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An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reactions to alglucosidase alfa infusions

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Abstract

Purpose—Pompe disease (PD) is a progressive metabolic myopathy for which the only available treatment is alglucosidase alfa (Myozyme®). Enzyme replacement therapy (ERT) has improved ventilator-free survival, and cardiac and motor functions in patients with infantile PD. However, for an adequate response to occur, a large amount of enzymes must be infused. In some patients, this may be problematic due to infusion-associated reactions (IARs) occurring in approximately 50% of patients receiving alglucosidase alfa infusions. Whilst the majority of these reactions are mild, life threatening hypersensitivity reactions may occur in some patients. In these patients desensitization is indicated to enable continued ERT safely. Infants and young children with PD and significant infusion reactions pose unique management challenges because of their young age, limited communication skills, variable presentation and underlying cardiomyopathy.

Methods/subjects—In 2 patients with PD who experienced significant ERT-related reactions: an infant (IgE positive) and a young child (IgE negative), we implemented a desensitization protocol, that started by administering a reduced dose of alglucosidase alfa (10 mg/kg weekly) instead of the standard (20 mg/kg biweekly) using serial micro-dilutions that were individually prepared and delivered in a highly regulated manner based on patients' clinical manifestations and tolerance.

Results—Successful desensitization was achieved in both patients, allowing them to eventually continue to receive the full dose of ERT safely.

Conclusion—Therapeutic demands in infants and young children with PD need to be tailored according to the patient presentation, and underlying cardiac and fluid-volume status. Desensitization allowed both patients to continue alglucosidase alfa treatment at the recommended dose without prolonged interruption of therapy, or further reactions.

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Keywords

Alglucosidase alfa; Infantile Pompe disease; Hypersensitivity reactions; Desensitization

1. Introduction

Pompe disease (PD) is a lysosomal storage disorder (LSD) caused by defficiency of lysosomal acid alpha glucosidase (GAA) [1]. Alglucosidase alfa (Myozyme®, Lumizyme®, Genzyme Corporation, Cambridge, MA) is the only available enzyme replacement therapy that has been approved for treatment of PD. The standard recommended dose is 20 mg/kg every 2 weeks [2], some infants have required doses up to 40 mg/kg every 2 weeks (PSK personal experience). Infants with PD who have been treated with alglucosidase alfa showed improved longevity, ventilator-free survival, cardiomyopathy and motor functions [3–5]. However, as is the case with other forms of protein based therapy [6–10], infusion of alglucosidase alfa has been associated with reactions (IARs) of variable severity. This has been underscored in the boxed warning included in the prescription package of alglucosidase alfa where IARs reportedly occur in 51% of patients on ERT [2]. Clinical trials and post-marketing safety studies showed that 1% of patients treated with alglucosidase alfa developed anaphylactic shock and/or cardiac arrest that required life-support measures, and 14% developed allergic reactions that involved at least 2 of 3 body systems [2]. In infants and young children with PD, IARs generally are mild, producing non-specific symptoms, such as headache, dizziness, nausea, vomiting, fatigue, sweating, and pruritis during or after treatment. Severe or significant hypersensitivity reactions range from limited reactions such as generalized hives to more severe, multi-systemic reactions that may include cardiac (e.g., hypotension, tachycardia), respiratory (e.g., bronchospasm, dyspnea, laryngeal edema), cutaneous (e.g. rash, urticaria, angioedema) and/or gastrointestinal (e.g., abdominal pain or cramping, vomiting) manifestations. Hypersensitivity reactions are usually but not always IgE-mediated, while IARs are non-immune mediated and are IgE-negative [11]. General measures against anaphylactic reactions including premedication with antihistamines, antipyretics, and/or corticosteroids, short interruption of the infusion and slowed infusion rates have been successful in the management of IARs in patients receiving ERT due to other LSDs [12–14]. However, when these measures fail to prevent severe/recurrent reactions, desensitization is indicated and has allowed a child with Gaucher disease [15] and an adult with late onset Pompe disease to continue ERT [16]. Desensitization protocols in infants and young children with PD require vigilance to special considerations such as the need for administration of a large amount of protein for clinical benefits to occur, and the restricted amount of fluid intake allowed due to underlying cardiomyopathy. We present herein, the clinical presentation and management details of 2 patients with early onset PD who have undergone successful desensitization to alglucosidase alfa after individualized modifications were made to the standard protocol. The first patient had infantile PD and was IgE-positive; the second patient had severe juvenile-onset PD and was IgE-negative. After desensitization, both patients continued to receive alglucosidase alfa at the standard dose of 20 mg/kg every 2 weeks without suffering from further reactions.

2. Subjects/methods and results

2.1. Case 1: child with infantile PD and IgE-positive and recurrent, severe reactions

A 5 year old male child was prenatally diagnosed with infantile PD after the death of an affected older sibling. Post-natal enzyme studies on dried blood spots and skin fibroblasts showed markedly reduced GAA activity and positive cross reactive immunologic material (CRIM) on Western blot. Cardiac assessment 5 days after birth revealed mild concentric left

ventricular hypertrophy with normal left ventricular function. The standard dose of alglucosidase alfa infusion (20 mg/kg every other week) was started at 15 days of life. On treatment, the child showed increased vigor in his extremities, and progressive motor development. ERT was administered without incident until infusion 8 when the patient suffered from recurrent episodes of mild urticaria. The vital signs remained stable, but the child became more irritable and agitated with each infusion, and the urticarial eruptions continued to occur, despite reduction of the infusion rate, temporary interruption of the infusion, and pretreatment with diphenhydramine. These reactions continued through infusion 11 while the child was receiving the lowest recommended rate of alglucosidase alfa (1 mg/kg/h). After infusion 12, testing for alglucosidase alfa specific IgE antibodies was positive. Accordingly, pretreatment with an antihistamine was discontinued to avoid masking manifestations of anaphylaxis. Other tests showed a low IgG antibody titer (1:200), no complement activation, but serum tryptase was elevated. During infusions 12–18, the rash became increasingly more generalized, involving both the trunk and extremities. Due to the progressive nature of these recurrent reactions, positive Ig E status, and inadequate responsiveness to general measures against anaphylaxis, the patient was considered at high risk for a systemic hypersensitivity reaction. After discussing the benefits and risks of desensitization with the parents, a consent was obtained. At infusion 19, the patient was started on a desensitization protocol using micro-dilutions after reducing the dose of alglucosidase alfa to 10 mg/kg, weekly, instead of the standard recommended dose of 20 mg/kg every 2 weeks (Table 1). During desensitization, the patient experienced flushing, urticarial, and macular rashes 20 min after starting the 0.5 mg/kg/h infusion rate. This reaction was treated by reducing the infusion time, giving diphenhydramine, and stopping the infusion until the rash resolved and the patient was hemodynamically stable. The infusion was restarted at half the dose the patient was receiving at the time of the reaction (i.e. 0.25 mg/kg/h); and slowly increased to the full dose as tolerated. The patient continued to receive the next six infusions (19–24) weekly at a slower ramp up dose to that which caused a significant reaction. After two successive infusions with no reactions, the child was given the standard dose of alglucosidase alfa (20 mg/kg for every other week) in gradually increasing concentrations, administered cautiously as micro-dilutions (Table 1). He is currently receiving the standard dose of alglucosidase alfa (20 mg/kg bi-weekly) without the use of micro-dilutions over a period of 3.7 h with no reactions. The child is able to climb, run and his echo and electrocardiograms have remained normal.

2.2. Case 2: child with severe IgE-negative infusion-associated reactions

A 6 year old male child was diagnosed with severe juvenile onset PD at the age of 3.5 years. During infancy, he had delayed gross motor milestones. At 18 months, he was able to walk until he developed progressive muscle weakness and was no longer able to ambulate or sit up. This was followed by respiratory insufficiency necessitating tracheostomy and ventilator support. Echocardiograms and electrocardiograms were normal. The diagnosis of PD was made after muscle biopsy showed extensive vacuolization with glycogen accumulation, and molecular testing revealed a homozygous mutation of the GAA gene, c1655T>C. CRIM status was positive in fibroblasts by Western blot. Alglucosidase alfa infusion was started at 20 mg/kg biweekly according to the standard ramp-up protocol [2], administered in increments of 1, 3, and 5 mg/kg/h, every 30 min and 7 mg/kg/h for the remainder of the infusion. Premedication with acetaminophen (15 mg/kg) and diphenhydramine (1.25 mg/kg) was routinely administered based on institutional practice. Initially, the patient tolerated ERT without incident, and showed increased physical activity, until infusion 6; when he developed a major reaction, 15 min after starting the 3 mg/kg/h rate. Symptoms included flushing, agitation, increased tracheotomy secretions, hypotension, tachycardia, and respiratory distress with hypoxia, followed by lethargy, bradycardia, and decreased responsiveness. The infusion was stopped, the patient was bag ventilated, and an IV bolus of

normal saline was given. Twenty five minutes later, he recovered back to his baseline vital signs, oxygen saturation, and responsiveness. One hour after remaining stable, the infusion was resumed at 0.5 mg/kg/h (half the prior dose/rate) for 30 min; then the infusion was increased to 1, 3, 5, and 7 mg/kg/h every 30 min as tolerated. Infusion 7 was started at the rate of 0.5 mg/kg/h for 30 min (last safe rate), but just before increasing the rate to 1 mg/kg/h, he experienced another systemic reaction.

The infusion was stopped, 1 mg/kg IV of dexamethasone was given, and the patient was closely observed. Three hours later, the infusion was resumed at 0.25 mg/kg/h (half the initial dose), then increased to 0.5, 1, 3, 5, and 7 mg/kg/h every 30 min. Prior to infusion 8, IV dexamethasone (1 mg/kg) was added to the pre-medication protocol. Algucosidase alfa infusion was initiated at the rate of 0.25 mg/kg/h for 30 min, then gradually increased in accordance to the preceding infusion protocol. However, at the rate of 1 mg/kg/h, another systemic reaction occurred. Again, the infusion was stopped, and a second dose of IV dexamethasone (1 mg/kg) was given, causing symptoms to resolve within 30 min. The infusion was restarted 90 min later at the rate of 0.25 mg/kg/h, gradually increasing the dose to 0.5, 0.75, 1, 3, 5, and 7 mg/kg/h every 30 min as tolerated. Immunological studies done after infusions 7 and 8 revealed negative serum IgE titers, and complement activation, and normal serum tryptase.

IgG antibody titers specific to alglucosidase alfa rose to 1:12,800, and 1:51,200 respectively. Because the patient could no longer tolerate ERT safely even with premedication, the risks and benefits of desensitization were discussed with the parents, who consented to the intervention. Desensitization started at infusion 9, when the dose of alglucosidase alfa was reduced to 10 mg/kg/dose weekly instead of the standard regimen. Premedication with diphenhydramine and acetaminophen remained in the protocol. Micro dilutions of alglucosidase alfa were prepared and administered as delineated in Table 2. During desensitization, the patient remained asymptomatic until reaching the dose of 1.5 mg/kg/h, when he developed a major systemic reaction associated with anxiety, flushing, tachycardia, hypotension, and hypoxia with desaturation. The infusion was stopped, supplemental oxygen was administered, in addition to normal saline (10 ml/kg IV bolus), IM epinephrine (0.15 mg) for wheezing, and IV dexamethasone (1 mg/kg). The symptoms resolved after 30 min, with stabilization of the vital signs at baseline; then the infusion was resumed, 90 min later at the last safe rate (Table 2). Micro-dilutions were modified to a lower concentration at infusion 10 (Table 2) and administered per protocol with minor non-systemic reactions occurring, and resolving after decreasing the rate and/or administering diphenhydramine, during infusions 10 and 11.

At infusion 13, the dose of alglucosidase alfa was increased to a maximum of 4 mg/kg/h, then 10 days later at infusion 14 the dose was increased to 15 mg/kg following 2 successive infusions without incident. The infusion was started at 17 mcg/kg/h, and completed at 6 mg/kg/h. For infusion 15, the dose was increased to the standard dose of 20 mg/kg administered at rates similar to the prior infusion. He is currently tolerating the standard dose, without the need for micro dilutions, administered over 5 h with continued premedication per institutional protocol. Despite, his muscle weakness, he is now less easily fatigued and no longer requires frequent naps or additional rate support on his ventilator when awake. He demonstrates more vigor, good fine motor control and can communicate verbally in full sentences over his ventilator.

3. Discussion

The amount of therapeutic protein delivered to patients with PD is the largest compared to patients on ERT for other disorders. This is due to the high dose of ERT required for a

clinical benefit to occur, adding yet, another challenge to the management of infants and young children with PD and significant IARs. In this report, we described the clinical scenario of 2 children with PD who completed their desensitization protocols successfully. Table 3 outlines the principals of desensitization in infants and young children on alglucosidase alfa. Drug desensitization is defined as the induction of a temporary state of immune tolerance to a compound responsible for a hypersensitivity reaction. It is performed by administering increasing doses of the causative medication over a short period of time (hours–days) until the total cumulative therapeutic dose is delivered without incident, this could only be maintained by continuous administration of the causative medication [17]. It is a high-risk procedure used only in patients in whom therapeutic alternatives are less effective or not available after a risk/benefit analysis. This requires a multidisciplinary team approach, where skilled pharmaceutical staff, infusion nurses and clinicians trained and equipped to handle anaphylactic reactions work together. Successful desensitization is achieved when the patient reaches the full therapeutic dose and tolerates repeated administrations of this dose until the therapeutic course is completed [17,18]. The first step in managing hypersensitivity reactions is to have a high index of suspicion and recognize the warning signs of a significant reaction. Signs of an impending significant reaction may be deceiving, appearing as an isolated cutaneous lesion, and/or sudden irritability or crying in infants. Unlike adults, infants and young children with PD are unable to verbalize or describe their symptoms accurately. Therefore, clinicians should rely on parents' intuitive observations, and encourage them to report any unusual signs or symptoms during and after the infusion. Some patients warrant more vigilance, such as those with acute illness at the time of the infusion, and patients known to have recurrent IARs; or those who receive ERT at very high rates, or test positive for IgE, although anaphylaxis could also occur in IgE-negative patients. After a potential hypersensitivity reaction has been identified, certain principles apply to all patients regardless of the cause as: discontinuation of the infusion, symptom-specific medical intervention, and drawing blood for laboratory tests. Prophylactic anti-histaminics are not recommended in patients who have a history of IgE-positive hypersensitivity reactions, as this may mask early symptoms of a hypersensitivity reaction; especially in infants and young children with PD who have compromised communication skills; where a cutaneous reaction may be the primary sign of a significant reaction. It is important to restart at the last "safe" rate, gradually increasing the dose, rate and concentration. Given the high cost of ERT and the need to modify the dose given as micro dilutions between infusions, it is prudent to prepare the medication doses in small batches as needed. In addition to these 2 patients, at least 10 other patients with PD have been successfully desensitized using this practical approach (PSK personal communication).

4. Conclusions

Meeting therapeutic demands of infants and young children with PD and severe IAR to alglucosidase alfa is a challenge. Desensitization may sometimes be indicated in children, as well as in adults with PD and has led to a reduction in the number and severity of hypersensitivity reactions, allowing patients to continue ERT without prolonged periods of interrupted therapy or severe reactions. The key to successful desensitization in infants and young children with PD is careful monitoring, and tailoring treatment according to their specific presentation, needs and underlying cardiac and fluid-volume status.

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Table 1

Patient 1. Child with infantile PD, IgE positive and recurrent significant reactions.

Modified desensitization protocol for severe reactions to alglucosidase alpha infusions (Standard recommended dose is 20 mg/kg biweekly)	**Individualized protocol based on age (clinical presentation), weight (kg), cardiac status, arrhythmia risk, fluid tolerance, and IgE status**
• Total dose given was 10 mg/kg weekly • Micro-dilutions were used for the first 2 h of the infusion • The infusion rate was increased every 30 min and every hour the concentration was increased • The remainder of the infusion was given at one-half the standard ramp up step-up rate as: 0.5, 1.5, 2.5, and 3.5 mg/kg/h • Infusions (19–24) were administered using this protocol. **After two successive infusions were tolerated using the initial micro dilution preparation** ** **modifications were made as follows:** • The standard total dose of 20 mg/kg every other week was given in gradually increasing concentrations, administered cautiously as separate micro dilutions (the first and second seen across the table in bold) • The remainder of the infusions was administered at approximately half the usual step-up rate 15–30-minute increments as tolerated • The rate was increased over time until the infusion time lasted approx 4 h, 15 min	• ****Initial micro-dilutions were prepared as follows at infusion 19:** • 0.05, 0.5, 5, and 50 mcg/ml • Resulting infusions were given as: 0.045, 0.15, 0.45, and1.5 mcg/kg/h, with increments every 30 min. • The remainder of the infusion was mixed at 1 mg/ml stepping up every 30 min if no IAR occurred • The total volume infused was 143 ml over approximately 6 h. • **First micro dilution started at** 6.65 mcg/ml, resulting in infusion of 6 mcg/kg/h, then 20 mcg/kg/h • **Second micro-dilution started at** 66.5 mcg/ml resulting in infusion of 60 mcg/kg/h, then 200 mcg/kg/h • **The remainder was administered at half the usual step-up rate** (15-minute increments) each of 0.5,1, 2, 3.3. and 5 mg/kg/h • Total infusion time was 6 h and 30 min

Table 2

Patient 2. Child with juvenile onset PD, IgE negative and recurrent major systemic reactions.

Desensitization approach for severe reactions to alglucosidase alpha infusions Standard recommended dose 20 mg/kg biweekly	**Individualized protocol based on age (clinical presentation), wt (kg), severity of systemic reactions, Ig E status**
Desensitization protocol started at infusion 9 • Total dose to be administered was approximately 10 mg/kg weekly • Micro-dilutions were prepared and administered as shown across. Infusion rate was increased every 30 min and the concentration was increased every hour. • Premedication was given (1 h before infusion) as: acetaminophen, diphenhydramine +/− dexamethasone	**Micro-dilutions for infusion 9** • Micro dilutions were prepared as 0.07, 0.8 mcg/ml • The remainder of the infusion was mixed at 1.75 mg/ml. • The resulting infusion rates were given as follows: (0.035, 0.12, 0.41, 1.36) mcg/kg/hr, and (0.5, 1.5 and 2.5) mg/kg/hr every 30 min. • Infusion protocol modification after major systemic reaction during infusion 9 at the dose of 1.5 mg/kg/h • Infusion was stopped • Infusion was later restarted at a rate of 0.5 mg/kg/h (last safe rate) for one hour, then increased to 0.75, and 2.5 mg/kg/h each for 1 h • The remainder was given at 3.7 mg/kg/h until the end of the infusion
General measures for major reactions • Stop infusion, until the patient is back to baseline with no symptoms (see text for details)	
Administer as needed • Supplemental oxygen • IV bolus of normal saline (as tolerated) • IV dexamethasone • IM epinephrine • Restart infusion at the last safe rate, then increase the dose/rate slowly and gradually as tolerated	**Microdilutions for infusion 10** • Micro dilutions were prepared as 1 and 100 mcg/ml • The remainder of the infusion mixed at 1.87 mg/ml would be given at gradually increasing infusion rates.

Table 3

Desensitization principles for infants and young children on alglucosidase alfa.

Evaluate the immune status
• If IgE is positive, do not pre-treat with antihistamines, antipyretics or steroids as this may mask primary manifestations of an immune reaction leading to anaphylaxis
• If IgE is negative, prophylactic premedication may be used, if blood pressure is low—encourage fluid intake based on volume status
Minimize volume for infants with cardiomyopathy
Introduce 1/2 the standard dose weekly until tolerated
Prepare micro dilutions of alglucosidase alfa and cautiously infuse, adjusting the dose/rate based on the patients clinical manifestations and tolerance
If a reaction occurs
• Monitor the patient carefully and record vital signs, if symptoms progress, stop the infusion and administer anaphylaxis medications as needed.
• Restart IV at last “safe” dose rate for 15–30 min, then resume planned infusion.
• When resuming infusion observe carefully for early onset of recurrent symptoms.
• If reaction symptoms/signs are recurrent and mild: slow down the infusion to the last safe rate before developing the reaction, if symptoms persist or become more severe stop the infusion immediately and treat the reaction according to the clinical findings.
• Carefully document at the time of the reaction: all symptoms/signs, in addition to the infusion number and dose/rate at which symptoms occurred
Reassess the dose and rate of the micro-dilution used, modifying the dose/rate as indicated based on patients’ response to each infusion before preparing the next infusion—consider lengthening the “safe rate” duration and making step-up rates more gradual when needed.
After 2 successive infusions have been administered successfully at 1/2 the standard dose weekly; recalculate to deliver 3/4 of the dose, every 10 days; when tolerated, administer the full dose at a modified rate scheduled to be given every 2 weeks until the standard recommended rate is achieved. Micro dilution calculations should be made in mcg/kg/h or mg/kg/h.