ATGAM®

lymphocyte immune globulin,
anti-thymocyte globulin (equine) sterile solution

For Intravenous Use only

DESCRIPTION

ATGAM sterile solution contains lymphocyte immune globulin, anti-thymocyte globulin (equine). It is the purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes. ATGAM is a transparent to slightly opalescent aqueous protein solution. It may appear colorless to faintly pink or brown and is nearly odorless. It may develop a slight granular or flaky deposit during storage. (For information about in-line filters, see POSOLOGY AND METHOD OF ADMINISTRATION, Administration.)

Before release for clinical use, each lot of ATGAM is tested to assure its ability to inhibit rosette formation between human peripheral lymphocytes and sheep red blood cells *in vitro*. In each lot, antibody activity against human red blood cells and platelets is also measured and determined to be within acceptable limits. Only lots that test negative for antihuman serum protein antibody, antiglomerular basement membrane antibody and pyrogens are released.

Each milliliter of ATGAM contains 50 mg of horse gamma globulin stabilized in 0.3 molar glycine to a pH of approximately 6.8.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ATGAM sterile solution is a lymphocyte-selective immunosuppressant as is demonstrated by its ability to reduce the number of circulating, thymus-dependent lymphocytes that form rosettes with sheep erythrocytes. This antilymphocytic effect is believed to reflect an alteration of the function of the T lymphocytes, which are responsible in part for cell-mediated immunity and are involved in humoral immunity. In addition to its antilymphocytic activity, ATGAM contains low concentrations of antibodies against other formed elements of the blood. In rhesus and cynomolgus monkeys, ATGAM reduces lymphocytes in the thymus-dependent areas of the spleen and lymph nodes. It also decreases the circulating sheep-erythrocyte-rosetting lymphocytes that can be detected, but ordinarily ATGAM does not cause severe lymphopenia.

The mechanism of ATGAM-induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocytes. Lymphocyte depletion may be caused by complement dependent lysis and/or activation-induced apoptosis. In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes which results in partial activation and induction of T lymphocyte anergy.

The mechanism of ATGAM therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, ATGAM directly stimulates the growth of hematopoietic stem cells and release of hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

In general, when ATGAM is given with other immunosuppressive therapy, such as antimetabolites and corticosteroids, the patient’s own antibody response to horse gamma globulin is minimal.

Clinical efficacy and safety

Acute treatment of renal transplant rejection

The use of ATGAM for acute allograft rejection was evaluated in three different treatment applications:

1. In one randomized controlled study, ATGAM treatment was substituted for standard therapy (i.e., bolus doses of intravenous steroids) in living related transplant recipients experiencing their first rejection episode and was proven effective in reversing the rejection episodes in all treated subjects.

2. Results from randomized controlled studies in the United States in patients with steroid-resistant rejection episodes showed that ATGAM, when administered in conjunction with standard therapy, yielded efficacy results superior to those of standard therapy alone.

3. The effect of ATGAM when administered in conjunction with standard therapy at the time of diagnosis of the first rejection episode was studied under two different protocols with living donors and cadaveric transplants. The results from these studies showed a statistically significant improvement in rejection resolution and functional graft survival associated with ATGAM therapy.

The effectiveness of ATGAM in acute renal allograft rejection was also demonstrated in other controlled and non-controlled studies performed in various medical centers. In these studies, ATGAM was administered at time of diagnosis of the first rejection episode at a range of 10 to 15 mg/kg per day for 14 days, followed by alternate day therapy for a total of 21 doses in 28 days.

Treatment of aplastic anemia

ATGAM was evaluated in 5 clinical studies that enrolled a total of 332 patients with aplastic anemia who were evaluable for efficacy, including patients who had aplastic anemia of idiopathic or presumed immunologic aetiology and patients with aplastic anemia secondary to other conditions. Of these, 252 patients were treated with ATGAM 160 mg/kg which was administered in equally-divided doses over 4 or 8 or 10 days; 115 patients (46%) received ATGAM as the only immunosuppressive agent while CsA was co-administered to 137 patients (54%).

The response rate in individual studies ranged from 39% to 68%, with the higher rates seen in the more recent studies that included CsA (see Table 1). ATGAM has induced instances of partial or complete hematologic recovery and improved survival in patients with aplastic anemia of known or suspected immunologic aetiology in patients who are unsuitable for bone marrow transplant.

160 mg/kg (total dose) administered over 8 or 10 days

Study 3-197, Study 3-198, Study 5000

In 3 controlled clinical studies completed in the 1980's, 115 evaluable patients with moderate (Study 3-197 and Study 5000) to severe (all 3 studies) aplastic anemia who were not candidates for bone marrow transplantation were administered eATG at 160 mg/kg bw over 8 or 10 days; patient ages ranged from 1 to 76 years. Hematologic response rates for eATG-treated patients ranged from 39% to 52% in these three studies, and survival rates were 50% or more. See Table 1 for more details.

160 mg/kg (total dose) administered over 4 days

(Scheinberg 2011)

A total of 120 treatment-naïve patients (60 per arm), with severe aplastic anemia, 2 to 77 years of age, were randomized to receive either eATG at 40 mg/kg bw/day for 4 days or rabbit anti-thymocyte globulin (rATG) at 3.5 mg/kg/day for 5 days. Each treatment arm also included CsA at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) given in divided doses every 12 hours for at least 6 months, with the dose adjusted to maintain trough blood levels of 200 to 400 ng/mL. The primary endpoint was hematologic response at 6 months, defined as no longer meeting the criteria for severe aplastic anemia. The observed rate of hematologic response at 6 months was in favour of eATG compared with rATG (68% vs 37%, respectively [p< 0.001]). The overall survival rate at 3 years differed significantly between the two regimens: 96% in the eATG group compared with 76% in the rATG group (p=0.04) when data were censored at the time of stem cell transplantation, and 94% compared with 70% (p=0.008) in the respective groups when stem cell transplantation events were not censored.

(Scheinberg 2009)

A total of 77 patients with severe aplastic anemia, 4 to 78 years of age, participated in a prospective, randomized study comparing eATG/ciclosporin (CsA)/sirolimus with standard eATG/CsA immunosuppressive therapy. Thirty-five patients received eATG/CsA/sirolimus and 42 patients received standard eATG/CsA. Intravenous eATG was administered at a dose of 40 mg/kg bw/day for 4 days and CsA was given at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) for 6 months. Based on randomization, oral sirolimus was given at 2 mg/day in adults or 1 mg/m^2/day in children less than 40 kg for 6 months. The primary endpoint of the study was hematologic response rate at 3 months, defined as no longer meeting the criteria for severe aplastic anemia.

After a planned interim analysis of 30 evaluable patients in each arm, accrual to the eATG/CsA/sirolimus arm was closed, as the conditional power for rejecting the null hypothesis was less than 1%. The overall response rate at 3 months was 37% for eATG/CsA/sirolimus and 57% for eATG/CsA, and at 6 months was 51% for eATG/CsA/sirolimus and 62% for eATG/CsA. The overall survival at 3 years for patients in the eATG/CsA/sirolimus arm was 97%, and was 90% in the eATG/CsA arm. See Table 1 for more details.

Table 1. Key Clinical Studies With ATGAM For The Treatment of Aplastic Anemia*

Study	eATG+ comparator or other therapy	No. of subjects analysed	Response rate (endpoint)[a]	*P* Value	Survival rate (time point)	*P* Value
160 mg/kg (total dose) administered over 8 days or 10 days						
Study 3-197 (20 mg/kg for 8 days)	eATG	21	47%[b]/ 52%[c] (3 mo)	<0.01[b]/ <0.01[c]	62%[d] (12 mo)	NA
	Supportive care only	20	6%[b]/ 0%[c] (3 mo)			
Study 3-198 (16 mg/kg for 10 days)	eATG + OXY + Bone marrow infusion	23	43%[b]/ 39%[c] (3 mo)	Not reported	83% (12 mo)	=0.14
	eATG + OXY	18	44%[b]/ 39%[c] (3 mo)		59% (12 mo)	
Study 5000	eATG + Androgen	26	42% (6 mo)	>0.9	55%[e] (24 mo)	=0.65

Table 1. Key Clinical Studies With ATGAM For The Treatment of Aplastic Anemia*

Study	eATG+ comparator or other therapy	No. of subjects analysed	Response rate (endpoint)[a]	*P* Value	Survival rate (time point)	*P* Value
(20 mg/kg for 8 days)	eATG + Placebo	27	44% (6 mo)		50%[e] (24 mo)	
160 mg/kg (total dose) administered over 4 days						
Scheinberg 2011	eATG + CsA	60	68% (6 mo)	<0.001	96%[g]/94%[h] (36 mo)	=0.04[g]/= 0.008[h]
	rATG[f] + CsA	60	37% (6 mo)		76%[g]/70%[h] (36 mo)	
Scheinberg 2009	eATG + CsA + sirolimus	35	51% (6 mo)	Not reported	97% (36 mo)	=0.30 (log-rank)
	eATG + CsA	42	62% (6 mo)		90% (36 mo)	

Abbreviation: OXY: oxymetholone.
* These clinical studies were conducted from 1979 to 2010.
[a] Hematologic response was defined differently in different studies, confidence intervals added where available.
[b] Sponsor's evaluation of response.
[c] Investigator's evaluation of response.
[d] This survival estimate includes the 21 subjects who were randomized to receive eATG, plus another 11 subjects who received eATG after crossing over from the control group.
[e] Patients with severe aplastic anemia only.
[f] CsA was discontinued at 6 months in the rATG group.
[g] Subjects who had stem cell transplantation were censored.
[h] Subjects who had stem cell transplantation were not censored.

Immunogenicity

Antibody against horse IgG was assessed in two clinical studies performed in renal transplant patients treated with ATGAM; 9% to 37% of treated patients show detectable levels of anti-horse IgG antibodies. The potential of neutralizing antibodies in renal transplant patients is unknown and its clinical significance has not been established.

The incidence of anti-horse antibody formation in aplastic anemia patients is unknown.

Pharmacokinetic properties

Distribution

During infusion of 10 to 15 mg/kg/day, the mean peak value (n=27 renal transplant patients) was found to be 727±310 µg/mL.

Metabolism and elimination

The half-life of equine immunoglobulin after ATGAM infusion was found to be 5.7±3.0 days in renal transplant patients. The range for half-life was 1.5 to 13 days.

Pharmacokinetic in special groups of subjects or patients

Ethnicity

A clinical study examined the pharmacokinetics of ATGAM in 6 adult Japanese patients with moderate or severe aplastic anemia. When administered via intravenous infusion at a dose of

10 mg/kg/day (N=3) or 20 mg/kg/day (N=3) for 8 days, the mean concentration was 1180±240 µg/mL and 2060±340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

THERAPEUTIC INDICATIONS

Renal allograft recipients

ATGAM sterile solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode. Data accumulated to date have not consistently demonstrated improvement in functional graft survival associated with therapy to delay the onset of the first rejection episode.

Aplastic anemia

ATGAM is indicated for use in adults and in children aged 2 years and older for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation.

When administered with a regimen of supportive care, ATGAM may induce partial or complete hematologic remission. In a controlled trial, patients receiving ATGAM showed a statistically significantly higher improvement rate compared with standard supportive care at 3 months. Improvement was defined in terms of sustained increase in peripheral blood counts and reduced transfusion needs.

The usefulness of ATGAM has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

To date, safety and efficacy have not been established in circumstances other than renal transplantation and aplastic anemia.

CONTRAINDICATIONS

Do not administer ATGAM to a patient who has had a severe systemic reaction (e.g., anaphylactic reaction) during prior administration of ATGAM or any other equine gamma globulin preparation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Only physicians experienced in immunosuppressive therapy in the treatment of renal transplant or aplastic anemia patients should use ATGAM.

Patients receiving ATGAM should be treated in facilities equipped and staffed with adequate laboratory and supportive medical resources. Patients should be carefully monitored during and after therapy with ATGAM for adverse events. Treatment of the adverse events should be instituted in accordance with local guidelines.

Precise methods of determining the potency of ATGAM have not been established, thus activity may potentially vary from lot to lot.

The safety and effectiveness of ATGAM have been demonstrated only in renal transplant patients who received concomitant immunosuppressive therapy and in patients with aplastic anemia.

Dilution of ATGAM in dextrose injection, USP, is not recommended, as low salt concentrations may result in precipitation. The use of highly acidic infusion solutions is also not recommended because of possible physical instability over time.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of ATGAM. Clinical signs associated with anaphylaxis, other infusion associated reactions, and serum sickness and associated symptoms such as rash, arthralgia, pyrexia, chills, and pain have been reported (see UNDESIRABLE EFFECTS). Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome, which can be fatal.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of ATGAM.

Anaphylaxis/skin testing

Discontinue ATGAM if anaphylaxis occurs. To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients before commencing treatment is strongly recommended (see POSOLOGY AND METHOD OF ADMINISTRATION).

General

Because ATGAM sterile solution is an immunosuppressive agent ordinarily given with corticosteroids and antimetabolites, watch patients carefully for signs of leukopenia, thrombocytopenia, or concurrent infection.

Infection

Because this product is made using equine and human blood components, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Due to the nature of the immunosuppressive effects of ATGAM, opportunistic infections (bacterial and fungal) are very common. Sepsis has also been reported. There is an increased risk of viral reactivation (e.g., cytomegalovirus [CMV] infection, Epstein–Barr virus [EBV] infection, herpes simplex virus [HSV]). Monitor patients closely for concurrent infection. In one study it has been found that it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents administered concomitantly with ATGAM. If infection occurs, institute appropriate adjunctive

therapy promptly. On the basis of the clinical circumstances, a physician should decide whether or not therapy with ATGAM will continue.

In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind.

Thrombocytopenia and neutropenia

Treatment with ATGAM may exacerbate thrombocytopenia and neutropenia. Consider discontinuing therapy if severe and unremitting thrombocytopenia or leukopenia occurs.

Renal and liver function tests

In other support studies in patients with aplastic anemia and other hematologic abnormalities who have received ATGAM, abnormal test results of liver function (SGOT, SGPT, alkaline phosphatase) and renal function (serum creatinine) have been observed. In some trials, clinical and laboratory findings of serum sickness were seen in a majority of patients.

Concomitant use of vaccines

The safety and effectiveness of immunisation with vaccines and treatment with ATGAM have not been studied. Vaccination is not recommended in conjunction with ATGAM therapy as the effectiveness of the vaccines could be reduced. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy.

Pediatric population

Experience in children with renal allograft transplants is limited.

Elderly population

Clinical experience in a limited number of elderly patients (≥65 years of age) has not identified differences in responses between the elderly and younger patients.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to ATGAM may appear. Under these circumstances, monitor patients especially closely during and after therapy with ATGAM.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during and up to 10 weeks after cessation of therapy.

Pregnancy

ATGAM was not teratogenic in rats or monkeys. Studies in animals have shown reproductive toxicity (see PRECLINICAL SAFETY DATA). These effects are not considered relevant to humans.

There are no adequate and well-controlled studies in pregnant women. There is a limited amount of data from the use of ATGAM in pregnant women. The outcome of pregnancies cannot be determined. ATGAM should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

In animal studies, ATGAM was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys (Macaca fascicularis). It is not known whether ATGAM is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding neonates and infants from ATGAM, a decision should be made whether to discontinue breast-feeding or to discontinue the drug taking into account the importance of the drug to the mother.

Fertility

Administration of ATGAM to cynomolgus monkeys (Macaca fascicularis) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility (see PRECLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect of ability to drive or use machines have been performed. Given the potential adverse reactions that may be experienced (e.g., dizziness, convulsion, confusional state, syncope), caution should be taken when driving or using machinery while on this medication.

UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions (occurring in greater than 10% of patients) are thrombocytopenia, leukopenia, rash, arthralgia, pyrexia, and chills.

The adverse drug reactions (ADR) reported with ATGAM during clinical trials or through post-marketing experience are presented in the table below. Adverse drug reactions are listed by MedDRA System Organ Class and Preferred Term, and frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2. Adverse Drug Reactions and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in All Patients[a]

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known (cannot be estimated from available data)
Infections and Infestations	Localised infection, Infection	Herpes simplex	Sepsis, Encephalitis			Hepatitis viral, Systemic infection,

Table 2. Adverse Drug Reactions and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in All Patients[a]

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known (cannot be estimated from available data)
						Epstein–Barr virus infection, Cytomegalovirus infection
Blood and Lymphatic System Disorders	Neutropenia, Thrombocytopenia, Leukopenia	Haemolysis, Lymphadenopathy				Anemia, Granulocytopenia, Hemolytic anemia, Pancytopenia, Eosinophilia
Immune System Disorders	Serum sickness		Anaphylactic reaction			
Metabolism and Nutrition Disorders		Hyperglycemia				
Psychiatric Disorders			Agitation			Confusional state, Disorientation
Nervous System Disorders		Headache, Paraesthesia, Syncope, Dizziness	Seizure			Dyskinesia, Tremor
Eye disorders			Periorbital edema			
Cardiac Disorders		Bradycardia, Tachycardia				Cardiac failure congestive
Vascular Disorders	Hypertension	Thrombophlebitis, Hypotension	Iliac vein occlusion			Deep vein thrombosis, Vasculitis
Respiratory, Thoracic and Mediastinal Disorders		Dyspnea, Cough, Epistaxis	Pleural effusion, Laryngospasm, Pulmonary edema			Hiccups, Apnea, Oropharyngeal pain
Gastrointestinal Disorders	Diarrhea	Abdominal pain, Nausea, Vomiting, Abdominal pain upper, Stomatitis, Gastrointestinal hemorrhage				Gastrointestinal perforation, Oral pain
Skin and Subcutaneous Tissue Disorders	Rash	Urticaria, Pruritus	Night sweats, Dermatitis allergic, Toxic epidermal necrolysis			Hyperhidrosis
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia	Back pain, Myalgia				Flank pain, Muscle rigidity, Pain in extremity

Table 2. Adverse Drug Reactions and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in All Patients[a]

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known (cannot be estimated from available data)
Renal and Urinary Disorders			Proteinuria, Renal artery thrombosis			Kidney enlargement, Acute kidney injury
Congenital, familial, and genetic disorders						Aplasia
General Disorders and Administration Site Conditions	Pyrexia, Pain, Chills, Edema	Chest pain, Malaise, Infusion site pain	Infusion site erythema, Asthenia			Infusion site swelling
Investigations	Liver function test abnormal		Renal function test abnormal			
Injury, Poisoning and Procedural Complications		Arteriovenous fistula thrombosis	Wound dehiscence			Kidney rupture

[a]The calculated frequency was based on number of subjects among the total of 476 subjects in the 6 in-house CTs and also among 137 subjects in 2 NIH studies and the highest frequency from the 2 datasets was selected for assigning the frequency category.

The recommended management for some of the adverse reactions that could occur with treatment with ATGAM follows:

1. **Anaphylaxis** is uncommon but serious and may occur at any time during therapy with ATGAM. Stop infusion of ATGAM immediately; administer 0.3 mL aqueous epinephrine (1:1,000 solution) intramuscularly. Administer steroids; assist respiration; and provide other resuscitative measures. DO NOT resume therapy with ATGAM.

2. **Hemolysis** can usually be detected only in the laboratory. Clinically significant hemolysis has been reported rarely. Appropriate treatment of hemolysis may include transfusion of erythrocytes; if necessary, administer intravenous mannitol, furosemide, sodium bicarbonate, and fluids. Severe and unremitting hemolysis may require discontinuation of therapy with ATGAM.

3. **Thrombocytopenia** is usually transient in renal transplant patients; platelet counts generally return to adequate levels without discontinuing therapy with ATGAM. Platelet transfusions may be necessary in patients with aplastic anemia (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and POSOLOGY AND METHOD OF ADMINISTRATION).

4. **Respiratory distress** may indicate an anaphylactoid reaction. Discontinue infusion of ATGAM. If distress persists, administer an antihistamine, epinephrine, corticosteroids, or some combination of the three.

5. **Pain in chest, flank, or back** may indicate anaphylaxis or hemolysis. Treatment is that indicated above for those conditions.

6. **Hypotension** may indicate anaphylaxis. Stop infusion of ATGAM and stabilize blood pressure with pressors if necessary.

7. **Chills and fever** occur frequently in patients receiving ATGAM. ATGAM may release endogenous leukocyte pyrogens. Prophylactic and/or therapeutic administration of antihistamines, antipyretics, or corticosteroids generally controls this reaction.

8. **Chemical phlebitis** can be caused by infusion of ATGAM through peripheral veins. This can often be avoided by administering the infusion solution into a high-flow vein. A subcutaneous arterialized vein produced by a Brescia fistula is also a useful administration site.

9. **Itching and erythema** probably result from the effect of ATGAM on blood elements. Antihistamines generally control the symptoms.

10. **Serum sickness-like symptoms** in aplastic anemia patients have been treated with oral or IV corticosteroids. Resolution of symptoms has generally been prompt and long-term sequelae have not been observed. Prophylactic administration of corticosteroids may decrease the frequency of this reaction.

OVERDOSE

Because of its mode of action and because it is a biologic substance, the maximal tolerated dose of ATGAM sterile solution would be expected to vary from patient to patient. To date, the largest single daily dose administered to one patient, a renal transplant recipient, was 7,000 mg administered at a concentration of approximately 10 mg/mL Sodium Chloride Injection, USP, approximately seven times the recommended total dose and infusion concentration. In this patient, administration of ATGAM was not associated with any signs of acute intoxication or late sequelae.

A maximum therapeutic dose has not been established therefore the definition of overdose for ATGAM has not been clearly defined. Some renal transplant patients have received up to 50 doses in 4 months, and others have received 28-day courses of 21 doses followed by as many as three more courses for the treatment of acute rejection. The incidence of toxicologic manifestations did not increase with any of these regimens; however close monitoring of the patient is recommended.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Renal allograft rejection treatment and prophylaxis – adult patients

Adult renal allograft patients have received ATGAM sterile solution at the dosage of 10 to 30 mg/kg of body weight daily. The few children studied received 5 to 25 mg/kg daily. ATGAM has been used to delay the onset of the first rejection episode and at the time of the first rejection episode. Most patients who received ATGAM for the treatment of acute rejection had not received it starting at the time of transplantation.

Usually, ATGAM is used concomitantly with azathioprine and corticosteroids, which are commonly used to suppress the immune response. Exercise caution during repeat courses of ATGAM; carefully observe patients for signs of allergic reactions.

Delaying the onset of allograft rejection: Give a fixed dose of 15 mg/kg daily for 14 days, then every other day for 14 days for a total of 21 doses in 28 days. Administer the first dose within 24 hours before or after the transplant.

Treatment of rejection: The first dose of ATGAM can be delayed until the diagnosis of the first rejection episode. The recommended dose is 10 to 15 mg/kg daily for 14 days. Additional alternate day therapy up to a total of 21 doses can be given.

Do not infuse a dose of ATGAM in less than 4 hours.

Treatment of aplastic anemia – adult patients and children aged 2 years and older

Dosage recommendations are based on body weight (bw).

The recommended total dose of ATGAM is 160 mg/kg bw, administered as part of standard immunosuppressive therapy, as follows:
- 16 mg/kg bw/day over 10 days or
- 20 mg/kg bw/day over 8 days or
- 40 mg/kg bw/day over 4 days

The recommended infusion duration for the 40 mg/kg dose regimen is 12 to 18 hours. Do not infuse a dose of ATGAM in less than 4 hours.

Special populations

Renal and hepatic impairment

Specific clinical studies have not been performed to assess the effect of renal or hepatic impairment on the pharmacokinetics of ATGAM.

Pediatric population

Currently available data in children less than 18 years of age are described in section PHARMACODYNAMIC PROPERTIES.

Elderly population (≥65 years of age)

Renal allograft recipients

In general, the dose for an elderly patient should be selected with caution, usually starting at the low end of the dosage range (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Aplastic anemia

Clinical experience in elderly patients has not identified differences in responses between the elderly and younger patients. Therefore, no dose adjustment is recommended for elderly patients.

Skin testing

Before the first infusion of ATGAM, it is strongly recommended that patients be tested with an intradermal injection of 0.02 mL of a 1:1,000 dilution (5 µg horse IgG) of ATGAM in sodium chloride injection, USP and a contralateral sodium chloride injection control. Use only freshly diluted ATGAM for skin testing. The patient, and specifically the skin test, should be observed every 15 to 20 minutes over the first hour after intradermal injection. A local reaction of 10 mm or greater with a wheal or erythema, or both, with or without pseudopod formation and itching or a marked local swelling should be considered a positive test.

The predictive value of this test has not been proven clinically. Allergic reactions such as anaphylaxis have occurred in patients whose skin test is negative. In the presence of a locally positive skin test to

ATGAM, serious consideration to alternative forms of therapy should be given. The risk to benefit ratio must be carefully weighed. If therapy with ATGAM is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and with a physician familiar with the treatment of potentially life threatening allergic reactions is in attendance.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of ATGAM see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and UNDESIRABLE EFFECTS.

Preparation of solution

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. However, because ATGAM is a gamma globulin product, the ATGAM concentrate and diluted solution are transparent to slightly opalescent, colorless to faintly pink or brown, and may develop a slight granular or flaky deposit during storage.

ATGAM (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

Dilute ATGAM for intravenous infusion in an inverted bottle of sterile vehicle or bag of sterile vehicle so that the undiluted ATGAM does not contact the air inside.

Add the total daily dose of ATGAM to an inverted bottle or bag of one of the following sterile vehicles below (also see Incompatibilities and shelf life):

- 0.9 % sodium chloride solution,
- Glucose solution/sodium chloride solution:
    - 50 mg/mL (5%) glucose in 0.45% (4.5 mg/mL) sodium chloride solution
    - 50 mg/mL (5%) glucose in 0.225% (2.25 mg/mL) sodium chloride solution

Due to possible precipitation of ATGAM, it is not recommended to dilute with glucose solution alone (see Incompatibilities and shelf life).

The recommended concentration of the diluted ATGAM is 1 mg/mL in the sterile vehicle. The concentration should not exceed 4 mg of ATGAM per mL. The diluted solution should be gently rotated or swirled to effect thorough mixing.

Any unused product or waste material should be disposed of in accordance with local requirements.

Method of administration

Following dilution, ATGAM is intended for intravenous use and administration via a high-flow central vein is preferred.

Monitor the patient continuously throughout the infusion for possible allergic reactions (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and UNDESIRABLE EFFECTS). Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered.

Diluted ATGAM should be at room temperature before infusion. ATGAM is appropriately administered into a vascular shunt, arterial venous fistula, or a high-flow central vein, using an in-line filter (not supplied) with a pore size of 0.2 to 1.0 micron. The in-line filter should be used with all infusions of ATGAM to prevent the administration of insoluble material that may have developed in the concentrate. The use of high-flow veins will minimize the occurrence of phlebitis and thrombosis.

Infusion volumes of 250 mL to 500 mL may be used. The infusion volume of the diluted solution should take into consideration factors such as patient's hemodynamic status, age, and weight. Following administration, it is recommended to flush the intravenous line.

Treatment of aplastic anemia - concomitant immunosuppressive therapy and pre-medication

ATGAM is most commonly administered with ciclosporin.

It is recommended to administer pre-medication with corticosteroids and antihistamines prior to infusion of ATGAM in accordance with local treatment guidelines. Anti-pyretics may also increase the tolerability of ATGAM infusion (see UNDESIRABLE EFFECTS).

Incompatibilities and shelf life

Drug product

Refer to outer carton for expiration date.

Diluted solution

ATGAM, once diluted, has been shown to be physically and chemically stable for up to 24 hours at concentrations of up to 4 mg per mL in the following diluents: 0.9% sodium chloride injection, 5% dextrose and 0.225% sodium chloride injection, and 5% dextrose and 0.45% sodium chloride injection.

Diluted solution should be kept at 20-25°C. The solution should be used within 24 hours (including infusion time).

ATGAM must not be mixed with other medicinal products except those mentioned above.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

QUALITATIVE AND QUANTITATIVE COMPOSITION

ATGAM sterile solution, containing 50 mg of horse gamma globulin/mL, is supplied as follows: 5 x 5 mL ampoules (Type I clear glass).

List of excipients

Glycine
Water for injections
10% solution sodium hydroxide (to adjust pH)
10% solution hydrochloric acid (to adjust pH)

SPECIAL PRECAUTIONS FOR STORAGE

Drug product

Store in a refrigerator at 2°C to 8°C (36°F to 46°F). **DO NOT FREEZE**. Keep the ampoules in the outer carton in order to protect from light.

Diluted solution

For storage conditions of diluted solution, see Incompatibilities and shelf life.

PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard identified for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity and pre-/post-natal development studies have not been conducted on ATGAM.

Fertility

Administration of ATGAM to cynomolgus monkeys (Macaca fascicularis) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility.

Pregnancy

ATGAM was not embryotoxic, fetotoxic, or teratogenic in rats, after doses similar to doses used in humans. An increase in hypoplastic cervical vertebrae was observed in rat fetuses at doses of 100 mg/kg/day administered ATGAM during organogenesis.

In cynomolgus monkey (Macaca fascicularis) reproduction studies, ATGAM was embryotoxic and fetotoxic. Maternal toxicity was observed with ATGAM doses of 20 mg/kg/day after 14 days of dosing with maternal deaths occurring at doses of 40 mg/kg/day. Fetal deaths occurred in dams treated with 20 mg/kg/day during the first part of organogenesis, but not in dams treated during the latter part of organogenesis. The maternal and fetal deaths were attributed to maternal anemia due to red blood cell antigen that humans do not share. Therefore, this toxicity is not considered relevant to human fetal development.

PRODUCT OWNER

Pfizer Inc
New York,
United States

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