

A successful desensitization protocol for horse-derived antithymocyte globulin in severe aplastic anemia

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Abstract

Background: Horse antithymocyte globulin (h-ATG) (ATGAM[®]) is the first choice of treatment in very severe patients with aplastic anemia who do not have any HLA matched sibling donor. h-ATG is a heterologous serum that may cause anaphylaxis. Alternative treatment strategies must be planned in case of hypersensitivity. Desensitization must be considered in patients without an alternative treatment of choice. We aimed to present the h-ATG desensitization protocol and consider its effectiveness in patients with aplastic anemia who are hypersensitized with h-ATG and do not have an alternative treatment of choice.

Methods: Skin prick tests were performed with non-diluted solution in eight very severe patients with aplastic anemia who are followed up in Ege University Children's Hospital. Although skin prick test was found negative in these eight patients, different dilution h-ATG intradermal tests were performed and found positive in all patients. h-ATG desensitization program was started to these hypersensitized patients.

Results: Desensitization program was started to six male and two female very severe patients with aplastic anemia whose ages were between seven and 19 yr (median: 12.9 yr). All of the patients completed the desensitization program. While local reaction was seen in two patients, systemic reaction was seen in one patient and late reaction was seen in one patient during and after desensitization program.

Conclusion: A successful desensitization program with h-ATG in children with aplastic anemia is presented. Even though there is not an exposure before to such high allergy potential heterologous serum, skin tests should be performed and desensitization must be started to patients who are hypersensitized to h-ATG. As the expected effectiveness of the treatment is so much, the desensitization protocol can be carried out safely and effectively with trained staff although allergic reactions can be seen.

Background

Acquired aplastic anemia is a rare disease which is characterized by pancytopenia secondary to hypoplastic bone marrow (1). Although its etiology is unknown, it is thought to be secondary to immune-mediated destruction of stem cells and progenitor cells (2, 3). Hematopoietic stem cell transplantation is curative (4). Equine-derived antithymocyte globulin (ATGAM[®]) is the first choice of treatment in severe patients with aplastic anemia who do not have any HLA matched sibling donor. It inhibits the proliferation of active T lymphocytes which has cytolytic effect on the hematopoiesis.

Horse-derived ATG is a sterile gammaglobuline that is collected and isolated as monomeric IgG from the horses which are hypersensitized to human thymocyte lymphocytes. It has been used in the treatment of aplastic anemia since 1978 (3). It contains 50 mg horse-derived gammaglobuline protein per 1 milliliter. It may cause severe side effects and anaphylaxis because it is a high molecular weight heterologous serum. Allergic sensitization possibility is high, even if in the first exposure to the heterologous serum antigens. Because of that, allergic skin test (epidermal and intradermal) should be performed in both the first and repeated exposures to the ATG. An intradermal ATG test dose should be carried out

prior to ATG treatment. Alternative treatment modalities should be planned in case of positive skin test. Although there is a high risk of allergy and anaphylaxis, desensitization should be considered in the patients who do not have any alternative treatment modality and who are hypersensitized to ATG (4).

The aim of this study was to show the desensitization protocol of ATG which can avoid severe allergic reactions and the results of desensitization protocol.

Method

Eight very severe patients with aplastic anemia (three of them had taken rabbit ATG before) who were treated at Ege University Children's Hospital had skin prick test with non-diluted h-ATG solution before treatment with h-ATG. During the test, histamine 1 mg/ml was used as positive control and 0.9% NaCl was used for negative control. Intradermal skin tests were performed with 0.02–0.05 ml of 1/1000 (50 µg/ml), 1/100 (500 µg/ml), and 1/10 (5000 µg/ml) dilutions of ATG. For all dilution >10 mm, enduration was considered as positive for desensitization protocol. Horse-ATG treatment was given in the Pediatric Hematology Unit to the patients whose intradermal skin test was negative. Horse-ATG desensitization program was given to the eight patients who must get antithymocyte globulin treatment and who had hypersensitization detected in skin test (<http://www.fda.gov.tr>, ATGAM, product information, November 2005; Pharmacia & Upjohn Company, ATGAM, product information).

Premedication regimen was given to all patients before desensitization protocol. Premedication was performed with methylprednisolone (1–2 mg/kg/dosage) three times 1, 7, and 12 h before the desensitization (total max. dosage 60 mg); hydroxyzine (1 mg/kg, max. 25 mg) and ranitidine (1 mg/kg) intravenously 1 and 12 h before the desensitization.

Desensitization was started with 1/1000 dilution 0.1 ml (0.005 mg) h-ATG intravenously, and the dosage was increased with 30-min intervals by 1/1000, 1/100, 1/10, 1/1 dilutions, respectively. By 18 steps, the planned treatment dosage was recovered. All of the patients finished the desensitization protocol.

The daily total h-ATG dosage was calculated before the desensitization, and four different concentrations (*C*, *B*, *A* solutions, and full dosage solution) were prepared with 0.9% NaCl. *C* solution was 1/1000 diluted, *B* solution was 1/100 diluted, *A* solution was 1/10 diluted, and 1/1 non-diluted full dosage drug was prepared. *Solution C* was used in steps 1–6, *solution B* was used in steps 7–10, *solution A* was used in steps 11–14, and *full dosage* was used in steps 15–18. Horse-ATG desensitization schema for patient V is given as a sample in Table 1 (Patient V, Weight: 29, Daily dose of treatment: 580 mg).

Total desensitization time is 510 min (8.5 h) for each patient. For seven patients, h-ATG treatment dosage was 20 mg/kg/day for 8 days and only one patient had taken 40 mg/kg/day for 4 days. All patients were monitored in every 15 min for blood pressure, heart rate, breath rate, and oxygen saturation. All the treatment duration was followed up by a pediatric allergy specialist.

Table 1 Ege university children allergy unit – ATG desensitization treatment protocol

Time	Step of dosage	Dosage (ml)	Cumulative dosage (mg)	Tolerance
C. 1/1000				
0 min	1	0.1 ml (0.005 mg)	0.005 mg	Tolerated
30 min	2	0.5 ml (0.025 mg)	0.03 mg	Tolerated
60 min	3	1 ml (0.05 mg)	0.08 mg	Tolerated
90 min	4	2 ml (0.1 mg)	0.18 mg	Tolerated
120 min	5	4 ml (0.2 mg)	0.38 mg	Tolerated
150 min	6	8 ml (0.4 mg)	0.78 mg	Tolerated
B. 1/100				
180 min	7	1 ml (0.5 mg)	1.28 mg	Tolerated
210 min	8	2 ml (1 mg)	2.28 mg	Tolerated
240 min	9	4 ml (2 mg)	4.28 mg	Tolerated
270 min	10	8 ml (4 mg)	8.28 mg	Tolerated
A. 1/10				
300 min	11	1 ml (5 mg)	13.28 mg	Tolerated
330 min	12	2 ml (10 mg)	23.28 mg	Tolerated
360 min	13	4 ml (20 mg)	43.28 mg	Tolerated
390 min	14	8 ml (40 mg)	83.28 mg	Tolerated
Full 1/1				
Dosage				
420 min	15	1 ml (50 mg)	133.28 mg	Tolerated
450 min	16	2 ml (100 mg)	233.28 mg	Tolerated
480 min	17	3 ml (150 mg)	383.28 mg	Tolerated
510 min	18	4 ml (200 mg)	583.28 mg	Tolerated

mg, milligram, ml, milliliter.

Results

The desensitization results of eight very severe acquired patients with aplastic anemia who must receive h-ATG between 2012 and 2013 at Ege University Children Hospital are reported retrospectively in this study. The patients' ages were between seven and 19 (median: 12.9) years and 6 (75%) patients were male. None of the patients had allergic disease in history. Horse-ATG was the only choice of treatment in all of the patients in this study, but they all had hypersensitivity in skin testing. In our study group, skin prick tests were negative for all patients; 50% of them gave positive reaction with 1/1000 intradermal skin test, one patient gave reaction with 1/100 dilution, and three patients gave reaction with 1/10 dilution. The general characteristics of patients are shown in Table 2.

During the desensitization, two patients (25%) had local reactions and one patient (12.5%) had systemic reaction. One patient (12.5%) developed late reaction. Although *C*, *B*, and *A* solutions were given uneventfully, all reactions were seen during the full dosage in the desensitization. The desensitization reactions were summarized in Table 3. Left auricular urticarial lesion was seen in patient 1 in 3 cc 1/1 dilution, and the rest of the total dosage (1/1 diluted 4.5 cc) was given after adrenalin injection. Patient 2 had 39°C fever after the completion of the desensitization and fever regressed with paracetamol treatment. Patient 3 had headache, 38.7°C fever, and

Table 2 Characteristics of patients

	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI	Patient VII	Patient VIII
Gender	Female	Male	Male	Male	Male	Male	Female	Male
Age(yr)	12.5	19	15	16.5	7.5	7	10	16
SPT	Non-react	Non-react	Non-react	Non-react	Non-react	Non-react	Non-react	Non-react
Positive control*	7 mm	4 mm	6 mm	6 mm	9 mm	10 mm	9 mm	6 mm
ID (1/1000) test	Non-react	Non-react	10 mm	10 mm	11 mm	11 mm	Non-react	Non-react
ID (1/100) test	8 mm	Non-react					Non-react	10 mm
ID (1/10) test	18 mm	13 mm					11 mm	
Side effects of desensitization	Yes	Yes	Yes	Yes	No	No	No	No
Rabbit ATG exposure	No	No	No	No	Yes (twice)	Yes	Yes	No
h-ATG exposure	No	No	No	No	No	No	No	No

*Positive control was histamine 1 mg/ml; SPT, skin prick test; ID, intradermal.

arthralgia before the last dose of 1/1 dilution (step 17), and for these findings, paracetamol was given. After the complaints regressed, the last dose was given. With last dose (step 18), urticarial lesions appeared on arms and face, which regressed after adrenalin intramuscular injection with antihistamines and dexamethasone. This patient was transferred to intensive care unit for monitoring and h-ATG treatment in the next days which were completed without any reactions. Patient 4 developed arthralgia 7 days after the end of treatment.

Although the urticarial lesions were accepted as allergic reactions, headache, fever, and arthralgia which were mostly seen during or at the end of full dosage phase were accepted as drug side effects.

Prednisolone, cyclosporine A, and G-CSF were started at the same time according to the severe aplastic anemia treatment protocol which is used in our clinic. Only the first day of h-ATG was given by desensitization program in Pediatric Allergy Unit. No other allergic reactions were seen

during the other days of h-ATG treatment which was taken in Pediatric Hematology Unit.

Discussion

Desensitization can be the only choice of treatment in case of drug hypersensitivity without an alternative treatment modality (5). Desensitization should be reserved for selected cases, because it is a risky treatment modality which has a high incidence of anaphylaxis.

Desensitization can be performed to the patients who have an urgent need for therapy or prophylaxis of a disease, when the drug concerned is irreplaceable or more effective than the potential alternatives, the potential benefit outweighs the potential risks, if the previous delayed drug reaction was not severe or life-threatening, and a non-cross-reacting pharmaceutical agent for treatment is not available (5). It is performed by administration of increasing doses of the medication concerned over a short period of time (from several hours to a few days) until the cumulative therapeutic dose is achieved and tolerated (6). The knowledge about the desensitization mechanisms and its molecular targets are limited. Mast cells and basophils are targeted in this duration, and mediators are released during the desensitization as they release mediators during hypersensitivity reactions secondary to drugs (6).

Horse antithymocyte globulin is a heterologous serum. Although mild side effects such as fever, hyperemia, urticaria, bulimia, and arthralgia can be seen frequently, hypotension, non-ischemic chest pain, reversible desaturation, thrombocytopenia, hemolysis, and even life-threatening anaphylaxis may occur rarely (7, 8). Mild anaphylactoid reaction (48%) in the first day of h-ATG is reported (8). Bielory et al. (9) reported that 28 (84.8%) of 33 patients who had given h-ATG had serum disease.

There are limited data on skin testing with sera and immunoglobulins, and definite recommendations on the value and test concentrations are not available (10). Before the first infusion of ATGAM, Pharmacia & Upjohn Company strongly recommends that patients should be tested with an intradermal injection of 0.1 ml of a 1:1000 dilution (5 µg horse IgG) of ATGAM; a reaction of 10 mm and over with a wheal or

Table 3 Characteristics of patients who had reactions during h-ATG desensitization

	Reactions	Step	Treatment of symptoms during desensitization
Patient I	Urticaria	Step 17	Adrenalin IM
Patient II	39°C fever	10 min after the end of treatment	Paracetamol (oral)
Patient III	Headache Arthralgia Fever (38.7°C)	Step 17	Paracetamol IV
Patient III	Urticaria	Step 18	Adrenalin IM, Antihistamines IV, Systemic steroid IV
Patient IV	Arthralgia	7 days after the end of treatment	Paracetamol (oral)

IM, intramuscular, IV, intravenous.

erythema, or both, with or without pseudopod formation and itching or a marked local swelling should be considered an ATG hypersensitivity. In selected cases, their recommendation is ATG desensitization (<http://www.fda.gov.tr>, ATGAM, product information, November 2005). But, as new manufacturer's product information recommendation that patients be tested with an intradermal injection of 0.02 ml of a 1:1000 dilution of ATGAM, a wheal three or more millimetre larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction should the drug be dosed intravenously (Pharmacia & Upjohn Company; ATGAM, product information).

We performed firstly epicutaneous skin prick test for diagnosis of ATG hypersensitivity. As all our patients gave negative results for epicutaneous skin prick test, intradermal skin test was performed by 1/1000 dilution as manufacturer's product information recommendation. It should be noted that the sensitivity and specificity for ATG skin testing have not been fully determined. It is also known that allergic reactions and anaphylaxis have occurred in patients with negative skin tests, so false-negative reactions are possible. At the same time, false-positive reactions are also possible. Because of high frequency of false negativity, as classical guidelines recommended, 1/100 and 1/10 diluted intradermal skin test was performed to the patients whose intradermal skin tests were negative (11). We thought that, 1/10 dilution of ATG was not the irritative dose for intradermal test because of urticarial side effects of desensitization in one of two patients. Bielory et al. reported that skin prick tests were positive in 3 of 36 patients, 57% of the intradermal skin tests were positive in 0.02 ml of 1/1000 (50 µg/ml) titers, 79% of the intradermal skin tests were positive in 1/100 titers, and 96% of intradermal skin tests were positive in 1/10 titers in their study. Bielory et al. reported that false-positive intradermal skin tests could be seen. In Bielory's study, the wheal reaction to 1/1000 dilution of ATG was 1.2 ± 0.3 mm, to 1/100 dilution was 2.6 ± 0.2 mm, and to 1/10 dilution was 4.4 ± 0.2 mm (4). That is why, Bielory recommended epicutaneous skin test. Brooks et al. (12) recommended to perform epicutaneous prick test and to perform 1/1000 diluted 0.02 ml intradermal skin test if epicutaneous skin test is negative. In Millar's study, intradermal skin test was performed with 0.1 ml ATG of 1/1000 dilution. One of Millar's patients whose intradermal test was negative developed severe allergic side effects, so treatment was stopped. When another patient had positive intradermal skin test with 0.1 ml in 1/1000 dilution, the skin test was repeated as Brooks et al. recommended (0.02 ml, 1/1000 dilution) and 10×10 mm wheal considered as positive (13).

Desensitization treatment is a temporary tolerance induction to the drug which causes hypersensitivity reaction (14). Bielory and Millar reported ATG desensitization protocols in the literature (4, 13). Millar used modified Bielory's protocol. There is no other h-ATG desensitization protocol scheme except their protocols. In Bielory's protocol, increasing dosages with 10-min intervals were given intradermally, subcutaneously, and intravenously, respectively, and the total daily dosage was completed as 24 h continuous infusion (4). The

protocol was carried out successfully in one patient and the other patient who used β blocker developed anaphylaxis. Millar et al. (13) used a similar protocol in which higher intradermal and subcutaneous dosages and lower intravenous dosages were administered. They used this protocol in two patients whose intradermal skin test was above 10 mm with the first dosage of 1/1000 diluted 0.1 ml ATG as manufacturer's product information recommended. Desensitization treatment was stopped in one patient who had both asthma and hypertension when he developed anaphylactic reaction in the continuous iv infusion portion. The other patient with rheumatoid arthritis developed hypotension and tachycardia in the continuous iv infusion portion which also necessitated the cessation of treatment. Different from the reported protocols, we gave h-ATG only intravenously in our protocol, and as classical guidelines recommended, increasing concentrations from 1/1000 to 1/100, 1/10, and 1/1 were used in drug desensitization program (6).

Although there is no consensus on the premedication necessity and the drug dosages used for premedication before desensitization, it may inhibit mild drug reactions and it may increase the success rates (6). It is shown that the tolerance to ATG is increased and the allergic reactions (serum disease, etc.) secondary to ATG are decreased by low-dose steroids (methylprednisolone 1 mg/kg/day) (15). Although the usage of antihistamines and steroids before desensitization is not necessary according to some protocols, it can repress the possible immediate allergic reactions (16). As most chemotherapeutic regimens steroids, antihistamines, and proton pump inhibitors are used with the same considerations, steroids and antihistamines can be used in premedication regimens (17–19). As a part of aplastic anemia treatment, prednisolone was given and simple premedication regimen (H1 + H2 antihistamines) was added to steroid (methylprednisolone) treatment.

Bielory et al. administered premedication regimen (prednisone, hydroxyzine vs. ranitidine) to two patients just before desensitization protocol. The protocol was performed in one patient successfully. The other one who used β blocker developed anaphylaxis (4). In Millar's study, one patient who received no premedication developed anaphylactic reaction, while the other patient who received methylprednisolone as part of the bone marrow transplantation protocol developed tachycardia and hypotension (13).

Premedication regimen was given to all our patients before desensitization protocol. There were one systemic reaction (headache, arthralgia, fever, and urticaria), two local reactions, and one late reaction. The cumulative dose of ATG was higher than others in the patient with systemic reaction.

Successful desensitization protocols for several drugs are reported. Drug hypersensitivity desensitization protocols have been developed and are used in patients with allergic reactions to antibiotics (mainly penicillin), insulins, sulfonamides, desferrioxamine, D-penicillamine, tetanus toxoid, heparin, chemotherapeutics, monoclonal antibodies and biologic agents, and many other drugs (6, 18, 20–23). Successful desensitization has been well documented in delayed hypersensitivity reactions with sulfonamide hypersensitivity in patients with HIV positive

and hypersensitivity to antibiotics in patients with cystic fibrosis (6, 17, 24).

The previous studies reported that slow desensitization protocols are more successful than fast desensitization protocols (6). Demoly et al. (25) reported a successful desensitization with 44 patients with HIV positive who are desensitized to trimethoprim sulphamethoxazole which lasted for 6 h, and no adverse reactions were seen in 96% of them. Our protocol was lasted for 8.5 h.

Conclusion

A successful desensitization program with h-ATG in children with aplastic anemia is presented. Even though there is not an exposure before to such high allergy potential heterologous serum before, skin tests should be performed and desensitiza-

tion must be started to patients who are hypersensitized to h-ATG.

As previous studies about ATG desensitization and skin tests reported, the irritative dosage of intradermal test for ATG is not known and false positivity and false negativity can be seen in even 1/1000 dilution. Thus, performing skin prick test and lower dose intradermal test is recommended. Although there is false positivity risk, intradermal skin test should be performed with 1/1000, 1/100, 1/10 dilutions and drug desensitization should be performed as anaphylaxis risk is high in patients with false-negative skin prick test and intradermal test. As the expected effectiveness of the treatment is so great, the desensitization protocol can be carried out safely and effectively with trained staff although allergic reaction risk is always present.

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