Review Article

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Anti-thymocyte globulin in haematology: Recent developments

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Anti-thymocyte globulin (ATG) is a polyclonal antiserum introduced into clinical medicine more than 30 years ago. It induces a broad non-specific immunosuppression. In haematology, standard indications are severe aplastic anaemia and prophylaxis and treatment of graft-versus-host disease (GVHD) (after allogeneic transplantation). For aplastic anaemia, ATG from horses has been found to be superior to ATG from rabbits. In the situation of allogeneic transplantation, ATG lessens the risk of chronic GVHD but may not improve survival. There is current controversy regarding which patients benefit most from ATG and what the ideal dosage is. It is likely that in the coming years a more specific immunosuppressive will be developed that will minimize GVHD while maintaining the graft-versus-malignancy effect.

Key words Anti-thymocyte globulin - graft-versus-host disease - immunosuppressive effect - myelodysplastic syndrome - severe aplastic anaemia

Introduction

Anti-thymocyte globulin (ATG) is a polyclonal IgG component prepared and collected from the serum of various animals (rabbit, horse, goat or pig) that have been immunized against human thymocytes or other lymphocytes. Historically, ATG was produced as an anti-lymphocyte serum that was a cytotoxic heterologous antibody directed against lymphoid cells. It was first produced by Russian immunologist Élie Metchnikoff by injecting rabbit lymph node cells into guinea pigs in 1899[1]. Levey and Medawar showed that anti-lymphocyte serum produced in rabbit against mouse thymus cells had immunosuppressive effects[2].

The first clinical use of ATG in the 1970s marks the dawn of immunotherapy in medicine. ATG or anti-lymphocyte globulin (ALG) raised in experimental animals against human cells was initially used for immunosuppression after solid organ transplantation[3]. The first hint that antiserum raised in horses may be active for severe aplastic anaemia (SAA) was in a study by Mathé *et al*[4]. In their report, 20 patients with various blood disorders (mostly leukaemias) were given marrow cells after pre-treatment with ALG. Among these 20 patients, two of four patients with SAA normalized or had improved blood counts (while the transplanted marrow was most likely rejected). Later, the Seattle team used ATG (raised in rabbits or goats) for the treatment of acute graft-versus-host disease (GVHD)[5]. Twelve of 19 patients with acute GVHD experienced a complete resolution of their skin rash.

Mechanism of action and adverse effects

ATG exerts its immunosuppressive effects by destroying lymphocytes in the recirculating pool. Well described mechanisms are *in vivo* depletion of T cells through complement-mediated intravascular lysis, apoptosis and phagocytosis in secondary lymphoid tissue and antigen-dependent cell-mediated cytotoxicity[6]. It is likely that not all T-cell subpopulations are targeted equally, but no recent studies have been done on this topic. The current indications and most common side effects of ATG are summarized in the Table. Adverse effects are either due to contaminating antibodies that are formed in animal serum or occur when human antigens used for immunization contain traces of red blood cells, platelets or serum proteins. This can cause haemolysis, thrombocytopenia and serum sickness, but is minimized by an elaborate purification process. The administration of ATG to humans exposes the recipient to heterologous proteins, which can lead to serum sickness or anaphylaxis in subsequent treatment with similar species ATG. There is always the risk of a serious and life-threatening anaphylaxis in pre-exposed patients. Besides direct immunological adverse effects, subsequent severe immunosuppression after its infusion increases vulnerability to serious bacterial, viral and fungal infections.

Anti-thymocyte globulin (ATG) for severe aplastic anaemia (SAA)

Aplastic anaemia is thought to be in many cases an immune-mediated haematopoietic precursor cell disorder where effector T lymphocytes target the haematopoietic stem cell resulting in pancytopenia, progressing to a point where the patient is dependent on transfusions. Standard treatments for SAA are intensive immunosuppression or in younger patients, an allogeneic

Table. Anti-thymocyte globulin drugs available worldwide and clinical profile

	Rabbit	Horse
Drug (manufacturer)	Thymoglobulin (Sanofi Genzyme, USA)[7] Grafalon (Neovii, Switzerland)[†]	Atgam (Pfizer, USA)[8] Thymogam (Bharat Serum and Vaccines Ltd., India)[††]
Source of antigen	Thymoglobulin (Human thymocytes) Grafalon (Human leukaemia cell line)	Human thymocytes
Indications and dosing[a]	*Severe aplastic anaemia* (*in combination with CSA*)[b]: 3.5 mg/kg daily for 5 days	*Moderate-to-severe aplastic anaemia*: 10-20 mg/kg daily for 8-14 days
	GVHD[b] *prevention*: 2.5-10 mg/kg divided over 3 daily doses	*Severe aplastic anaemia (in combination with CSA +/– eltrombopag)*[b]: 40 mg/kg daily for four days
	Steroid-refractory acute GVHD[b]: 2.5 mg/kg daily for 4-6 days	*Steroid-refractory acute GVHD*[b]: 30 mg/kg every other day for 6 doses or 15 mg/kg twice daily for 10 doses
Administration	Intravenous infusion through a 0.22 micron in-line filter Central line recommended First dose infused over at least 6 h Subsequent doses may be infused over 4 h	Intravenous infusion through a 0.2-1 micron in-line filter Central line recommended Doses must be administered over at least 4 h
Recommended pre-medications	Corticosteroids, acetaminophen and/or antihistamine	Corticosteroids, acetaminophen and/or antihistamine
Common and serious adverse effects	Infusion reactions (chills, headache, pruritus, diaphoresis, hypertension, hypotension, fever, dyspnoea and anaphylaxis) Skin rash, peripheral oedema Thrombocytopenia, leucopenia, profound and prolonged lymphopenia Opportunistic infections, viral reactivation Nausea, vomiting, constipation Hyperkalaemia Arthralgia, myalgia Serum sickness	Infusion reactions (chills, headache, pruritus, diaphoresis, fever, dyspnoea and anaphylaxis) Skin rash Thrombocytopenia, leukopenia, profound and prolonged lymphopenia Opportunistic infections, viral reactivation Chemical phlebitis (if administered peripherally) Serum sickness

[a]Use actual body weight for the calculation of dose for haematopoietic stem cell transplant conditioning regimens; [b]Off label use in the United States. CSA, cyclosporine; GVHD, graft-versus-host disease

Source: Refs 9-12; [†]*https://neovii.com/;* [††]*https://www.bharatserums.com/neurology.html*

stem cell transplant if a matched donor is available. Early SAA studies across the world in the 1990s showed a response rate of 61-77 per cent, with survival ranging from 88 (at 3 yr) to 55 per cent (at 7 yr)[13].

There is no general consensus about the preferred source of ATG. Commonly used sources are ATG from horses (h-ATG) and ATG raised in rabbits (r-ATG). A randomized controlled trial from the National Institutes of Health (USA) reported in 2011 on these two different sources of ATG used in SAA along with cyclosporine A (CsA)[9]. The study revealed inferior responses with r-ATG compared with h-ATG. This trial had 60 patients (the majority of adults) who were randomized to either h-ATG or r-ATG (mean ages of 37 and 31 yr, respectively). At a median follow up of 28 months, six-month haematological response (defined as no longer meeting the criteria for SAA) was 68 per cent in the h-ATG group and 37 per cent in the r-ATG group. The three-year rate of relapse and the three-year cumulative incidence of clonal evolution was not significantly different between the groups. Overall survival was 96 per cent in the h-ATG group and 76 per cent in the r-ATG group with censoring for stem cell transplantation[9].

A single centre retrospective study from Brazil involving 71 patients also reported better haematological response rates with h-ATG compared to r-ATG (59.5 vs. 34.5%) and two-year overall survival was also higher with h-ATG at 78.4 per cent compared to 55.4 per cent with r-ATG[14]. Both studies reported that r-ATG caused longer lymphopenia. In a multi-centre retrospective study from Europe on patients treated with immunosuppression with CsA and ATG from 2001 to 2012, the 12-month haematological response was not significantly different (84% with r-ATG vs. 79% with h-ATG). After a median follow up of 45 months, higher rates of mortality were seen in the r-ATG group (11.9%) versus the h-ATG group (6.5%), with almost double the rate of death from infection in the r-ATG group. Of note, the r-ATG group had more (50.3%) patients with non-severe AA (transfusion dependent) compared to the h-ATG group (29%), which could have potentially favoured the outcome for r-ATG[15]. A meta-analysis of three randomized controlled trials and 11 cohort controlled studies was reported in 2017. It comprised 1636 total patients, with 921 receiving h-ATG and 715 receiving r-ATG. The three-month response was better for h-ATG while four cohort studies showed similar response between the groups with little study heterogeneity. At the 12-month mark, only three cohort studies met the criteria for homogeneity and showed no difference in response. Similarly, early mortality from the pooled nine cohort trials with no heterogeneity and the risk of clonal evolution were similar in both groups. Interestingly, in this meta-analysis, a similar efficacy was reported for both sources of ATG in Asian cohorts, while non-Asian cohorts favoured h-ATG, presumed to be due to different treatment approaches, lifestyle and immunogenetics[16]. In many parts of the world, h-ATG is not available. Therefore, r-ATG is the next best choice. In a study from four Asian countries (Hong Kong, Malaysia, Taiwan and Thailand), 97 patients with SAA received r-ATG and were analyzed[17]. The 12-month overall response rate was 63.6 per cent and the two-year overall survival rate was 86.3 per cent. According to the authors, these results were comparable to historical controls obtained with h-ATG[17]. Two studies reviewed the outcome of patients with aplastic anaemia treated with h-ATG produced in India[18,19]. These studies included 30 and 91 patients, respectively, most having SAA. The overall response at two years in the larger study was reported as 68.1 per cent. Finally, Bacigalupo *et al*[20] published the outcome of 955 patients with aplastic anaemia treated in four European and four Asian countries between 2001-2008 and 2009-2012 with r-ATG. The patients were mostly young and most had SAA. Early mortality at 90 days decreased from 5.7 to 2.4 per cent in the later time period. Overall survival in the entire population was 70 per cent. One hundred and ten patients who did not respond subsequently underwent a haematopoietic cell transplant. The cumulative incidence of response to r-ATG was 37, 52 and 65 per cent at three and six months, and one year, respectively. At six months, multivariate analysis showed a worse prognosis in older patients, longer interval from diagnosis to treatment, and in patients with very severe disease.

Anti-thymocyte globulin (ATG) for myelodysplastic syndromes (MDS)

In lower risk myelodysplastic syndromes (MDS), a subset of patients responds to immunosuppressive treatment with ATG with or without CsA. In a small study from Paris, 45 per cent responded with improved blood counts and became transfusion independent. All 20 patients treated over 10 years were negative for the deletion 5q and a majority had a hypocellular marrow. Age and cellularity did not influence the likelihood of response; however, low B-cell count and a long duration of blood transfusions were associated with a lower response[21]. In a larger international

study on 256 selected patients, most with lower risk MDS, half of the patients responded and 11.2 per cent experienced a complete remission[20]. This study reviewed patients treated between 2006 and 2016. Patients with a hypocellular bone marrow had a better chance to achieve transfusion independence, whereas age, transfusion dependence, presence of a paroxysmal nocturnal haemoglobinuria clone and human leucocyte antigen (HLA) DR15 positivity did not influence the outcome. In both studies, h-ATG and r-ATG were used based on the availability. In the international study[22], h-ATG with CsA was more effective than ATG from rabbit or ATG without cyclosporine. Patients who responded had an excellent long-term outcome.

Anti-thymocyte globulin (ATG) for prophylaxis of chronic graft-versus-host disease (GVHD)

ATG is administered as part of a conditioning regimen for the prophylaxis of GVHD, both for acute and chronic cases. While it reduces GVHD, ATG also increases the risk of infection due to T-cell depletion, and in some situations, the risk of disease relapse increases due to diminished graft-versus-leukaemia effect[10]. In most studies, ATG from rabbits was used for GVHD. Since the half-life of r-ATG is about one month (Table), the administration of ATG not only depletes immune cells of the recipient, it also lyses T cells in the transfused stem cell product and part of the nascent immune cells after engraftment (*in vivo* T-cell depletion). The use of ATG has been increased in the last 15 yr due to increased use of unrelated donors and peripheral blood stem cells (which contain significantly more T cells than grafts derived from bone marrow)[10]. In the United States and Western Europe, currently, 20-50 per cent of allogeneic haematopoietic cell transplants are performed with *in vivo* depletion of T cells[23]. In the situation of reduced-intensity conditioning, ATG may also lower the risk of graft rejection.

A landmark prospective phase 3 study that involved myeloablative conditioning with or without r-ATG at a dose of 10 mg/kg for three days before a haematopoietic stem cell transplant (HCT) from HLA-identical siblings evaluated the use of ATG as prophylaxis for GVHD[24]. Of the 155 patients (83 in the ATG group and 72 without ATG), the incidence of acute GVHD was lower in the ATG group (but not significant). Pertaining to chronic GVHD, the two-year cumulative incidence was 32.2 per cent in the ATG group versus 68.7 per cent without ATG (P<0.001). The difference held true for limited and extensive chronic GVHD. The rate of infections was 57.8 per cent in the ATG group versus 54.2 per cent in the non-ATG group, and the rates of cytomegalovirus and Epstein-Barr virus reactivation or fungal infection was not significantly higher in the ATG group. The rate of non-relapse mortality at two years was 14 per cent for the ATG group versus 12 per cent for the control group and the two-year relapse-free survival was 59.4 versus 64.6 per cent, respectively. The two-year overall survival was 74.1 per cent with ATG versus 77.9 per cent without ATG. In a multivariate analysis, there was also no difference in survival with and without ATG. Finally, by one year after transplantation, 91 per cent of patients who received ATG were off immunosuppression compared to only 39 per cent in the non-ATG group[24].

Another double-blind randomized controlled trial involved 254 patients with acute myelogenous leukaemia (AML), acute lymphoblastic leukaemia and MDS undergoing a myeloablative conditioning regimen with (n=126) or without r-ATG (n=128)[25]. These patients had HLA-matched unrelated HCT (considered to be a higher risk) with either peripheral blood or bone marrow stem cells and received r-ATG at 20 mg/kg/day on three consecutive days before transplant. Of note, 30.9 per cent patients in the ATG group were unable to complete the three days of infusion. The time to engraftment of platelet and neutrophil was prolonged in the ATG group. The 180-day cumulative incidence of only grade 2-4 acute GVHD was significantly lower with ATG compared to without ATG. The two-year cumulative incidence of chronic GVHD was 16 per cent in the ATG group versus 38 per cent in non-ATG group (P<0.001) (lower both for moderate and severe chronic GVHD). The two-year overall survival was 59 per cent in the ATG group versus 74 per cent in the non-ATG group (P=0.034). In multivariate analysis, ATG was associated with inferior overall survival and progression-free survival. In both arms, survival without moderate to severe chronic GVHD was comparable. At two years, non-relapse mortality as well as cumulative incidence of disease relapse were higher (but not significant) with ATG than non-ATG. Cytomegalovirus reactivation as well as post-transplantation Epstein-Barr-associated lymphoproliferative disease was more frequent with the ATG group[25]. This study considerably dampened the enthusiasm for universal use of ATG as prophylaxis for GVHD.

An earlier multicentre phase 3 study involved around 200 patients undergoing myeloablative or

non-myeloablative regimen. This study used a different brand of r-ATG at a different dosage (total dose of 4.5 mg/kg over three days on days −3, −2 and +1 of HCT)[11]. As expected, the rate of acute GVHD at 30 and 100 days was lower for the ATG group compared to no ATG group. In addition, only 13 per cent of patients receiving ATG developed moderate-severe chronic GVHD versus 29 per cent who did not receive ATG (P=0.0083). Thirty seven per cent of patients treated with ATG were off immunosuppression by 12 months compared with only 16 per cent in the non-ATG group. There was no significant difference in non-relapse mortality, disease relapse, overall survival or serious infections[11].

At the 2018 meeting of the American Society of Hematology, data were reported from the multicentre EBMT (European Society for Blood and Marrow Transplantation) registry involving 1509 adult AML patients who had pre-transplant measurable residual disease status and underwent HCT from matched sibling or unrelated donors with or without the use of ATG[26]. The use of ATG was associated with decreased incidence of grade 3-4 acute GVHD, total and extensive chronic GVHD with better GVHD-free relapse-free survival. No difference was observed in non-relapse mortality, disease relapse, leukaemia-free survival or overall survival between the use of ATG or not[26]. In the same database, the use of ATG was investigated for Ph+ acute lymphoblastic leukaemia. While ATG significantly reduced chronic GVHD (35 vs. 52%, P<0.001), in a multivariate model, the risk of relapse was increased by 41 per cent, (P=0.02)[26]. Non-relapse mortality and overall survival were comparable. In a study of 833 allogeneic bone marrow transplants performed for SAA between 2013 and 2018, r-ATG was found to be more effective than h-ATG, possibly due to different pharmacokinetics[27]. Chronic GVHD was lower with r-ATG than with h-ATG for matched-related transplants but comparable in patients undergoing unrelated transplants. The overall survival at three years was comparable for matched related transplants but lower for matched unrelated transplants (75 vs. 83%). The authors concluded that r-ATG was standard for allogeneic transplants if *in vivo* T-cell depletion was planned[27]. In a case report, dramatic differences were observed when identical twins with SAA underwent allogeneic transplantation from the same donor but using different preparations of ATG[28]. Both ultimately engrafted, but r-ATG led to a very slow T-cell engraftment and low chronic GVHD. The h-ATG in the other twin led to fast T-cell engraftment, but the patient later developed significant chronic GVHD[28].

Anti-thymocyte globulin (ATG) for the treatment of refractory GVHD

The prognosis of steroid-refractory acute GVHD is generally poor. ATG is one of the standard treatments, especially in full-blown multiorgan acute GVHD, and if the patient did not get prophylactic ATG. In an earlier study using h-ATG, only 45 per cent of patients were alive at 18 months. The main causes of death were uncontrolled GVHD and infections[29]. In a more recent randomized study comparing an antibody to the interleukin-2 receptor to r-ATG, likewise, only about 45 per cent were alive at one-year post-transplant. In both treatment arms, viral infections (especially cytomegalovirus and Epstein-Barr virus) were common[12]. In a study from Japan, 2.5 mg/kg of r-ATG was found to be comparable (but less toxic) than higher doses for steroid-resistant acute GVHD[30].

Future developments

Where do we go from here? The data for allogeneic transplant show that the use of ATG with conditioning can lead to an earlier stop of post-transplant immunosuppression and significantly decreases the incidence of chronic GHVD. However, this comes with a price: non-relapse mortality, especially infections and in some instance, higher relapse rates and of course the cost of ATG. At present, we do not consider ATG as standard for all patients who undergo allogeneic HCT. Therefore, more research is necessary for fine-tuning the use of ATG, its dosing and its clinical indications[31]. One possible way to fine-tune the dose of ATG to the risk of GVHD is to adjust the dose according to the recipient's lymphocyte counts[32]. In an editorial, the continued use of ATG more than 30 yr after its introduction into clinical haematology was described as a fascinating story[33]. The current research focuses on optimizing dosages, mode of administration and indications. Biomarkers may help in guiding the need for strong immunosuppression. High-dose cyclophosphamide may be an alternative in some situations. It is likely that we will see (in the age of immunotherapy and T-cell engineering) a more specific immunosuppression. Targets will be different subpopulations of T cells, natural killer cells, regulatory T cells, chemokines and suppressive cytokines. For allogeneic transplantation, the aim is to preserve the graft-versus-malignancy effect while minimizing GVHD.

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