk/health/2012/12/pbr-road-test

Details of search strategies

i. EMBASE; exp *THYMOCYTE ANTIBODY/ AND exp *APLASTIC ANEMIA [Limit to: Human and English Language]

ii. MEDLINE; exp *ANTILYMPHOCYTE SERUM/ AND *ANEMIA, APLASTIC/ [Limit to: Human and English Language]

iii. Other reference sources used: Electronic Medicines Compendium www.medicines.org.uk;

iv. National Electronic Library for Medicines www.nelm.nhs.uk; AHFS via www.medicinescomplete.com; Martindale via www.medicinescomplete.com; Micromedex Healthcare Series;

v. Pfizer Medical Information

Declaration

The report editor has participated in an advisory board for an unrelated product and unrelated therapeutic field for a product co-developed or marketed by the manufacturer of Atgam®.