Anti-thymocyte globulin (horse) for the first-line treatment of aplastic anaemia

Review conducted by London and South East Regional Medicines Information

December 2012

Background

1. 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).

2. 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).

3. Antithymocyte globulin (ATG)

Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes, produced by the purification of sera from appropriately immunised animals, 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).

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ATG preparation used for the treatment of AA in the UK had been horse ATG (Lymphoglobuline®, Genzyme), however this was withdrawn from the market in 2007 and replaced by rabbit ATG (Thymoglobuline®, Genzyme). Rabbit ATG had previously been used mostly 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).

Atgam® (another horse ATG preparation) is approved in the US for the management of allograft rejection in renal transplant patients and for the treatment of moderate to severe AA in patients who are unsuitable for bone marrow transplantation (5). For AA the recommended dose regimen is 10-20 mg/kg daily for 8 to 14 days; additional alternate-day therapy up to a total of 21 doses can be administered. Because thrombocytopenia can be associated with its administration, patients may need prophylactic platelet transfusions to maintain platelets at clinically acceptable levels.

Atgam® is not licensed in the UK but is available on a named patient basis (6).
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:

- those with non-severe aplastic anaemia who are transfusion-dependent
- those with 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 in the 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, and recommended the following (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 2.5mg/kg/day for 5 days instead of 3.75mg/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 now available in the UK on a named patient basis (6).

Published data

ATG has been the standard treatment for AA in patients unsuitable for HSCT for many years. The studies supporting its efficacy date back to the early 1980s and show that horse ATG produces a haematopoietic response sufficient to eliminate the need for red cell and platelet transfusions in around 40-50% of patients. Almost all of those who respond 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 (as determined by sustained increases in peripheral blood cell counts and decreased transfusion requirements) at 3 months when compared with conventional supportive therapy alone. Patients with aplasia of longer than 9 months’ duration 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/or androgens) generally have a 1-year survival rate of about 60–70%; historical data indicate that the 1-year survival rate is about 25% in patients receiving conventional supportive therapy alone (7).

As ATG has been considered a standard treatment for AA for many years, this review focused on the evidence comparing horse ATG to rabbit ATG (the latter has been used in Europe since 2007 only because of the unavailability of the horse product). One large
prospective, randomised study was identified (NIH study) and this represents the best quality evidence currently available. Due to the availability of this, other prospective studies that made indirect comparisons with historical controls, and retrospective studies, have not been considered (the EBMT study is however discussed briefly).

Scheinberg et al conducted a randomised trial comparing horse ATG with rabbit ATG in the first-line treatment of patients with severe AA (9). The authors note that the majority of formal studies in the 1980s and 1990s used horse ATG, and they hypothesised that rabbit ATG would result in higher response rates (based on its efficacy in the transplant setting, among other reasons). A total of 120 consecutive patients (aged 2-77 years) were included in the study and randomised to horse ATG (Atgam® 40mg/kg daily for 4 days; n=60) or rabbit ATG (Thymoglobulin® 3.5mg/kg daily for 5 days; n=60), with ciclosporin (10mg/kg daily, or 15mg/kg daily for children under 12, every 12 hours continued for at least 6 months in both groups). There were no significant differences in demographic or clinical characteristics between the groups.

The primary endpoint was haematological response (defined as no longer meeting the criteria for AA) at 6 months – this was 68% (95% CI 56-80) with horse ATG and 37% (24-49) with rabbit ATG (p<0.001). The majority of those who responded did so within three months (response of 62% vs. 33%, respectively; p=0.002). The cumulative incidence of relapse at three years did not differ statistically significantly between the treatments (28% [9-43%] with horse ATG and 11% [0-25%] with rabbit ATG). Overall survival at three years was superior with horse ATG: 96% (95% CI 90-100%) versus 76% (61-95%) with rabbit ATG (p=0.04) when censored at the time of HSCT and 94% (88-100%) versus 70% (56-86%) when HSCT events were not censored (9).

As noted in an addendum to the BCSH guidelines on AA issued in 2011, similar results were observed in a preliminary analysis of 35 patients in study conducted by the EBMT (3). This was a non-randomised Phase II study of rabbit ATG (Thymoglobulin®) with ciclosporin in the first-line treatment of acquired AA (10). Although it did not contain a comparator arm, the authors sought to compare the response rate seen with that of a series of matched patients with AA treated after 1994 with a combination of horse ATG and ciclosporin (taken from the EBMT registry; n=105). At 6 months, there was a complete response in 3% and a partial response in 37% of those treated with rabbit ATG within the Phase II study. When compared to the matched patients, the best response rate (used as response rates at specific time points are not recorded in the registry) was 60% for rabbit ATG and 67% for horse ATG. Two-year rates of overall survival were 68% and 86%, respectively (p=0.009).

The EBMT SAAWP wrote a Comment article that was published in the Lancet in 2011, discussing these data (11). They note that as well as the above, three of four further retrospective studies have shown rabbit ATG to be associated with worse outcomes than horse ATG (the other reported similar results). They conclude that most studies [although the majority are limited in quality] show significantly superior response, survival and death rates with horse ATG compared to rabbit ATG; only two studies show equivalent results and none indicate superiority of rabbit over horse ATG. They discuss their recommendations regarding the first-line use of horse ATG (Atgam®) where available – as summarised above under guidance.

**Cost**

Atgam® is available on a named patient basis in the UK at a cost of £1905 (excluding VAT) for a pack of five vials, each vial containing 250mg (50mg/mL; 5mL) (6). For a course of treatment of 40mg/kg/day for four days, the costs can be estimated as follows:

- For a patient weighing 70kg, the dose would be 2,800mg (12 vials) per day
- Four a course of four days, this would be equal to 48 vials
48 vials would cost 48 x £1905/5 = £18,288
Including VAT at 20%, this would equal £21,945 for a course of treatment

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 25mg vials, each at a cost of £158.77 (excluding VAT) (12). For a course of treatment of 3.5mg/kg daily for five days, the costs can be estimated as follows:

- For a patient weighing 70kg, the dose would be 245mg (10 vials) per day
- Four a course of five days, this would be equal to 50 vials
- 50 vials would cost £7,940
- Including VAT at 20%, this would equal £9,530 for a course of treatment

Summary

Immunosuppressive therapy with antithymocyte globulin (ATG) (usually with ciclosporin) has been the standard first-line treatment for patients with aplastic anaemia who are not eligible for HSCT for decades.

Horse ATG (Lymphoglobuline®) was used first-line in the UK for many years but this was withdrawn from the market in 2007 - rabbit ATG (Thymoglobuline®) was then used as a substitute. However recently published data has shown that outcomes are inferior for this product compared to horse ATG and this has led to the BCSH recommending the first-line use of horse ATG specifically. A US preparation of horse ATG (Atgam®) is now available in the UK on a named patient basis.

The best located evidence comparing horse ATG to rabbit ATG in the first-line treatment of AA consists of a prospective, randomised study conducted by the NIH (n=120). When used in combination with ciclosporin, haematological response (68% vs. 37%) and estimated 3-year overall survival (96% vs. 76%) were both lower with rabbit ATG. As a result of this study, and other lower-quality supporting evidence, the European Blood and Marrow Transplant Severe Aplastic Anaemia Working Party recommend horse ATG be used in the first-line treatment of severe AA, with rabbit ATG being used only if this is not available.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per 100,000 population*</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithymocyte globulin (horse) (Atgam®) – not licensed in the UK</td>
<td>Aplastic anaemia</td>
<td>0.2</td>
<td>40mg/kg daily for four days</td>
<td>£4,110 (inc VAT)</td>
<td>NA (course of 4 days only)</td>
</tr>
<tr>
<td>Antithymocyte globulin (rabbit) (Thymoglobuline®)</td>
<td>Aplastic anaemia (off-label indication)</td>
<td>0.2</td>
<td>3.5mg/kg daily for five days</td>
<td>£1,900 (inc VAT)</td>
<td>NA (course of 5 days only)</td>
</tr>
</tbody>
</table>

*based on a body weight of 70kg. This considers drug costs only.
References


3) Guidance from the BCSH Aplastic Anaemia Writing Committee relating to recent prospective studies of rabbit antithymocyte globulin (ATG) used for a first course of immunosuppressive therapy (IST) in aplastic anaemia (issued July 2011)  

4) Thymoglobuline SPC (last reviewed 28/4/2012); accessed via www.medicines.org.uk

5) US prescribing information for Atgam® (last revised November 2005)  

6) Pfizer medicines information and customer contact team (personal communication; 28/6/12)

7) AHFS; accessed via www.medicinescomplete.com on 28/6/12

8) Micromedex: Drugdex evaluations; accessed 28/6/12


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

Details of search strategy:

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

Other reference sources used: Electronic Medicines Compendium www.medicines.org.uk; National Electronic Library for Medicines www.nelm.nhs.uk; AHFS via www.medicinescomplete.com; Martindale via www.medicinescomplete.com; Micromedex Healthcare Series; Pfizer Medical Information