



Letters

Successful desensitization of a patient with Fabry disease with agalsidase beta (Fabrazyme) anaphylaxis after omalizumab pretreatment

Fabry disease is a rare lysosomal storage X-linked genetic disorder caused by pathogenic variants in the α -galactosidase A gene (α -Gal A) resulting in glycolipid accumulation (mainly globotriaosylceramide or globotriaosylsphingosine) within cell lysosomes. Of note, 2 Fabry disease phenotypes in men include a severe form (1:22,570 men) characterized by a reduction in α -Gal A activity and accumulation of globotriaosylceramide in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes, resulting in progressive multiorgan failure and premature death and a milder form (1:1390 men) that develops later in life and is associated with varying levels of α -Gal A activity.^{1,2}

Multiple mutations have been reported for the α -galactosidase gene that encodes α -Gal A on the X chromosome.³ However, for both phenotypes, severe localized and systemic inflammation occurs after glycolipids bind to the toll-like receptor 4, are processed, and, then, presented to the T-cell receptors on invariant natural killer T cells (CD1d-restricted T cells) capable of rapidly responding to the lipid antigenic stimulation with release of proinflammatory cytokines (interleukin-1 β , tumor necrosis factor- α , and interleukin-6).⁴

Notably, 2 intravenous enzyme replacement therapies, agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme), administered every 2 weeks have been found to slow disease progression and improve patient outcomes, especially if started early in life before organ damage.⁵ Agalsidase beta has been reported to be sensitizing, as confirmed by positive skin prick or allergen-specific immunoglobulin E (sIgE) test results, which resulted in approximately 1% of individuals who experienced allergic reactions to receive replacement therapy.⁶ Most patients with Fabry disease who previously experienced anaphylaxis have been successfully managed with premedication alone or with recombinant agalsidase beta desensitization.^{7,8} Here, we report a case of a patient with adult-onset Fabry disease who developed anaphylaxis to agalsidase beta (Fabrazyme) but failed routine premedication and 3-bag desensitization until omalizumab pretreatment.

A 38-year-old man who was diagnosed as having Fabry disease at the age of 32 years with a history of a severe anaphylactic reaction owing to agalsidase beta infusion presented for an allergy consultation on August 8, 2012. He had been receiving Fabrazyme infusions (75 mg; 1 mg/kg $\times$ 75 kg) every 2 weeks for 5 years without problems until June 22, 2012, when he developed his first anaphylactic reaction. Before this event, he began missing doses or

getting half doses of Fabrazyme (32.5 mg) owing to a nationwide medication shortage. However, 3 months (May 8, 2012) before his initial presentation, he again started receiving the full 75 mg dose of Fabrazyme intravenously every 2 weeks. After approximately 6 weeks (June 22, 2012) of treatments, he developed diffuse hives, lip numbness, scratchy throat, itching, and shortness of breath beginning midway through the infusion, which required discontinuation and treatment with epinephrine (0.3 cm³, 1:1000 intramuscularly), diphenhydramine (100 mg intravenously), and oral prednisone. Approximately 3 weeks (July 18, 2012) after, another Fabrazyme infusion was attempted despite the previous reaction history, and a similar reaction occurred midway through the infusion, which required discontinuation and similar treatment. In the subsequent infusion, a similar reaction occurred despite pretreatment with intravenous diphenhydramine 50 mg and oral acetaminophen 650 mg and a decreased infusion rate. Each reaction occurred after he received 35 mg of Fabrazyme and got progressively worse with severe diffuse hives, chest tightness then associated with audible wheezing, and throat tightness.

During the allergy consultation, spirometry was obtained, revealing a forced expiratory volume in 1 second of 2.95 L (66% predicted) with 12% improvement in postbronchodilators to 3.3 L (78% predicted), consistent with reversible airflow obstruction; his fractional exhaled nitric oxide was elevated at 37 parts per billion (normal, <25 parts per billion). His total IgE was 30.5 KU/L, and aeroallergen sIgE test results were negative. His baseline tryptase level was 4.2 ng/mL. Skin prick testing to undiluted Fabrazyme revealed a 3 mm wheal/9 mm flare reaction. Intracutaneous testing using weight/volume (w/v) dilutions to Fabrazyme revealed an incremental increase in positive skin test reactions (1:100,000 w/v, 5 mm wheal/8 mm flare; 1:10,000 w/v, 9 mm wheal/12 mm flare; 1:1000 w/v, 9 mm wheal/15 mm flare). An enzyme-linked immunosorbent assay, performed following the manufacturer (Sanofi-Genzyme, Cambridge, Massachusetts), for Fabrazyme serum sIgE (no titers provided) and Fabrazyme sIgG (at a 1:6400 titer) was reported to be positive. In Fabrazyme clinical trials, up to 89% of treated patients developed high nonneutralizing sIgG titers within the first 3 months of exposure. These antibodies persist over time but may fluctuate up or down within different individuals. The patient's asthma was treated with a high-dose inhaled glucocorticoid/long-acting beta-agonist combination.

After 1 month, a 3-bag desensitization protocol was attempted with oral glucocorticoids, H1/H2 antagonists, and leukotriene receptor antagonist pretreatment resulting in diffuse hives, severe total body pruritus, and throat tightness after reaching 30 mg of Fabrazyme. Serum tryptase, drawn within 1 hour, was reported to be normal.⁹

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After further discussion, rituximab was initiated to reduce or eliminate B lymphocyte-producing Fabrazyme sIgE before Fabrazyme desensitization because it had previously been successfully used for a severe insulin allergic reaction in conjunction with omalizumab.¹⁰ After the patient received 6 rituximab infusions, a 3-bag desensitization was performed resulting in severe pruritic hives after 16 mg of Fabrazyme. Again, the serum tryptase level did not increase.

Subsequently, omalizumab was initiated on the basis of the severe insulin allergy case report.¹⁰ After receiving 5 monthly omalizumab 300 mg subcutaneous injections, a 3-bag desensitization protocol was performed that allowed him to tolerate the full 75 mg Fabrazyme dose without allergic manifestations. He continued receiving biweekly Fabrazyme infusions with monthly omalizumab for 6 months followed by bimonthly injections. A subsequent weight-based adjustment of Fabrazyme to 90 mg was also well tolerated, and he continues to do well with slowed disease progression.

This case represents an index report of a patient with Fabry disease, sensitized to Fabrazyme, who tolerated a 3-bag desensitization protocol only after omalizumab pretreatment. An attempt to induce tolerance to Fabrazyme with rituximab was unsuccessful, which may be related to its inability to remove memory B cells.¹¹ Conversely, omalizumab may have been successful owing to the blocking of circulating Fabrazyme sIgE antibody and down-regulation of high-affinity IgE Fc epsilon receptor 1 expression on mast cells and basophils. Omalizumab has previously been reported effective for suppressing anaphylactic reactions during aeroallergen, venom, or food immunotherapy, desensitization to aspirin, nonsteroidal anti-inflammatory drugs, insulin, progesterone, and carboplatin. Further investigation is required to better understand the mechanisms of omalizumab as pretreatment for attenuating or preventing severe allergic drug reactions. This case adds to the existing literature by supporting omalizumab use as a pretreatment strategy for the management of severe allergic drug or biologic reactions.

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