A 1-Bag/4-Step Rapid Desensitization Protocol to Reintroduce Agalsidase α in a Patient With Fabry Disease

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Fabry disease is an X-linked inherited lysosomal storage disorder caused by inborn mutations of the galactosidase gene that leads to deficiency of the enzyme α-galactosidase A [1]. This deficiency in turn results in the accumulation of globotriaosylceramide and other neutral glycolipids, which triggers inflammation and fibrosis of the skin, kidney, nervous system, and heart [2].

Enzyme replacement therapy (ERT) with agalsidase α (Aα), agalsidase ß (Aß), pegunigalsidase α, or migalastat (an oral therapy indicated in the presence of amenable mutations) is an effective treatment for Fabry disease. In the absence of such therapy, both the quality of life and life expectancy of affected individuals are severely compromised [2].

Approximately 14%, 67%, and 21% of patients receiving ERT with Aα, Aß, or pegunigalsidase α, respectively, may experience reactions during routine treatment. IgE-mediated reactions have been reported with Aα but not Aß [2].

Rapid drug desensitization (RDD) has proven effective in reintroducing drugs that have elicited an allergic

Table. Rapid Drug Desensitization Protocol With Agalsidase α.

Step	Rate, mL/h	Time, min	Volume infused per step, mL	Dose administered in this step, mg	Cumulative dose administered in this step, mg
1	10	15	2.5	0.36	0.36
2	20	15	5	0.72	1.08
3	40	15	10	1.44	2.52
4	80	61.9	82.5	11.88	14.4
Target dose, 14.4 mg					
Standard volume per bag, 100 mL					
Final rate of infusion, 80 mL/h					
Calculated target concentration, 0.144 mg/mL					
Standard time of infusion, 106.9 min					

reaction, enabling patients to continue treatment despite being allergic [3]. Phenotypes of reactions amenable to desensitization include type 1 (IgE and non–IgE-mediated reactions, including anaphylaxis), nonsevere delayed type IV T cell–mediated reactions, cytokine release reactions, and mixed reactions [4].

The basic principle of RDD protocols involves reintroducing the drug at suboptimal doses and doubling it at each step within a time period typically lasting 10-15 minutes [3]. To our knowledge, this is the first report of successful reintroduction of Aα following an immediate drug hypersensitivity reaction (DHR) using a 1-bag/4-step desensitization protocol [5].

The patient was a 26-year-old man diagnosed during family screening with Fabry disease due to a hemizygous GLA p.Cys63Ser mutation. Migalastat was not indicated. He was asymptomatic at diagnosis and began treatment following current treatment guidelines with recombinant Aα at a dose of 14.4 mg (0.2 mg/kg) every 2 weeks [6]. He tolerated the initial 4 doses well. However, with the fifth dose, he developed generalized pruritus and urticaria 60 minutes after the infusion began (50 mL/h). The infusion was interrupted, and he received intravenous (IV) methylprednisolone 80 mg and dexchlorpheniramine 5 mg, with resolution of symptoms after 1 hour. Tryptase levels taken 40 minutes after the reaction showed a nonsignificant increase to 7.2 µg/L from a baseline of 4.4 µg/L. The severity of the reaction was classified according to the Brown scale as grade 1 and according to clinical characteristics as phenotype 1 [7]. The patient gave his consent for this case report to be published.

An allergology study including prick test with Aα (1 mg/mL) and intradermal testing at increasing concentrations from 1/100 to full strength (1/1 dilution) yielded negative results. No response was recorded for the negative control, and a wheal measuring 5 mm in diameter was observed with histamine (0.1 mg/mL) used as a positive control.

Serum antibody analysis for Aα assessed using enzyme-linked immunosorbent assay revealed the presence of IgG antibodies (mean [SD], 1067.33 [41.60] µg/mL, lower cut-off of 42.98 [2.61] µg/mL and upper cut-off of 5055.41 [345.69] µg/mL), but not IgE (cut-off, 0.35 kU_A/L).

The patient underwent a drug challenge test with Aα. The result was positive, with immediate reappearance of pruritus and urticaria, which resolved rapidly with IV dexchlorpheniramine 5 mg.

In order to safely reintroduce Aα, a desensitization protocol adopted from the Brigham and Women's Hospital Drug Hypersensitivity and Desensitization Center [5] was recommended. This consisted of a 1-bag/4-step protocol (Table; Supplementary figure S1), with oral premedication (cetirizine 10 mg and famotidine 40 mg) administered 30 minutes before the procedure. No breakthrough reactions were observed during or after the protocol.

After 4 successful desensitizations, the final rate was increased to 120 mL/h. The patient received 38 treatment cycles with no further symptoms.

We demonstrated that the 1-bag/4-step RDD protocol is safe and effective for reintroducing Aα and continuing ERT in a patient with Fabry disease who had developed a grade 1 hypersensitivity reaction in the presence of circulating IgG and absence of IgE.

Aα and Aß share common antigenic determinants, with IgG antibodies to Aα and Aß present in around 55% and 80% of treated individuals, respectively. While IgE antibodies to Aα have not been documented, the presence of IgG to both isozymes indicates cross-reactivity between the 2 drugs [8].

These antibodies might impact the therapeutic response and treatment outcomes by reducing enzyme activity and increasing the number of infusion reactions [8]. In addition, the presence of IgE could lead to anaphylaxis with Aß, reported in 1% of patients undergoing replacement therapy with this enzyme, but not observed in patients receiving Aα. Furthermore, IgE antibodies against Aß have been linked to skin test reactivity [8].

The literature regarding desensitization with agalsidase is limited, focusing primarily on Aß, owing to the common practice of switching treatment to Aß after hypersensitivity reactions with Aα [9].

We demonstrated that as with other drugs [5], this 1-bag/4-step RDD protocol, which follows the basic principles of desensitization, can facilitate temporary tolerance to the drug.

Reactions to these enzymes diminish in frequency and severity over time as patients develop increased tolerance to the exogenous protein owing to declining antibody titers [10].

However, reintroduction of the drug by RDD may improve safety and induce the changes discussed above more quickly.

A 1-bag/4-step desensitization protocol would be recommended for patients at low risk of developing DHRs during desensitization, especially those with non–IgE-mediated DHRs, no evidence of mast cell release, mild cytokine release reactions, and no comorbidities that increase the risk of breakthrough reactions [7]. Once tolerance to a final infusion rate of 80 mL/h is established, gradual increases can be made while monitoring for tolerance to these adjustments (Supplementary figure S1). This approach can avoid the need to switch to Aß, minimize IgE-mediated sensitization, and prevent the risk of anaphylaxis.

In summary, the clinical case presented describes the successful reintroduction and continuation of treatment in a patient with Fabry disease following a grade 1 (non–IgE-mediated) DHR through desensitization to Aα using personalized premedication and a 1-bag/4-step RDD protocol.

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Conflicts of Interest

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