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BRIEF COMMUNICATION

Desensitization of two young patients with infantile-onset Pompe disease and severe reactions to alglucosidase alfa

V. Gragnaniello[1] · S. Fecarotta[1] · A. Pecoraro[2] · A. Tarallo[1] · A. Catzola[1] · G. Spadaro[2] · G. Parenti[1,3] · R. Della Casa[1,4]

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Abstract

Pompe disease is a metabolic myopathy, due to deficiency of alpha glucosidase, with a wide clinical spectrum. Enzyme replacement therapy is the only available treatment to improve morbidity and mortality, especially in infantile-onset form. However, some patients experience infusion-associated reactions, which may restrict their access to this treatment. We report on two patients (respectively 12 and 3 months old) with infantile-onset Pompe disease and severe cardiomyopathy, that presented with severe reactions during infusion of enzyme replacement therapy and were successfully desensitized with a new individualized protocol. Our protocol, using microdilution and a premedication with antihistamines, corticosteroids, and tranexamic acid, seems safe and effective and it may allow the continuation of therapy in Pompe patients resulting in the reduction of morbidity and mortality related to this disease.

Keywords Pompe disease · Acid alpha-glucosidase · Enzyme replacement therapy · Infusion · Associated reactions · Desensitization

Introduction

Pompe disease is characterized by lysosomal glycogen accumulation due to a deficiency of acid alpha-glucosidase (GAA). Patients present with a wide range of manifestations; particularly, classical infantile-onset Pompe disease (IOPD) occurs with hypotonia, hypertrophic cardiomyopathy, and death within the first year of life [1]. The only available treatment is the enzyme replacement therapy (ERT) with alglucosidase alfa, but some patients experience infusion-associated reactions (IARs) that may restrict their access to the treatment, and their management is not well identified. We report on two patients with IOPD presenting severe IARs during ERT infusion.

Case 1

A male child, diagnosed with IOPD at the age of 3 months (Table 1), was treated with specific ERT at the standard dose (20 mg/kg every other week). A few minutes after the start of the 16th infusion, at an infusion rate of 1 mg/kg/h, the patient presented a severe and generalized urticarial rash, unresponsive to antihistamines and corticosteroids, so the infusion was slowed and then stopped. Immunological test showed increased serum tryptase (20.6 μg/l) and activated complement. Specific serum immunoglobulin E (IgE) and eosinophil count were normal. IARs occurred again during the subsequent three infusions despite the reduction of drug concentration (until 0.25 mg/ml) and infusion rate (until 0.2 mg/kg/h) and a premedication with antihistamines and corticosteroids. So, an empiric personalized desensitization protocol was started, using micro-dilution (from 0.5 μg/ml) at an initial infusion rate of 1.1 μg/kg/h, with a gradual increase of rates and concentrations. Moreover, tranexamic acid (500 mg/day) was added to the premedication consisting

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✉ R. Della Casa
roberto.dellacasa@unina.com; roberto.dellacasa@ao-rummo.it

[1] Department of Translational Medical Sciences, Section of Pediatrics, Federico II University, Via S. Pansini 5, Naples, Italy

[2] Department of Translational Medical Sciences, Section of Allergy and Clinical Immunology, Federico II University, Naples, Italy

[3] Telethon Institute of Genetics and Medicine, Pozzuoli, Italy

[4] Present address: Section of Pediatrics and Adolescentology, "G. Rummo" Hospital, via R. Delcogliano, Benevento, Italy

Table 1 Patients' characteristics

	Case 1	Case 2
Clinical presentation	Hypotonia	
Biochemical tests: serum CK	Increased	
Electrocardiography	Short PR interval	
Echocardiography	Interventricular septum hypertrophy	Severe hypertrophic cardiomyopathy
GAA activity on dried blood spots (nv 1.86–21.9) μmol/l/h	/	0
GAA activity on lymphocytes (nv 21.4 ± 6.2) nmol 4 Mu/mg prot/h	2.2	0.5
GAA activity on fibroblasts (nv 64.4 ± 22.9) nmol/mg prot/h	0.8	/
GAA gene	Compound heterozygosity ([c.236_246del] + [c.1655T>C]	Homozygosity c1124G>T (p.R375L)
CRIM status (on Western blot)	Positive	
Premedication	Antihistamines, corticosteroids, tranexamic acid	
Desensitization		
Duration of infusion 1 (days)	5	
Initial concentration	0.5 μg/ml	15 μg/ml[b]
Initial rate	9 μg/h (1.1 μg/kg/h)	15 μg/h (2.5 μg/kg/h)[b]
Reduced dose	1 time (10 mg/kg)[a]	Never
Anti GAA IgE	Negative	
Return to standard protocol	24 months	3.5 months[b]

[a] Patient 1 has received a reduced dose (10 mg/kg) only the first time. From 2nd infusion with microdilution, he has received the entire dose (20 mg/kg)

[b] Faster protocol on the basis of previous experience (case 1)

of cetirizine (0.2 mg/kg/die), ranitidine (10 mg/kg/die), and deflazacort (2 mg/kg/die) from 72 h before the infusion. The patient tolerated ERT infusion that was administered at the fifth day. During the subsequent infusions, concentration and rate were progressively increased (Online Resource, Table S1) with only minimal skin reactions. The full dose was administered each time, except for the first infusion (reduced to 10 mg/kg). At 24 months, the time of infusion was reduced to 4 h without microdilution, in agreement with the standard protocol. After further 6 months, the premedication was progressively stopped.

Case 2

A 50-day-old male infant was diagnosed with IOPD (Table 1) and specific ERT was started at the standard dose (20 mg/kg every other week). One hour after the beginning of the third infusion, at an infusion rate of 3 mg/kg/h, the child developed generalized rash, facial swelling, cough, bronchospasm, and respiratory distress (SatO2 85%). So, the infusion was stopped and the patient was treated with oxygen, saline serum perfusion, antihistamines, and corticosteroids. Serum specific IgE and eosinophil count were normal. On the basis of our previous experience (case 1), an empiric personalized desensitization protocol was started using microdilution, from 15 μg/ml, at an initial infusion rate of 2.5 μg/kg/h, with a gradual increase of infusion rate and concentration. Moreover, a premedication with cetirizine 0.2 mg/kg/die, ranitidine 10 mg/kg/die, tranexamic acid 500 mg/die, and deflazacort 2 mg/kg/die was administered, from 72 h before the infusion. The patient's tolerance was excellent and the full dose was administered at the fifth day. Since then, he received ERT every 2 weeks increasing the rate and concentration (Online Resource, Table S2). Already after seven infusions, the standard protocol of alglucosidase infusion was reinstated and the premedication was progressively stopped without any adverse reaction.

Discussion

Pompe disease is one of the rare progressive myopathies for which there is an efficient treatment. However, the 5–14% of patients present significant allergic reactions to ERT (with a 1% experiencing anaphylactic shock/cardiac arrest), but about half experience IARs [2]. In most case of IARs, as in both our patients, symptoms

and laboratory tests are not consistent with an IgE-mediated mechanism. In these cases, the mechanism responsible is not understood but may be most consistent with release of cytokines or complement mediated.

Two approaches for the management of IARs have been described: premedication and desensitization.

Most of the premedication protocols provide for the prophylactic use of antihistamines, glucocorticoids, and antipyretics. These drugs failed in case 1. In case 2, the premedication was started at the same time as the desensitization protocol because of the patient's serious condition, so their effect cannot be separated. However, in both of our cases, we added tranexamic acid (500 mg/day) on the basis of the hypothesis that the employ of tranexamic acid would have reduced complement activation (as in case 1) and the risk of developing angioedema (as in case 2). Tranexamic acid functions in angioedema prophylaxis by inhibiting plasmin activation of kallikrein and that by interrupting the kinin generating cycle, but this has not been studied carefully and it remains a speculation [3]. In our patients, it seems efficient, but needs to be assessed in larger cohorts.

Desensitization is the induction of a temporary state of tolerance by increasing sub-therapeutic doses over a short period of time (from several hours to a few days) [4]. To our knowledge, desensitization to ERT has been described in seven patients with Pompe disease, five children (from 4 months to 6 years of age) and two adults [5–10]. Similar to previous reports, our desensitization protocol was based on the use of microdiluited drug solutions and the reduction of the infusion rates. Unlike some reported protocols, our approach enabled the administration of the entire dose of ERT for both patients, even if after several days. This is important for patients with severe symptoms of the disease, such as cardiomyopathy, that could compromise the life prognosis in case of transient worsening. Premedication with tranexamic acid could be especially used in patients with angioedema or IARs complement mediated. Even if our protocol was applied to the younger reported child (case 2), it seems to be safe as both our patients did not experience any severe IAR, in contrast to two previously described patients who had IARs including anaphylactic reactions requiring epinephrine injections [7, 9]. To conclude, the desensitization method we describe seems safe and effective and it may allow the continuation of ERT in Pompe disease patients resulting in the reduction of morbidity and mortality. The addition of tranexamic acid to premedication seems promising, but should be further investigated.

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References

1. Hirschhorn R, AJJ R (2001) Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A et al (eds) The metabolic & molecular bases of inherited disease, vol 8. McGrawHill, New York, pp 3389–3420
2. Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR et al (2009) Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genet Med 11(3):210–219
3. Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S et al (2017) Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. J Allergy Clin Immunol Pract 5(5):1307–1313
4. Gallay L, Petiot P, Durieu I, Streichenberger N, Berard F (2016) SWORD: a simplified desensitization protocol for enzyme replacement therapy in adult Pompe disease. Neuromuscul Disord 26(11): 801–804
5. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A et al (2010) General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. Allergy 65(11):1357–1366
6. Karagol IH, Bakirtas A, Yilmaz O, Topal E, Kucukcongar A, Ezgu FS et al (2014) Desensitisation of the youngest patient with Pompe disease in response to alglucosidase alfa. Allergol Immunopathol (Madr) 42(4):372–375
7. El-Gharbawy AH, Mackey J, DeArmey S, Westby G, Grinnell SG, Malovrh P et al (2011) An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reactions to alglucosidase alfa infusions. Mol Genet Metab 104(1–2):118–122
8. Baruteau J, Broomfield A, Crook V, Finnegan N, Harvey K, Burke D et al (2014) Successful desensitisation in a patient with CRIM-positive infantile-onset Pompe disease. JIMD Rep 12:99–102
9. Lipinski SE, Lipinski MJ, Burnette A, Platts-Mills TA, Wilson WG (2009) Desensitization of an adult patient with Pompe disease and a history of anaphylaxis to alglucosidase alfa. Mol Genet Metab 98(3):319–321
10. Capanoglu M, Dibek Misirlioglu E, Azkur D, Vezir E, Guvenir H, Gunduz M et al (2016) IgE mediated hypersensitivity and desensitisation with recombinant enzymes in Pompe disease and type I and type VI mucopolysaccharidosis. Int Arch Allergy Immunol 169(3):198–202