

Successful desensitization to antithymocyte globulin in a child with aplastic anemia

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Papers in the Grand Rounds section are patient case reports and literature review combined in a way that gives them high educational value. The papers lead off with a well-documented case report of an unusual drug experience (e.g., adverse drug reaction, some other unexpected drug response, experimental use of a drug). The case generally deals with a difficult therapeutic problem or dilemma that is commonly encountered but may be overlooked or misunderstood. (Esoteric or rare occurrences of minor importance do not make good Grand Rounds material.) A literature review puts the case in perspective with previously reported similar cases and alternative treatments. The review is integrated with related discussions of the new case being reported.

Aplastic anemia was first described in 1888, and since then there have been between 500 and 2500 cases of the disease reported each year.¹ Characterized by bone marrow aplasia and peripheral blood pancytopenia, aplastic anemia is considered to be an immune-mediated bone marrow disease.² The pathophysiology of aplastic anemia is thought to be an autoimmune attack by T lymphocytes against the bone marrow.³ The treatment of choice for children with aplastic anemia is an allogeneic bone marrow transplantation, using a human leukocyte antigen (HLA)-matched sibling donor.⁴ For children without matched siblings, the use of immunosuppressive therapy using antithymocyte globulin (ATG) in combination with other immunosuppressives such as cyclosporine and prednisone has produced a greater than 60% response

rate by six months.⁵⁻⁸ Patients appear to respond more quickly to ATG treatment regimens that include cyclosporine, with most only needing one course of immunosuppression. Repeat immunosuppressive treatment has been needed in patients who did not receive cyclosporine as part of their treatment regimen.² In a long-term follow-up study of patients who received ATG, corticosteroids, and cyclosporine, the actuarial relapse rate was 38% at 11 years after initial treatment.² While not

necessarily a cure of aplastic anemia, this is the preferred treatment strategy for children without an HLA-matched sibling.

ATG contains animal serum (usually equine) and has the potential to cause adverse reactions, varying from anaphylaxis to delayed-onset serum sickness. In patients with aplastic anemia, equine ATG is administered as prolonged i.v. infusions of 40 mg/kg over 10 hours on four consecutive days.^{3,9} It is recommended that an intradermal test dose of equine ATG (0.1 mL of 1:1000 dilution) be administered before the first i.v. infusion for all patients.^{3,10} Children who mount significant responses to such a test dose pose a dilemma for the clinician. A five-year case review at the Children's Hospital at Oklahoma University Medical Center, a 135-bed comprehensive pediatric center, revealed a 29% prevalence of significant hypersensitivity reaction to ATG. A successful desensitization protocol increases access to a potentially successful treatment for such children, whose outlook is otherwise poor. We describe an equine ATG desensitization regimen used in a four-year-old boy after he developed an immediate 14-mm wheal and flare acute hypersensitivity reaction to an equine ATG test dose.

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Case report

A four-year-old boy diagnosed with severe aplastic anemia did not have a sibling match for a bone marrow transplant. It was decided to use immunosuppression for initial treatment. He was to be started on a regimen of prednisone and cyclosporine, along with equine ATG. He received equine ATG 0.1 µg intradermally as his first test dose. After this dose, he developed an immediate 14-mm wheal and flare acute hypersensitivity reaction without wheezing or difficulty breathing. He was transferred to the pediatric intensive care unit where he was treated with single i.v. doses of diphenhydramine hydrochloride 1 mg/kg and methylprednisolone sodium succinate 2 mg/kg, with epinephrine hydrochloride 0.01 mg/kg at the bedside. He was then administered a desensitization regimen of four i.v. doses of equine ATG in gradually increasing amounts (0.1, 1, 10, and 100 µg), with vital signs checked before the first dose and every 5 minutes thereafter. The four doses were given at 15-minute intervals, followed by an infusion of equine ATG 0.16 mg/min over 10 minutes, with continuous monitoring of vital signs.

Following this desensitization process, we proceeded on to administration of full doses of equine ATG over the next four days. Thirty minutes before each full dose, he was premedicated with acetaminophen 15 mg/kg and diphenhydramine hydrochloride 1 mg/kg. Each day he was to receive equine ATG 40 mg/kg (690 mg total) in 690 mL of 0.9% sodium chloride with methylprednisolone sodium succinate 55 mg to run over 10 hours at 69 mL/hr. On day 1, 1.5 hours into his infusion, he began to shiver violently. His infusion rate was decreased to 35 mL/hr. The shivering stopped after 10–15 minutes, and we resumed the rate at 69 mL/hr. Nine hours into this infusion, the patient developed small, red, raised wheals and the infusion

rate was decreased to 30 mL/hr. Twelve hours into the infusion, he developed additional hives. The infusion was stopped and the patient was treated with i.v. diphenhydramine hydrochloride 1 mg/kg, which resolved the reaction.

On day 2, he was premedicated with diphenhydramine hydrochloride 1 mg/kg and acetaminophen 15 mg/kg 30 minutes before the equine ATG infusion. Because of his reaction on the previous day, the infusion was started at 1 mL/hr and increased gradually over the first hour as follows: at 15 minutes the rate was increased to 4 mL/hr; at 30 minutes, it was increased to 16 mL/hr; at 45 minutes, it was increased to 32 mL/hr; and at 60 minutes, it was increased to 57 mL/hr. After one hour at 57 mL/hr, the infusion was increased to the maximum rate of 69 mL/hr. Four hours into the infusion, the patient developed a 2-mm wheal on his right cheek and right leg. Five hours into the infusion, he developed a few more small wheals, which were successfully treated with diphenhydramine hydrochloride 1 mg/kg. On the subsequent days of infusion, the rate was increased to the maximum (69 mL/hr) over the first hour of infusion, and the patient had no further hypersensitivity reactions. This process was continued successfully for the rest of the four-day regimen. Because of the high doses of corticosteroid used in the infusion process, the patient was tapered off of the methylprednisolone over the next two weeks. The patient's blood counts responded well and continued to stabilize over the next five months; he was continued on cyclosporine for one year, until he exhibited a relapse of his aplastic anemia. At that time, he had a successful cord-blood transplant from an unrelated donor, and he continues to do well today.

Discussion

Aplastic anemia is described as pancytopenia with hypocellular bone

marrow.⁹ Many different factors, such as drugs, chemicals, toxins, viruses, and radiation, can cause bone marrow dysfunction, which may lead to aplastic anemia.¹¹ Drug-induced aplastic anemia is associated with a high mortality rate.¹¹ When a transplant is not feasible, immunosuppressive therapy with ATG, prednisone, and cyclosporine significantly improves survival, with long-term survival rates similar to those in patients treated with stem cell transplantation.² ATG contains antihuman T-cell antibodies that bind to the surface of circulating T cells, as well as T cells within the lymphoid organs, and create an immunosuppressive effect by reducing the number of functional T lymphocytes.³ Because the antibodies may activate the T cells before they are destroyed, there is a potential for release of cytokines from the T cells, which may produce a systemic inflammatory response manifested by hypotension, pyrexia, and rigors. This is different from the type I hypersensitivity response with anaphylaxis also seen with ATG, and can be managed by pretreatment with antihistamines and corticosteroids.^{12,13}

Equine ATG is obtained from the plasma or serum of horses that have been hyperimmunized with human thymus lymphocytes.¹⁰ The commercially available form of this product contains 50 mg/mL of equine immunoglobulin (Ig) G.¹⁰ In the treatment of aplastic anemia, equine ATG is administered at 40 mg/kg/day for four consecutive days.^{3,8} Since equine ATG is produced from heterologous sera, the possibility of adverse reactions, including anaphylaxis, exists.¹⁴ According to one source, anaphylaxis occurs in less than 5% of patients, but may occur at any time during therapy.¹⁵ Other common adverse reactions include pruritis (12.5%), rash (27%), and urticaria (12.5%).¹⁵ Despite these hypersensitivity reactions, equine ATG remains the preferred therapy in treating most pa-

tients with aplastic anemia because of good outcomes associated with its use.^{2,10,16,17} Because of the high incidence of hypersensitivity reactions in patients receiving equine ATG, clinicians should be prepared to administer a desensitization regimen to their patients who have a hypersensitivity response to the agent. When patients do not respond to the equine-derived ATG, clinicians may choose to try the rabbit-derived ATG instead of trying to desensitize the patient.³ Because rabbit ATG was not available at our institution during the time of this case, desensitizing the patient to the equine ATG was the best option.

While there are many available reports that describe desensitization protocols for various drug therapies, there are only a few describing ATG desensitization protocols. Immunosuppression may be manifested through several mechanisms including tolerance to self-antigens, interactions between the disease and the host's immune system, and induced immunosuppression.¹⁸ ATG achieves immunosuppression by a mechanism of induced immunosuppression, by causing a decrease in cellular immunity through a reduction in the number of functional T lymphocytes.^{3,18}

Case studies have shown that desensitization to equine-derived ATG is possible, allowing for ATG therapy in those patients who are hypersensitive to the heterologous serum.¹⁴ One case report discussed a six-year-old girl with idiopathic aplastic anemia who was referred for equine ATG therapy when initial treatment with prednisone and cyclosporine led to no improvement.¹⁰ After skin testing revealed a positive reaction, the patient was premedicated with oral prednisone, hydroxyzine hydrochloride, and ranitidine hydrochloride before receiving equine ATG at increasing concentrations until 15 mg/kg/day was achieved.¹⁰ The specific protocol used for this patient was 5, 50, 500, and 5000 µg/mL, 0.02 mL

intradermally at 10-minute intervals; 50, 100, 300, 1000, 3000, and 5000 µg/mL, 0.5 mL subcutaneously at 10-minute intervals; and 0.5, 1, and 2 mg/min intravenously for 10 minutes each and then 15 mg/kg continuously infused over 24 hours.¹⁰ She was kept at this concentration for 10 days without any major complications, undergoing successful desensitization and receiving a full course of equine ATG.

Another report described a 17-year-old boy who developed aplastic anemia after a liver transplantation.¹⁹ Even after a positive skin test, equine ATG was determined to be the best treatment and he was started on a desensitization schedule. The patient was given prednisone, ranitidine, and diphenhydramine. His desensitization protocol began with equine ATG at a concentration of 0.01 mg/mL, infused at a rate of 0.1 mL/hr over 15 minutes.¹⁹ The concentration and rate gradually increased to a maximum concentration of 1 mg/mL infused at a rate of 94 mL/hr over 24 hours. Once a full therapeutic dose of ATG was given, the patient developed generalized urticaria, which was treated with diphenhydramine and resolved at the end of the four-day treatment regimen. In both of these cases of successful desensitization, the patients were premedicated with antihistamines and glucocorticoids.

While these two cases were successful, there were difficulties during the desensitization process, as seen with the second patient's hypersensitivity reactions. Because of patients' varying degrees of sensitivity to equine ATG, desensitization regimens may be difficult to implement. According to two case reports involving ATG use in adults, therapy had to be discontinued because of the severity of the patients' hypersensitivity reactions.¹⁴ And, while skin testing is recommended to help determine hypersensitivity status before administration of equine ATG,

it may not always be accurate. In one adult patient, skin testing was performed and shown to be negative; however, several hours into the first dose, equine ATG had to be discontinued and was not readministered because of severe reactions to the ATG.¹⁴

The sensitivity and specificity of equine ATG skin testing are not yet fully known; false-negative and false-positive tests are possible.²⁰ Patients who exhibit a positive skin test should be carefully evaluated before receiving equine ATG, and a risk-benefit judgment must be made before moving forward with treatment. Conversely, patients with negative skin tests should be carefully monitored for signs of hypersensitivity during infusion with equine ATG, and clinicians should be prepared to stop the infusion and provide appropriate treatment at the first sign of symptoms. Our patient had an immediate wheal reaction to the test dose but did not exhibit wheezing or hypotension. We proceeded with the desensitization process in an intensive care setting and used antihistamines and corticosteroids to control the reaction. Even after the desensitization process, he still continued to have symptoms during the therapeutic infusions, which were managed by slowing the infusion and administering diphenhydramine.

Our patient was similar to the two successful cases previously mentioned. First, he was four years old and the other two patients were also pediatric. All three patients were premedicated with antihistamines and corticosteroids before starting the desensitization process. The desensitization protocols were similar in that they all involved gradually increasing doses of equine ATG, followed by the full therapeutic dose. Additional doses of diphenhydramine resolved the urticaria seen in our patient during administration of the full dose of ATG, just as it did in the case describing the 17-year-old boy.

The use of daclizumab, a humanized monoclonal antibody, might offer a new option for the treatment of aplastic anemia. In a recent study, 17 aplastic anemia patients, ages 9–67 years, received 1 mg/kg of daclizumab every two weeks for three months.²¹ No toxicity was seen, and 38% of the evaluable patients (6 of 16) responded to treatment, defined as a hematologic response in at least one of the affected peripheral blood values. Although this was a small study, it offers an additional option for immunosuppression in these patients, although larger studies are needed.

It is clear that successful desensitization to equine ATG is achievable in children with aplastic anemia. A successful desensitization protocol increases access to a potentially successful treatment for these children. As each patient may encounter different reactions to equine ATG during therapy, clinicians may find it necessary to deviate from the desensitization protocol so as to meet the needs of each patient.

Conclusion

A desensitization protocol including diphenhydramine and glucocorticoid led to a successful treatment with equine ATG in a four-year-old patient with aplastic anemia.

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