








Successful Desensitization in a Patient with Fabry Disease with Agalsidase Beta Anaphylaxis: A Rare Case Report

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ABSTRACT

A 35-year-old man had been diagnosed with Fabry disease ten years ago and was being treated with intravenous agalsidase beta. He was referred to our clinic due to having a history of a severe anaphylactic reaction during infusion of agalsidase beta at the eighth year of treatment on August 4, 2020. He had received agalsidase beta for eight years with premedication without any problem until the last dose when the patient had hypotension (80/60 mmHg) and excessive sweating after taking 0.074% (7 mg) of the total dose. Oxygen saturation measured with a pulse oximeter had been normal (96%). There were no symptoms or signs related to the respiratory or gastrointestinal systems or the skin. This reaction had been interpreted as anaphylaxis, and the infusion had been immediately stopped, and intravenous 1mg/kg methylprednisolone and intramuscular 0,5 mg adrenalin administered rapidly. Subsequently, 1000ml 0.9% NaCl had been given intravenously. His vital signs and symptoms recovered with no other complaints within 15 minutes. According to our clinical assessment, the reaction was an anaphylaxis. Since he had to take enzyme therapy, we decided to apply agalsidase beta infusion with the 12-step, 3-bag desensitization protocol. The patient completed the protocol successfully in 351 minutes, without any hypersensitivity reactions. Consequently, the patient was scheduled to receive agalsidase beta with this desensitization protocol and successfully received the last four doses.

Keywords: Fabry disease, agalsidase beta, desensitization, anaphylaxis

INTRODUCTION

Fabry disease is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the α -galactosidase A gene (α -Gal A), resulting in glycolipid accumulation (mainly globotriaosylceramide or globotriaosylsphingosine). Affected individuals include homozygous males and heterozygous females (carrier) (1,2). The progressive accumulation of glycolipid leads to cellular dysfunctions in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes, resulting in multiorgan failure and premature death. Enzyme replacement therapy (ERT), including agalsidase alpha (Replagal) or agalsidase beta (Fabrazyme), is administered to prevent mortality or morbidity due to this disease at present. A patient who had an

anaphylactic reaction with agalsidase beta and continued to receive regular treatment successfully with the agalsidase beta desensitization protocol is presented in this case report.

CASE

A 35-year-old man diagnosed with Fabry disease ten years ago had been treated with intravenous agalsidase beta. The patient's history revealed that his kidneys and eyes had been affected at the time of the diagnosis, and he had been put on 10 mg/d ramipril and taken agalsidase beta infusion therapy for eight years.

He was referred to our clinic due to having a history of a severe anaphylactic reaction during infusion of agal-

sidase beta at the eighth year of treatment on August 4, 2020. Eight years ago, at the second dose of agalsidase beta infusion, he had experienced a reaction with chills, tremors, and dyspnea. The reaction had been treated, and infusions had continued with oral 32 mg/d methylprednisolone 6 hours before infusion as a premedication every two weeks at the pediatric metabolism clinic. He has received agalsidase beta for eight years with premedication without any problem until the last dose when the patient had hypotension (80/60 mmHg) and excessive sweating after taking 0.074% (7 mg) of the total dose. Oxygen saturation measured with a pulse oximeter had been normal (96%). There had been no symptoms or signs related to the respiratory or gastrointestinal systems or the skin. This reaction had been interpreted as anaphylaxis; the infusion has been immediately stopped, and intravenous 1mg/kg methylprednisolone and intramuscular 0.5 mg adrenalin had been administered rapidly. Subsequently, 1000ml 0.9% NaCl had been given intravenously. On follow-up, the axillary temperature had risen to 37.6 °C, and oral ibuprofen had been given. His vital signs and symptoms had recovered with no other complaints within 15 minutes. The serum tryptase level was not measured during this reaction.

His medical history did not reveal any drug or other allergic reactions. The patient did not take any suspicious medication or food on the reaction day and did not exercise. The laboratory tests were as follows: hemoglobin:12.8 gr/dl, hematocrit: 38.2%, MCV:73.7 fL, RDW: 16.3%, leukocyte:10x10³/μL, neutrophil:7.9x10³/μL, eosinophil:0.1x10³/μL. Liver, kidney, and thyroid function tests; C-reactive protein, and total immunoglobulin E levels were within normal limits. The baseline tryptase level was 2.23 μg/L. Skin prick and intradermal tests with agalsidase beta were not performed since the time interval was only two weeks after the anaphylaxis. According to our clinical assessment, the reaction was an anaphylaxis. At that time, there was no alternative agalsidase drug on the market in Turkey, and since he had to take enzyme therapy, we decided to apply agalsidase beta infusion with the 12-step, 3-bag desensitization protocol (Table I) recommended by Castells (3). Six hours before the procedure, premedication with oral 32 mg methylprednisolone, 50 mg ranitidine, and 50 mg hydroxyzine was given (4,5). The starting dose was 0.0095 mg (0.01% of the total dose) of agalsidase beta, and doses were doubled every 15 minutes. The patient completed the protocol successfully in 351 minutes, without any hypersensitivity reactions. Con-

sequently, the patient was scheduled to receive agalsidase beta with this desensitization protocol and successfully received the last four doses.

DISCUSSION

According to the current literature, the ERT administered in Fabry disease successfully diminishes symptoms and prevents late complications. It has been reported that ERT provides clinical stabilization for up to 10 years in these patients. Therefore, it is advised to continue giving ERT (6,7). Intravenous 1mg/kg agalsidase beta is given in 4 hours biweekly doses to these patients.

As far as we know, only two reported cases in the literature have received agalsidase beta infusion successfully with the desensitization protocol after an anaphylaxis (8,9). Ours is the third in the world, and the first case reported from Turkey.

DuBuske et al. tried to show that agalsidase beta specific IgE could be decreased if Rituximab and 3-bag desensitization were used for the patient who had suffered

Table I: Protocol for intravenous desensitization with agalsidase beta.

Step	Solution	Rate, mL/h	Time, min	Amount, mL	Cumulative dose, mg
1	1	5	15	1.25	0.01187
2		10	15	2.5	0.03562
3		20	15	5	0.08407
4		40	15	10	0.17812
5	2	5	15	1.25	0.29687
6		10	15	2.5	0.53437
7		20	15	5	1.00937
8		40	15	10	1.95937
9	3	10	15	2.5	4.33437
10		20	15	5	9.08437
11		40	15	10	18.5843
12		75	186	296	95.0000

Target dose: 95 mg agalsidase beta

Volume: 250 mL of normal saline solution (SS)

Solutions: Solution 3: 95 mg agalsidase beta in 250 mL SS,

Solution 2: 225 mL SS + 25 mL solution 3,

Solution 1: 225 mL SS + 25 mL solution 1

Premedication: Methylprednisolone/ Ranitidine/Hydroxyzine (6 h before desensitization)

Total time: 351 minutes

anaphylaxis with agalsidase beta (8). However, the patient had pruritic hives again as before. Then, subcutaneous 300 mg omalizumab was administered with the 3-bag desensitization protocol. The patient tolerated the total dose of agalsidase beta without any hypersensitivity reaction. In their report, both the skin prick and the intradermal tests were positive, in addition to the presence of agalsidase beta specific IgE and IgG.

Talreja et al. reported a case who received the drug with premedication (25 mg of intravenous diphenhydramine, 20 mg of oral famotidine 20 minutes before agalsidase beta infusion) and the 12-step desensitization protocol (9). The patient's skin prick and intradermal tests and agalsidase beta specific IgE were positive. We could not perform skin tests in our case due to the short time interval between the test and the reaction.

Agalsidase beta can cause many adverse events. The most common adverse events with agalsidase beta therapy are mild to moderate infusion-associated reactions (IAR) including rigors, fever, nausea, vomiting, headache, tremor, dyspnea, somnolence, and chest pain (10). IARs can occur due to neutralizing antibodies (9,11). The rate of antibodies is 40% in males, and they cause the treatment to be ineffective. The risk of IARs appears to be higher in some patients whose agalsidase beta-specific IgG levels are high (12,13). Smid et al. noticed that most ERT-related reactions have appeared in the first 13 infusions (13). Neutralizing antibodies are encountered in 73% of the patients treated with agalsidase beta (14). Notably, in Bodensteiner's study, the six patients were male with very low or undetectable endogenous α -Gal activity levels, and all developed IgG antibodies (15). During clinical trials, it has been observed that IARs occurred more often in patients who were IgG-positive, and that the frequency and severity of IARs diminished over time in most patients due to infusion rate optimization, preinfusion medication, and increased tolerance to the exogenous protein since antibody titers often decline with time (16-18). Targeted immunosuppressive therapies can be considered if the level of neutralizing antibodies reaches saturation. A specific protein bound to antibodies is promising for the future (7).

Hypersensitivity reactions due to agalsidase beta therapy have been reported to be rare. Although some immediate reactions such as anaphylactic shock have been reported, IgE-mediated immune mechanisms have rarely been shown with positive skin tests (14). We can-

not be sure whether this immediate reaction was due to an IgE-mediated mechanism or nonimmunological mast cell degranulation as the underlying mechanism. It was interesting that the patient had experienced an IAR eight years ago, and he had been taking the treatment with premedication until July 2020 without any problems. Later he had anaphylaxis. In addition, there was no culprit drug or sustained or documented infection to diminish the agalsidase beta tolerance in his medical history. We could not precisely define the reason of the breaking point. Most likely, it could be described as an early-type hypersensitivity reaction.

In conclusion, our patient was the first case reported from Turkey and the third one in the world. The desensitization protocol worked well and can therefore be recommended for cases of immediate hypersensitivity reactions to agalsidase beta. He continues to receive biweekly agalsidase beta infusions successfully with premedication and desensitization.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Authorship Contributions

Concept: **Gülseren Tuncay, Ozge Can Bostan, Mehmet Erdem Cakmak**, Design: **Gülseren Tuncay, Ozge Can Bostan, Mehmet Erdem Cakmak, Saltuk Bugra Kaya**, Data collection or processing: **Gülseren Tuncay, Ozge Can Bostan, Mehmet Erdem Cakmak, Saltuk Bugra Kaya**, Analysis or interpretation: **Gülseren Tuncay, Ebru Damadoglu, Gül Karakaya, Ali Fuat Kalyoncu**, Literature search: **Gülseren Tuncay, Ozge Can Bostan, Ebru Damadoglu, Gül Karakaya, Ali Fuat Kalyoncu**, Writing: **Gülseren Tuncay, Ozge Can Bostan, Ebru Damadoglu, Gül Karakaya, Ali Fuat Kalyoncu**, Approval: **Gülseren Tuncay, Ozge Can Bostan, Mehmet Erdem Cakmak, Saltuk Bugra Kaya, Ebru Damadoglu, Gül Karakaya, Ali Fuat Kalyoncu**.

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