Successful Desensitisation in a Patient with CRIM-Positive Infantile-Onset Pompe Disease

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Abstract Pompe disease (PD) is a severe life-threatening disease in which enzyme replacement therapy (ERT) with alglucosidase alfa is the only treatment available. Recently it has been shown that antibody formation may have a significant adverse effect on response to ERT. We report a cross-reactive immunologic material (CRIM)-positive PD infant who developed severe infusion-associated reactions (IARs) after 15 uneventful months of ERT. We successfully got the child to tolerate the ERT by a desensitisation protocol. We diluted the total amount of standard alglucosidase alfa infusion (20 mg/kg/dose) to 1/100 (0.2 mg/kg/dose). The original infusion rates were maintained. We doubled this dose every week. No premedication was given. In 8 weeks, we reached the standard dose without any IAR. No further reactions have been observed during 6 months of follow-up. Importantly, clinical deterioration that was observed during the period of reduced enzyme delivery has almost completely reversed. We conclude that this

protocol was effective in our patient, while being safe and easy to follow, and may be suitable in selected cases.

Introduction

Pompe disease (Glycogen storage disease type 2, OMIM 230300) is a rare neuromuscular disorder due to defective lysosomal acid alpha-glucosidase. As a result, glycogen accumulates, predominantly in skeletal muscle fibres. The disease encompasses a wide clinical spectrum. Classical infantile-onset Pompe disease (PD) develops skeletal and cardiac myopathy; untreated infants usually die without treatment within the first year of life (van den Hout et al. 2003). Juvenile and adult phenotypes are characterised by a progressive myopathy with little or no hypertrophic cardiomyopathy.

Enzyme replacement therapy (ERT) with recombinant alglucosidase alfa (Myozyme®, Genzyme Corporation, Cambridge, MA) is the only treatment available. This improves cardiomyopathy and muscular weakness, and prolongs lifespan (Nicolino et al. 2009).

The development of IgG specific for alglucosidase ('neutralising' antibody) has been shown to significantly diminish the efficacy of ERT (Banugaria et al. 2011). An important factor determining IgG production is the cross-reactive immunologic material (CRIM) status of the patient (Kishnani et al. 2010). Patients who are CRIM negative are more likely to develop antibodies. CRIM-positive patients can also develop antibodies, albeit normally a more attenuated response, which ultimately tends to be self-resolving (Kishnani et al. 2007). High-sustained antibody titres CRIM-positive patients have a similar poor outcome compared to CRIM-negative patients (Banugaria et al. 2011). Elevated IgG antibody titres are also associated with

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Table 1 Scheme of Alglucosidase alfa desensitisation protocol. Example for a patient of 10 kg

Week	Dilution	Dose	i.e. for 10 kg
–1	1	20 mg/kg	200 mg over 2 h30
1	1/100	0.2 mg/kg	2 mg over 2 h30
2	1/50	0.4 mg/kg	4 mg over 2 h30
3	1/25	0.8 mg/kg	8 mg over 2 h30
4	2/25	1.6 mg/kg	16 mg over 2 h30
5	4/25	3.2 mg/kg	32 mg over 2 h30
6	8/25	6.4 mg/kg	64 mg over 2 h30
7	16/25	12.8 mg/kg	128 mg over 2 h30
8	1	20 mg/kg	200 mg over 2 h30

infusion-associated reactions. Overall, approximately 95 % of patients treated by alglucosidase alfa develop IgG antibodies, 52 % of patients experienced IAR (Nicolino et al. 2009), and amongst them type-I hypersensitivity reactions in 1 %, and severe allergic reactions in 14 % (Lipinski et al. 2009).

We report successful desensitisation in a patient with CRIM-positive Pompe disease who developed IARs associated with IgG antibody to alglucosidase.

Case Report

A female infant was diagnosed at the age of 5 days with Pompe disease. She was the second child of consanguineous parents, born after an uncomplicated antenatal course. The diagnosis was suspected on the basis of a previously affected sibling, and confirmed soon after birth. She was initially slow to feed and required a nasogastric tube. However, this soon resolved completely. Echocardiography showed a mild hypertrophic cardiomyopathy with normal cardiac function. The diagnosis was confirmed by demonstrating deficiency of leukocyte acid alpha-glucosidase activity. Genotyping of the affected sibling had revealed homozygosity for the pathogenic mutations c.1927G>A (pGly643Arg) of the GAA gene: This was predicted to be associated with a positive CRIM status, using a previously described method (Bali et al. 2012). Enzyme replacement therapy (ERT) with Myozyme® (alglucosidase alfa 20 mg/kg/dose) was started at 2 weeks of age, initially weekly for 12 weeks, then fortnightly.

The initial response to ERT was good, with normal growth and development at 1 year of age. Oral feeding was successfully established by 8 weeks. The cardiomyopathy improved as well.

Urinary tetraglucose level decreased rapidly after start of ERT and normalised in 3 weeks (Table 1).

At the age of 15 months, she developed a severe IAR (irritability, coughing, desaturations) until 92 % of arterial saturation of oxygen (SaO₂), florid rashes of the trunk secondary extended to face and limbs, facial swelling, tachycardia with heart rate > 150 bpm, preserved blood pressure) within minutes of commencing an infusion with a rate of 1 mg/kg/h. She continued to have similar IAR with subsequent infusions. Despite various measures such as administration at a slower rate and premedication including chlorphenamine, paracetamol and intravenous methylprednisolone, she continued to react up to a point where she was unable to receive further ERT.

All tests for IgE specific for the enzyme were negative. Plasma tryptase was normal. Complement levels showed normal C3 and initially normal C4 level at 0.17 g/L (normal 0.14–0.54) at the time of the first IAR but C4 decreased 5 months later to a minimum of 0.04 g/L suggestive of an activation of the classical complement pathway. As these levels decreased 3 months after the restart of ERT at a dose of 20 mg/kg, complement activation is unlikely related to the IAR. Her IgG titre specific for the enzyme was elevated at 1/6,400; however, the level was identical 3 months before the IAR and remained at this level after she was desensitised.

After some discussion, an empiric protocol was devised, based on an initial dilution of 1/100 (0.2 mg/kg) of her normal dose (20 mg/kg) for the first infusion administered without premedication in the same volume of fluids as usual (50 mL) and at the same rate of infusion (4 mL/h for 30 min, then 12 mL/h for 30 min, then 20 mL/h for 30 min, then 28 mL/h for the rest of the infusion). The dose was doubled every week. After 8 infusions, the normal dose of Myozyme® was administered without any further reaction (Table 1). It was given weekly for the next 10 weeks to compensate for previous lower dose infusions. The normal fortnightly protocol of 20 mg/kg/dose of alglucosidase infusion was then reinstated without incident.

The interval between the last well-tolerated infusion and return to the normal dose after desensitisation was 18 weeks. During this period, the patient initially showed progressive weakness but then started improving. Cardiac parameters remained stable. After a first increase when ERT was interrupted, urinary tetraglucose has remained mildly elevated (Fig. 1).

During 9 months of follow-up, no further IARs were experienced and home infusions were recommenced. Her motor development progressed steadily and she was able to walk independently at 19 months old. At 20 months old she developed a nystagmus, which revealed a severe myopia with a refractive error of –10 dioptres. This nystagmus improved considerably with appropriate glasses. 4 months after the end of this protocol, IgG titre anti alglucosidase alfa remained unchanged at 1/6,400.

Fig. 1 Hex4 levels. Diagnosis and onset of IAR are indicated by *black* and *white arrows* respectively. Normal range is indicated below the discontinued line. Desensitisation is indicated with the hatched bar

Discussion

We present a patient whose IARs have resolved after the use of a desensitisation programme. The mechanism responsible for IARs is not understood but may be most consistent with release of cytokines. Many symptoms are not consistent with an IgE-mediated mechanism and tests for IgE are usually negative. Likewise, there is no obvious correlation with titres of IgG to the enzyme in the infantile Pompe patients (Burton and Whiteman 2011). Indeed the persistence of the same IgG antibody titres in our patient after resolution of the IARs also argues against these being IgG-mediated responses.

Three approaches to the management of potential IAR to therapeutic proteins in LSDs have been described: standard prevention and management, immunomodulation and desensitisation.

The standard prevention and management uses antihistamines and corticosteroids prophylactically. In case of any potential IAR, these drugs associated with slowing the rate of ERT's infusion, and/or antipyretics were sometimes enough to control IAR and allowed a restart of well-tolerated ERT. Immunomodulation has been successfully used in several patients. The principle of this is prevention/amelioration of the antibody response. The most widely used protocol involves suppression of B lymphocyte response using a combination of rituximab and methotrexate (Messinger et al. 2012) commencing prior to the first dose of enzyme. However this regime results in significant risk of infection secondary to hypogammaglobulinemia (from rituximab) and bone marrow suppression (from methotrexate). There are also unanswered questions about the long-term effects of such immunomodulatory agents.

Reappearance of antibodies following successful initial suppression has been reported: This has been attributed to failure to suppress long-term memory. Some initial success using either conventional immunomodulation (Messinger et al. 2012) or bortezomib has been reported (Banugaria et al. 2013).

Another potential strategy is desensitisation. Desensitisation is the induction of a state of tolerance in a patient hypersensitised to an allergen by increasing sub-therapeutic doses. Classically used for IgE-mediated reactions (hypersensitivity type I), it has been used for drugs non-IgE-mediated hypersensitivity reactions (Cernadas et al. 2010). Despite extensive experience (Castells et al. 2008), the underlying molecular and cellular basis is poorly understood but may involve depletion of allergic mediators, modification of signal transduction, generation of allergen-specific T-regulatory cells inducing of a tolerant state in peripheral T cells or 'blocking' IgG antibodies (Cernadas et al. 2010; Wachholz and Durham 2003; Akdis and Akdis 2007).

As our patient was CRIM positive, it was felt that immunomodulation, with its attendant risks, would be too aggressive. Desensitisation was therefore considered. Various approaches to desensitisation have been attempted. Transient interruption or slower rates of infusions have been successfully attempted in other patients with mucopolysaccharidosis II, VI or Fabry disease (Burton and Whiteman 2011; Bodensteiner et al. 2008; Kim et al. 2008). Desensitisation has been previously described in a child with Gaucher disease (Peroni et al. 2009) and 3 patients with infantile, juvenile and adult forms of PD, respectively (El-Gharbawy et al. 2011; Lipinski et al. 2009). These desensitisation protocols used serial microdilutions of an initial 10 mg/kg/week infusion increasing as tolerated until the every 2 weeks maintenance dose is reached of 20 mg/kg/dose in 6 and 7 weeks, respectively. This has been successfully tried in patients with either IgE positive with low IgG titres or IgE negative with high IgG titres. More than 13 patients have been reported so far. This more rapid desensitisation protocol offers the advantage to a rapid return to normal dosing. However, the protocol is complicated, potentially prone to human error, and often requires an intensive care environment.

The slower desensitisation that we describe avoids these problems. However, the patient is on lower doses of enzyme for a longer period. Our protocol seems also to be safe as our child did not experience any IAR in contrast to the 3 patients described by El-Gharbawy & Lipinski who had IARs including anaphylactic reactions requiring epinephrine injections in 2 patients. These were mixed patients: IgE negative with high IgG antibodies titres (El-Gharbawy et al. 2011) or IgE positive with low IgG antibodies titres (Lipinski et al. 2009). Not all patients may

be able to tolerate this, and so it may not be suitable in every case. Indeed during the 8 weeks of desensitisation, administered doses of enzyme remain under the recommended doses. Despite a quick decrease of Hex4 and clinical improvement of a transient muscle weakness in our patient, we advise to avoid this new protocol for patients with severe symptoms of the disease that could compromise the life prognosis in case of transient worsening.

In our experience, the IgG antibody titre is not modified by desensitisation as reported by Lipinski.

Conclusion

We report the efficacy of a new desensitisation protocol in a CRIM-positive infantile-onset Pompe patient who was previously experiencing serious infusion-associated reactions. The protocol is practical, easy to implement and well tolerated. Experience with larger cohorts is needed to confirm our observations.

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