

Management of Patients Receiving Antithymocyte Globulin for Aplastic Anemia and Myelodysplastic Syndrome

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Antithymocyte globulin (ATG) is a polyclonal antibody preparation with well-described efficacy in the treatment of severe aplastic anemia (AA) and in the treatment and prevention of acute rejection of renal transplantation. In addition, the benefit of ATG in the treatment of graft-versus-host disease in hematopoietic stem cell transplant (HSCT) and myelodysplastic syndrome (MDS) continues to be explored. Two preparations of ATG currently exist: Atgam® (Pfizer Inc., New York, NY) and Thymoglobulin® (Genzyme Corporation, Cambridge, MA). Atgam is a purified gamma globulin solution obtained by the immunization of horses with human thymocytes. Thymoglobulin is a purified immunoglobulin prepared from hyperimmune serum of rabbits immunized with human thymic lymphocytes (Gorantla et al., 2000). The result is a product rich in antihuman T cell antibodies. These antibodies bind to the surface of circulating T cells and T cells within lymphoid organs, reducing the number of functional T lymphocytes and creating an immunosuppressive effect (Gaber et al., 1998; Gorantla et al.). Antibodies to other hematopoietic cells have been reported (Pfizer Inc., 2002). These additional antibodies react against platelets, neutrophils, and red blood cells (RBCs) and may cause a transient decrease in peripheral blood counts

Antithymocyte globulin (ATG) is used commonly in patients with severe aplastic anemia and those undergoing renal transplant. Its utility also is being explored in the treatment of myelodysplastic syndrome, conditioning regimens for hematopoietic stem cell transplant, and prophylaxis of graft-versus-host disease. As indications for ATG expand, knowledge regarding its administration and management of associated toxicities is needed. These toxicities range from life-threatening anaphylaxis associated with the infusion to flu-like symptoms that occur one to two weeks after the infusion. Adverse effects are classified according to the severity and system impacted. Mild toxicities respond to comfort measures and include fever, chills, urticarial rash, and vomiting. Moderate toxicities require acute interventions and include fluid-responsive hypotension, nonischemic chest pain, and reversible oxygen desaturation. Severe toxicities require intensive support and include those refractory to earlier intervention. Management of these toxicities usually is limited to fluid resuscitation and noninvasive monitoring. Occurrence of infusion-related toxicities may require premature discontinuation of therapy. Therefore, an educated healthcare team and interdisciplinary clinical management guidelines are important to ensure the safe administration and complete course of ATG.

Key Words: aplastic anemia, antilymphocyte serum, myelodysplastic syndrome

during ATG administration. Although the origins of Atgam and Thymoglobulin are different, the administration issues are similar. The focus of this article will be on Atgam (40 mg/kg per day) and Thymoglobulin

(3.5 mg/kg per day) in patients with AA and MDS.

Application in AA and MDS

AA is an acquired hematologic disorder characterized by pancytopenia and hypocellular bone marrow. The pathophysiology of AA is hypothesized as an autoimmune attack mediated by T lymphocytes against the bone marrow (Young, 2002; Young & Maciejewski, 1997). In severe AA, patients may require immediate medical and supportive therapy for life-threatening infection or bleeding. To move beyond supportive care into the realm of treatment, factors such as age, degree of neutropenia, and availability of a human leukocyte antigen- (HLA-) matched donor must be considered. Bacigalupo et al. (2000) presented three treatment recommendations based on two important predictors of outcome: age and neutrophil count (see Table 1). Allogeneic HSCT is the recommended

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TABLE 1. INITIAL TREATMENT RECOMMENDATIONS FOR PATIENTS WITH APLASTIC ANEMIA

AGE (YEARS)	NEUTROPHIL LEVEL	TREATMENT
All children Adults ≤ 40	Not applicable Absolute neutrophil count (ANC) ≤ 300	Bone marrow transplant (BMT) ^a
Adults > 40	Not applicable	Immunosuppression
Children ≥ 10 Adults ≤ 40	ANC ≥ 300	Controversial; BMT or immunosuppression

^a Human leukocyte antigen-matched donor

Note. Based on information from Bacigalupo et al., 2000.

treatment option for younger patients (≤ 40 years) with a neutrophil count less than or equal to 300. However, not all patients can receive this treatment because transplant is contingent on the availability of an HLA-matched donor. Therefore, in patients who do not have a donor, immunosuppression becomes the treatment option of choice.

In the 1970s, ATG was identified as a treatment option for severe AA because it significantly improved survival compared to supportive care that consisted of blood products and antibiotic therapy (Speck et al., 1981; Speck, Gluckman, Haak, & van Rood, 1977). In 1983, the first randomized study was published demonstrating a significantly improved survival with ATG over supportive care (Champlin, Ho, & Gale, 1983). Bacigalupo et al. (1993) demonstrated improvement in response, but not survival, when adding androgens to the ATG-alone regimen. Current practice, however, is based on larger studies by Rosenfeld, Kimball, Vining, and Young (1995) and Frickhofen et al. (1991), who noted response rates from 70%–80% by six months with combination treatment of ATG and cyclosporine (CSA). Although response rates are high with ATG and CSA, the relapse rate is significant, requiring reinstitution of CSA therapy (Young, 1999). If patients with AA are unresponsive to Atgam, a course of Thymoglobulin may be considered. Response rates to Thymoglobulin, defined in this study as transfusion independence, are reported at 77% (Di Bona et al., 1999).

MDS is a bone marrow disorder characterized by clonal hematopoiesis, bone marrow failure with progression, and transformation to acute leukemia (Dansey, 2000). The prognosis of patients with MDS ranges from months to years based on factors used in making treatment decisions, including age, performance status, severity of anemia, and the international prognostic scoring system risk class (Alessandrino et al., 2002; Bowen et al., 2003). Treatment options

range from supportive care to active treatment such as allogeneic HSCT, a potentially curative therapy. Supportive care options include management of the symptoms by administering growth factors and blood product transfusions. Active treatment options can include hematopoietic growth factors, hypomethylating agents, immunosuppressive therapy, danazol, chemotherapy, and transplantation (Alessandrino et al.).

Like AA, MDS may have a component of autoimmune marrow destruction mediated by T lymphocytes. Therefore, ATG is hypothesized to be an effective treatment for MDS. The findings of a trial conducted at the National Institutes of Health (NIH) showed a 34% response rate, defined as transfusion independence (Molldrem et al., 2002). These findings have been supported in subsequent trials, but small sample sizes and study designs limit their generalizability (Aivado et al., 2002; Asano et al., 2001; Killick et al., 2003). Currently, ATG remains an experimental treatment option for MDS.

Antithymocyte Globulin Administration

Before infusing ATG, consideration must be given to a patient's risk factors. At a minimum, this should include assessing disease severity and comorbid conditions, skin testing for Atgam as indicated by the manufacturer, ensuring adequate resource availability, and establishing vascular access.

A patient's history is reviewed and a physical examination is given prior to the initiation of treatment to fully assess risk potential. This includes any significant allergy history, specifically to horses or rabbits. This is important because the ATG product will contain serum from horses or rabbits and could cause a severe reaction in patients who are allergic. In addition, a history of significant cardiac conditions such as congestive heart failure, hypertension, or arrhythmias

should be assessed. The latter may influence a patient's tolerance of infusion-related toxicities. Patients on a beta antagonist may have a stunted cardiovascular response to an allergic reaction and may not respond to medications administered for anaphylaxis. This group of patients should be evaluated by a cardiologist for supervised discontinuation of their beta antagonist prior to ATG skin testing and initiation of therapy. In addition, older patients may develop symptomatic anemia more readily during treatment than younger patients.

Although rare (< 3%), anaphylaxis has been reported with ATG administration (Millar & Grammer, 2000). Because of the potential for serious allergic reactions, the manufacturer of Atgam has recommended skin testing prior to treatment, although the predictive value has not been proven clinically. In contrast, skin testing is not recommended prior to administering Thymoglobulin because it is a poor predictor of anaphylactic reactions (Genzyme Corporation, 2002). To maximize the value of the skin test, patients must avoid antihistamines for a minimum of 72 hours prior to skin testing. Skin testing can be accomplished by placing an intradermal injection of a 1:1,000 dilution of Atgam (5 mcg horse immunoglobulin G) and a contralateral injection of normal saline as a control. The injection should be observed every 15–20 minutes for one hour. A local reaction of a 10 mm wheal or more with erythema should be considered a positive test (Pfizer Inc., 2002).

Atgam administration usually is guided by the results of the skin test. If the skin test is negative, the length of infusion will range from four to six hours. This is also the standard duration of infusion for the administration of Thymoglobulin. If the Atgam skin test is positive, suggesting sensitivity to the product, the process of desensitization is recommended prior to the initiation of therapy. Desensitization should be performed in collaboration with an allergy specialist and a practitioner who are available to activate emergency orders. The desensitization procedure lasts from two to four hours, ending with a 24-hour infusion of Atgam for the duration of the treatment.

Prior to the start of the desensitization procedure or the infusion of full-dose ATG, patients should receive premedications consisting of acetaminophen (650 mg), diphenhydramine (25–50 mg), and prednisone (1 mg/kg per day) to ameliorate infusional toxicities. In addition, emergency medications and equipment must be available to ensure safe administration. Resources should include nurses, physicians, and pharmacy staff who are knowledgeable about the expected

toxicities and the appropriate algorithm for clinical response. Moreover, medications such as antibiotics, antiemetics, and antipyretics and emergency supplies such as oxygen and suction need to be readily available. Administration can be performed safely outside of the intensive care unit (ICU) where resources and expertise exist. If a patient has a significant past medical history or comorbid conditions, preemptive transfer to the ICU may be necessary to maximize safety.

Central venous access should be established prior to the initiation of the infusion. ATG can be given through peripheral access; however, phlebitis has been documented (Pfizer Inc., 2002). In addition, mild and moderate toxicities require rapid management. To avoid interrupting ATG administration, multiple lumens are desirable to assist in the timely management of toxicities and transfusion support.

Toxicities

Because ATG is derived from either horse or rabbit sources, a variety of toxicities results from the immunologic response to this foreign substance. Recognizing these toxicities and implementing clinical management guidelines can help to ensure a safe and complete course of therapy (see Table 2). The toxicities experienced by patients receiving ATG are categorized by severity and system impacted. Although the majority of the toxicities are manageable, the potential for life-threatening complications dictates strict practice guidelines (see Figure 1). The severity and frequency of toxicities to ATG are greatest on the first day of infusion and diminish with each subsequent day. Upon the completion of the full treatment course, toxicities generally subside with the exception of cutaneous changes.

General

Anaphylaxis is the most serious complication, requiring frequent monitoring for the initial hour of the first day of treatment (Ferns & Chojnacka, 2003). Beyond the first hour, the side effects are a result of a delayed immune response, which generally can be managed while continuing the ATG infusion. These additional toxicities usually are mild and include rigors, urticarial rash, nausea, and vomiting; they are responsive to comfort measures.

Hematologic

When ATG therapy is initiated, complete blood cell counts should be assessed daily because ATG, in addition to reducing T lym-

TABLE 2. INFUSIONAL TOXICITIES OF ANTITHYMOCYTE GLOBULIN

TOXICITY	SEVERITY			INTERVENTION
	MILD	MODERATE	SEVERE	
General				
Rigors, muscular discomfort, nausea, vomiting	X	X		Steroids (prednisone 1 mg/kg per day); antihistamines (diphenhydramine 25–50 mg IV or by mouth every six hours as needed), meperidine (25–50 mg IV every three to four hours as needed), antiemetics
Anaphylaxis			X	Airway management, antihistamines, steroids, epinephrine
Hematologic				
Thrombocytopenia, anemia	X	X		Platelet and red blood cell transfusion to avoid bleeding and symptomatic anemia
Neutropenia (absolute neutrophil count)		501–1,000	< 500	Assessment of potential sites of infection
Neutropenic fever		X	X	Empiric antibiotic therapy, acetaminophen (650 mg by mouth every four hours)
Pulmonary				
Oxygen desaturation	X	X		Oxygen therapy
Refractory desaturation, adult respiratory distress syndrome			X	Airway management, intensive care unit support
Cardiovascular				
Hypotension	X	X		Fluid resuscitation
Refractory hypotension			X	Circulatory management, intensive care unit support
Chest pain		X	X	Electrocardiogram, rule out ischemia
Cutaneous				
Rash, pruritus, urticaria	X	X		Antihistamines, topical steroids

phocytes, can decrease platelet, neutrophil, and RBC levels. In select populations of patients (e.g., older adults), platelet and RBC transfusions should be administered prior to the ATG infusion when symptomatic anemia or thrombocytopenia is predicted. When no signs or symptoms of bleeding or risk or presence of symptomatic anemia exist, administration of blood products can follow the daily ATG infusion. Concomitant administration of blood products should be avoided with ATG infusions. Avoiding simultaneous administration maximizes the benefit of blood products and prevents any confusion related to a transfusion reaction versus ATG reaction (Higgins, 2000). If a 24-hour infusion is required, these concerns are acknowledged, but concomitant administration of blood products and ATG is accepted.

Infectious

Most patients receiving ATG will develop a fever as a result of the drug. Dearden, Foulkner, Lee, Gordon-Smith, and Marsh (1998) studied neutropenic patients (n = 39 with AA receiving ATG; n = 38 with acute leukemia) with fever. Positive cultures were shown in 10% (n = 4) of patients with AA who had no

other signs or symptoms of infection. The difference between the number of positive cultures in the AA group (10%) versus the acute leukemic group (86%) was significant (p = 0.001). These authors concluded that most fevers in neutropenic patients undergoing ATG therapy are not infectious in origin. Because of the potential for grave outcomes in patients with absolute neutrophil counts (ANCs) less than 500, those with severe neutropenia who develop fevers should be treated with empiric antibiotics (Shelton, 2003). For patients with ANC's from 501–1,000, the decision to add antibiotics should be based on a patient's clinical status. In either scenario, antibiotic therapy may be abbreviated when ATG is completed if no source of infection is identified, the fever resolves, and the patient remains clinically stable.

Pulmonary

During the initial hour of the first dose of ATG, concerns regarding airway management should be evaluated as part of a potential anaphylactic reaction. Otherwise, desaturation during ATG treatment can occur as a secondary effect of less serious side effects such as fever and rigors. Most patients

General principles

- Preantithymocyte globulin (ATG)
 - History and physical examination
 - Prepare for skin test (Atgam® only) and avoid antihistamines and beta antagonist therapy.
 - Administer premedications prior to initiation of infusion.
 - Have resources readily available and emergency equipment (oxygen, suction) at the bedside.
- During ATG
 - The initial infusion rate is 10% of the total volume per hour (e.g., 500 cc will start at 50 cc per hour for 15 minutes). If no signs of adverse reaction develop, the infusion rate can be advanced to complete the infusion as prescribed.
 - Patients must remain on the nursing unit during infusion.

First day of ATG

- Inform ordering practitioner of initiation of ATG.
- Remain with the patient during the first 15 minutes and measure and record vital signs (temperature, pulse, respiration, blood pressure, oxygen saturation)
 - Immediately prior to initiating infusion
 - Then every 15 minutes for one hour
 - Then every 30 minutes for one hour
 - Then every hour until infusion is completed.
- Monitor for adverse reaction (flushing, rash, pruritus, shortness of breath, chest pain) continually during the first 15 minutes of the first dose and then every hour until the infusion is completed.

Subsequent days of ATG

- Measure and record vital signs
 - Immediately prior to initiating infusion
 - 30 minutes after initiating infusion
 - Then every hour until infusion is complete.
- Monitor for adverse reaction every four hours.

FIGURE 1. PRACTICE GUIDELINE FOR PATIENTS RECEIVING ANTITHYMOCYTE GLOBULIN

respond to minimal low-dose oxygen therapy as immediate management for this symptom.

Adult respiratory distress syndrome (ARDS) has been reported as a rare complication of ATG therapy (Dean, Amend, & Matthay, 1987; Maillard et al., 1999; Murdock, Lawless, Collins, Huml, & Pifarre, 1987; Walton & Gualtiere, 1998; Zomas et al., 1995). Signs and symptoms of ARDS have been reported to begin as early as a few hours after the start of therapy. In all cases reported in the literature, ATG was discontinued. Out of these five case reports, two resulted in death and the remaining three patients recovered fully.

Cardiovascular

Cardiovascular changes may occur during ATG administration. These changes include

hypotension and tachycardia resulting from the immune response and systemic vasodilatation. Patients generally respond to fluid resuscitation as immediate management for these symptoms. To treat the underlying immune response, systemic antihistamines also should be considered. In addition, patients may report chest pain along with generalized muscle pain or spasm. These symptoms require immediate evaluation to rule out cardiac ischemia; myocardial infarction has not been reported as a complication of ATG (Docherty, 2002a, 2002b).

In a case series reported by Millar and Grammer (2000), toxicities such as hypotension and oxygen desaturation resulted in termination of therapy. All administration toxicities in these cases resolved with medical management; however, treatment was not initiated. A retrospective analysis of 66 subjects at the NIH reported that severe reactions occurred in 15% of patients but required discontinuation in only 6%, all of whom had MDS (Bevans, Nunez, Wisch, & Chamberlain, 2001).

Miscellaneous

Dermatologic reactions such as rash, pruritus, and urticaria are seen frequently in patients receiving ATG. These infusional reactions can be relieved with antihistamines such as diphenhydramine. Patients also may benefit from topical creams to ameliorate itching or oral agents such as hydroxyzine.

Hepatic toxicities also have been reported (Killick, Marsh, Booth, & Gordon-Smith, 1997). An elevation of serum alanine transaminase frequently is isolated with no clinical changes evident. In the majority of cases reported, the liver function abnormality was transient and returned to normal within one month. The cause of this acute and sometimes extreme change remains unclear.

Serum sickness is an additional reaction following ATG administration occurring in approximately 86% of patients (Bielory et al., 1986). It is a type II hypersensitivity reaction presenting 7–14 days after initiation of ATG. Although frequent, the symptoms generally are well tolerated and include fever, rash, and arthralgias; they can be managed with corticosteroids.

Patient Education

Patients preparing to undergo ATG therapy frequently are newly diagnosed and require information related to their disease and pending treatment. Because ATG includes known toxicities, information related to the regimen should be readily available (see Figure 2). This includes education about

Protocol- and Condition-Specific Education

Preparation phase

- Identify allergies (e.g., horse, rabbit).
- Obtain Atgam® skin test and avoid antihistamines and beta antagonist therapy.
- Place temporary central venous access device.
- Obtain drug information: antithymocyte globulin, prednisone, antihistamines, acetaminophen, meperidine, antibiotics, antiemetics.

Administration

- Patient must remain on the nursing unit during drug administration.
- Give over four to six hours or 24 hours continuous infusion if desensitization is required.
- Mild infusional side effects are expected and include fever, chills, nausea, rash, arthralgias, and mild hypotension.
- Moderate and severe side effects are possible, including shortness of breath, chest pain, and dizziness.
- Possible interventions include fluid bolus, medications, and intensive care unit transfer.
- Changes in transfusion requirement during treatment are expected.

Discharge and follow-up

- Provide protocol- and condition-specific education (e.g., neutropenic precautions).
- Response time is three to six months.
- Delayed side effects include serum sickness with rash, flu-like symptoms, and arthralgias.
- Treat serum sickness with steroids.
- Follow-up should be routine and/or research specific.

FIGURE 2. PATIENT EDUCATION

their course of treatment, expected side effects, and management. Patients should be taught to report any changes, including dizziness, nausea, rash, chest tightness, headache, or shortness of breath. Patient education should include an emphasis on the importance of early reporting of symptoms to allow for prompt intervention.

Nursing Implications

Although patients receiving ATG require a multidisciplinary team, nurses are essential in maximizing the safety of this therapy. The nurse responsible for administering ATG must ensure that the appropriate guidelines are activated (see Figure 1). This effort begins with an understanding of patients' risk factors regarding their illness and potential response to the Atgam skin test and subsequent ATG administration. When preparing for administration, the nurse must ensure that all resources are readily available, including additional team members, vascular access device access, and emergency supplies. Furthermore, the availability and timely administration of pre- and emergency medications

are essential. If nurses, patients, and family members are knowledgeable about expected toxicities, any that occur can be identified and managed early and irreversible complications can be avoided.

Conclusion

The applications for ATG continue to expand. Although patients may experience toxicities, ATG can be given safely in a non-ICU setting where a standard approach to patient management has been established. This approach should include establishing vascular access, assessing disease severity and comorbid conditions, and ensuring adequate resource availability. The administration procedure should include skin testing, specific infusion procedures, and monitoring guidelines. Finally, a consistent approach to toxicity management and staff who are familiar with these procedures are essential.

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Rapid Recap

Management of Patients Receiving Antithymocyte Globulin for Aplastic Anemia and Myelodysplastic Syndrome

- Antithymocyte globulin (ATG) is approved for use in aplastic anemia and renal transplant. Its use is being explored in more settings such as myelodysplastic syndromes and stem cell transplantation.
- ATG administration can cause a wide range of toxicities, from fever and chills to hypotension and possible anaphylaxis.
- Sensitivity testing and careful assessment of patients' comorbid conditions prior to ATG administration can help health-care providers to anticipate potential problems.
- Ensuring the availability of resources and emergency medications and equipment is important prior to administration.
- With clinical management guidelines and a well-educated healthcare team, ATG can be administered safely in a non-intensive care unit setting.

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