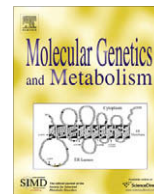




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Brief Communication

Desensitization of an adult patient with Pompe disease and a history of anaphylaxis to alglucosidase alfa[☆]Shawn E. Lipinski^{a,*}, Michael J. Lipinski^b, Autumn Burnette^c, Thomas A. Platts-Mills^c, William G. Wilson^a^a Division of Medical Genetics, Department of Pediatrics, University of Virginia Health System, Charlottesville, VA, USA^b Department of Internal Medicine, University of Virginia Health System, Charlottesville, VA, USA^c Asthma and Allergic Diseases Center, University of Virginia Health System, Charlottesville, VA, USA

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ABSTRACT

We report on the successful desensitization of an adult female with Pompe disease who had previously experienced anaphylaxis to intravenous alglucosidase alfa therapy. The starting alglucosidase alfa dose for desensitization was 10 mg/kg with gradual dose escalation and desensitization via serial dilution was completed over five infusions. This methodology serves as a means to desensitize patients with prior anaphylactic response to alglucosidase alfa so that enzyme replacement therapy can be utilized.

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Introduction

Pompe disease, also termed glycogen storage disease type II or acid maltase deficiency, is a rare autosomal recessive lysosomal storage disorder caused by a total or partial deficiency of the enzyme acid alfa-glucosidase (GAA). The enzymatic defect results in lysosomal glycogen accumulation in multiple tissues, most notably in cardiac and skeletal muscle. The disease can range from a severe lethal form in infants to a later onset progressive disorder in adults resulting in significant morbidity and eventually death. The adult (late onset) form is characterized by progressive proximal muscle weakness and respiratory insufficiency, with greater variation in age of symptom onset (childhood to adulthood), clinical presentation, and disease progression with death usually resulting from respiratory failure [1].

Alglucosidase alfa (Myozyme[®]; Genzyme Corporation, Cambridge, MA, USA) was approved by the FDA in 2006 and is currently the only available pharmacologic treatment for Pompe disease. While treatment with enzyme replacement therapy may improve quality of life and survival [2,3], severe allergic reaction to alglu-

cosidase alfa may prevent patients from receiving potentially beneficial therapy.

Patient history

Our patient was diagnosed with Pompe disease at 28 years of age after noticing muscle weakness following limited exertion. Family history was negative for muscle or neurological disease. Neurological evaluation demonstrated significant insertional activity and early recruitment on electromyography and serum creatine kinase was elevated at 1359 U/L. Muscle biopsy and skin biopsy with enzyme analysis confirmed the diagnosis of Pompe disease with normal glycogen content and low alfa-glucosidase activity. Molecular testing was performed prior to the patient entering an alglucosidase alfa clinical trial and two deleterious alleles in the GAA gene were reportedly identified; the results of which are not available. She also has a history of hypothyroidism (now on thyroid replacement therapy), psoriasis, psoriatic arthritis, migraines, and a latex allergy.

There was no therapy for Pompe disease when she was diagnosed. She was enrolled in a clinical trial for ERT with alglucosidase alfa (study AGLU02704) in 2006 but her initial infusion was complicated by urticaria. A second infusion, given twelve days later, was complicated by headache, throat fullness, facial flushing, urticaria, chest tightness, wheezing and mild oxygen desaturation, resulting in her discharge from the clinical trial. She presented to

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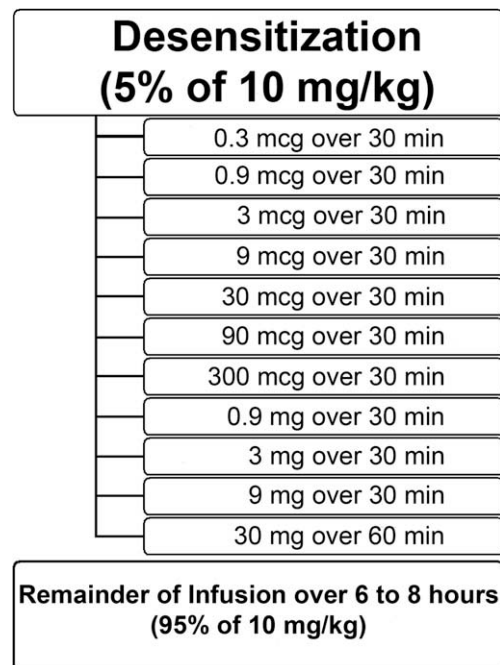


Fig. 1. Schematic for alglucosidase alfa desensitization and infusion for an 85 kg patient who would receive a total infusion of 850 mg (10 mg/kg). During the desensitization, the initial 5% of the dosage is infused in slowly increasing amounts over a long duration of time. The final 95% of the dosage is infused over a 6–8 h period following the initial desensitization for a total infusion time of 12–14 h. Dose should be adjusted accordingly for patient weight.

our Genetics Clinic one year later with symptoms of progressive muscle weakness and sleep apnea and wished to attempt enzyme replacement therapy again, since alglucosidase alfa had been subsequently FDA-approved.

After reviewing risks of therapy, the patient was electively admitted to the Medical Intensive Care Unit for administration of alglucosidase alfa therapy. The patient's treatment protocol was modified from the recommended 20 mg/kg dose given once every two weeks to 10 mg/kg given weekly. The starting dose for desensitization was 10 mg/kg, serially diluted with an initial dilution of 1/10,000, and administered incrementally, with increasing concentrations every 30 min (Fig. 1). Thus, the patient was desensitized with 5% of the 10 mg/kg dose over the first 6 h with the remaining 95% given over the next 6–8 h. The first four infusions were given one week apart, and infusions five and six were successfully tolerated two weeks apart. Except for infusion four, immunoglobulin E (IgE) antibody

status was assessed prior to each infusion by a product-specific ELISA test, performed by the Genzyme Corporation Clinical Specialty Laboratory. Immunoglobulin G (IgG) antibody status was assessed prior to each infusion. A numerical titer value is given when antibody status is found to be positive. Serial dilution skin testing and intradermal testing were performed prior to infusions, which consisted of skin prick testing with 1:1000 and 1:100 followed by intradermal testing with 1:1000, 1:100, and 1:10.

The first three infusions were accompanied by urticaria, facial flushing, and chest tightness, requiring treatment with diphenhydramine, albuterol, famotidine, IV solumedrol, and epinephrine. Alglucosidase alfa was increased to 20 mg/kg for the next six infusions, but the patient developed hives on infusion nine. Because of concern for continued allergic reactions in the outpatient setting, the 10 mg/kg weekly schedule was resumed. IgE antibody to alglucosidase alfa was positive prior to the first infusion and negative prior to the second infusion. Immunoglobulin G antibody titers to alglucosidase alfa increased from 800 to 1600. All skin prick tests were negative. For skin testing #1–5, histamine control results (wheal only) were as follows: 5 × 5, 6 × 10, 5 × 7, 6 × 5, and 7 × 7 mm. Serial dilution skin testing revealed negative skin prick testing and a 7 × 8 mm wheal (1:100 dilution) on intradermal testing. Table 1 includes IgE levels, IgG levels, skin prick testing, allergic reactions during desensitization/infusion, and management for reactions. Complement testing was negative and tryptase levels were 6.04 and 5.4 µg/L on weeks #9 and #38, respectively.

Discussion

In a recently published clinical trial, 95% of patients treated with alglucosidase alfa were positive for IgG antibodies to alglucosidase alfa [3]. Most pediatric patients develop antibodies in the first three months of therapy. Interestingly, the trial also demonstrated that 52% of the patients experienced infusion-associated reactions [3]. In clinical trials and postmarketing safety experience with alglucosidase alfa, approximately 1% of patients developed anaphylactic shock and/or cardiac arrest during alglucosidase alfa infusion that required life-support measures while approximately 14% of patients treated with alglucosidase alfa have developed significant allergic reactions (<http://www.myozyme.com>). Despite previous anaphylaxis, our patient was able to tolerate desensitization to alglucosidase alfa with only minor reactions, and was able to reach full dosing. She continues on her weekly treatment regimen and now receives premedication of diphenhydramine and prednisone as she occasionally develops mild urticaria. Because of the history of anaphylaxis in our patient, there was concern that

Table 1
Results for IgE and IgG antibody titers, skin testing, and reactions following desensitization and infusion of alglucosidase alfa. A positive immunoglobulin result is denoted by + and negative is denoted by – and titer levels are presented in parentheses. W/F is short for wheal and flare.

Infusion #	Dose (mg/kg)	IgE Ab to alglucosidase alfa	IgG Ab to alglucosidase alfa (titers)	Intradermal skin testing results	Reactions during infusion	Management for reactions
1	10	+	+(800)	1:100 7 × 8 mm W/F	Facial flushing, few hives, chest tightness	Benadryl, albuterol, famotidine, solumedrol
2	10	–	+(1600)	1:10 7 × 9 mm W/F	Few hives, shortness of breath, decreased peak expiratory flow	Benadryl, albuterol, solumedrol, epinephrine IM injection
3	10	–	+(1600)	1:10 3 × 3 mm W/F	Single hive on left knee	Benadryl
4	20	n/a	+(1600)	1:10 3 × 3 mm W/F	None	n/a
5	20	–	+(1600)	1:100 6 × 6 mm W/F	None	n/a
6	20	–	+(800)	n/a	None	n/a
7	20	–	+(1600)	n/a	Hives, chest tightness	Benadryl

she might not be a candidate for ERT. Desensitization to the recombinant enzyme has been successful for her, and has allowed treatment to proceed. Other therapeutic modalities such as chaperone therapy are under study that might be of use in patients who cannot be treated with ERT [4]. The method which we describe to desensitize patients with a prior anaphylactic response to alglucosidase alfa may enable initiation of therapy that may be vital in reducing morbidity and mortality in this disease.

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