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Case report

SWORD: A simplified desensitization protocol for enzyme replacement therapy in adult Pompe disease

Laure Gallay [a,b], Philippe Petiot [c], Isabelle Durieu [d], Nathalie Streichenberger [b,e], Frederic Berard [f,g,*]

[a] Department of Clinical Immunology, Edouard Herriot University Hospital, 5 place d'Arsonvaal, 69437 Lyon Cedex 03, France
[b] INMG, CNRS UMR 5310–INSERM U1217, University Lyon 1, France
[c] Department of Neurology, Croix-Rousse Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, Grande rue de la croix rousse, 69004 Lyon, France
[d] Department of Internal and Vascular Medicine, Lyon Sud University Hospital, 69495 Pierre Bénite, France
[e] Department of Neuropathology, Hospices Civils de Lyon, Neurology and Neurosurgery Pierre Wertheimer University Hospital, Boulevard Pinel, 69500 Bron, France
[f] Department of Allergy and Clinical Immunology, Hospital Center Lyon Sud, 69495 Pierre Bénite, France
[g] University Lyon 1, France

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Abstract

Pompe disease is an inherited lysosomal disease in which there is a decrease or absence of acid alpha-glucosidase activity. This enzyme defect induces glycogen storage in different tissues, especially muscle and heart, resulting in muscle weakness, respiratory failure and heart disease. Substitutive enzyme replacement therapy (ERT) dispensed every two weeks is the only treatment that has shown benefits. However, this treatment induces hypersensitivity for half of the treated patients. Reactions range from mild to severe, sometimes requiring ERT suspension and anti-anaphylaxis drug administration. Understandably, high amount of acid alpha-glucosidase infusion seems to be identified by the immune system as a danger associated molecular pattern, and induce an immune reaction, involving sometimes, but not always, immunoglobulin E (IgE) production and activating mast and basophil polynuclear cells. Considering the lack of therapeutic alternatives and the proved benefit of ERT, desensitization finds its place here. We hereby report the case of a patient for whom a simplified desensitization protocol ("SWORD": Start With One Regular Drop) was successfully achieved, allowing ERT to be pursued, resulting eventually in clinical improvement.

Keywords: Pompe disease; Enzyme replacement therapy; Hypersensitivity; Desensitization; Simplified protocol

1. Introduction

The Pompe disease (PD), also called glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency in the activity of the lysosomal enzyme acid alpha-glucosidase (GAA). The clinical spectrum of PD is extremely broad, varying from a severe infantile form leading to cardiorespiratory failure in the first few months of life, to the more frequent adult-onset muscular manifestations occurring in the adulthood with frequent diaphragmatic implication. In the early onset, the prognosis is dark and has been considerably modified by the enzyme replacement therapy (Myozyme®, Genzyme). In the adult form, a significant improvement in walking distance and stabilized pulmonary function has been reported [1]. It has to be pointed that during this treatment, 35% of the patients presented a reaction associated with infusion (RAI), and severe anaphylaxis was also reported in few cases. Considering the benefit of the ERT and the lack of alternative therapy, desensitization has been tried in rare cases [2–4]. We report two patients suffering from PD, presenting severe anaphylaxis while on ERT infusion, who have successfully undergone desensitization, and propose a simplified protocol that could be used for this aim.

2. Case reports

A 44-year-old woman, with no personal history or allergy, had presented a progressive proximal weakness and predominant atrophy on pelvic girdle for two years. Pulmonary and cardiac

* Corresponding author. Professional address: Department of Allergy and Clinical Immunology, Hospital Center, Lyon Sud, 69495 Pierre Bénite, France, University Lyon 1, France. Fax: +33 04 78 86 15 26.
E-mail address: Frederic.berard@chu-lyon.fr (F. Berard).

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investigations were subnormal, with just a mild restrictive and obstructive ventilatory defect. Creatine kinase level was moderately high (250 UI/l). In the family, two sisters were also affected by a proved diagnosis of PD. Our patient's enzyme study showed markedly reduced GAA activity. The genetic analysis found 2 mutations: C.1_15T>G in intron 1 and C.1636+1G>C in intron 11. The PD diagnosis was confirmed and initiation of ERT was decided, following the standard protocol and doses (20 mg/kg every 2 weeks). The four first infusions were well-tolerated, induced just mild myalgia and asthenia. At the fifth ERT session, 20 minutes after infusion started, at a rate of 20 ml/hour, the patient presented a grade III anaphylactic reaction: bronchospasm with 80% desaturation and hypotension with systolic blood pressure decreasing quickly to 80 mmHg. The infusion was stopped, and she received oxygenotherapy, saline serum perfusion and 80 mg of intravenous corticosteroid. The clinical course was rapidly favorable. Per-anaphylaxis biological investigations were normal, including eosinophil counts, tryptase and complement C3/C4/CH50. Specific anti-ERT immunoglobulin E (IgE) was negative in the blood. Immediate skin tests (pricks and intra dermal tests at 1:1000, 1:100, 1:10 and finally 1:1 dilution) were also negative. Because of this serious adverse immune reaction, ERT was stopped. Two years later, the patient presented a progressive clinical alteration; reintroduction of ERT was discussed and finally decided. New infusions of ERT were performed and organized in the intensive care unit.

A simplified desensitization protocol – SWORD (Table 1) – was set up using a very slow flow, initially counting drop by drop, waiting 10 minutes between each step, and progressively increased until reaching the standard maximal flow and giving the complete ERT dose to the patient. Technically, two perfusion pockets were joined in a common piping. One with the ERT diluted solution (identical dilution to the standard one), which flow was carefully managed with a Dosi-Flow®, and another one of saline solution dispensed with a continuous flow. Mixed together, this resulted in a simple system allowing slow increments of ERT doses (Fig. 1). The first re-infusion was given in March 2013. Pre-medication was systematically given, composed of antihistamines (cetirizine 2 tabs) and Montelukast (anti leukotriene) 10 mg given one hour before infusion. The patient's tolerance was excellent and infusion duration was six hours. During the second desensitization session, the patient did a breakthrough with anxiety, crying and abdominal pain. The infusion was stopped for fifteen minutes and Polaramine 5 mg intravenous was given. The infusion was resumed after reinsurance, and the complete ERT dose was reached after six additional hours without any further problem. Subsequently, ERT was given following this simplified protocol every two weeks (still ongoing in January 2016), reaching each time the full dose, without complication. The clinical tolerance is still very good and treatment shows a significant efficiency regarding the recent improvement of the clinical test and the respiratory investigations.

The SWORD protocol was communicated to two other French teams in charge of two ERT hypersensitivity cases during PD treatment, among which one managed a complete desensitization and the other one is still ongoing.

3. Discussion

Pompe disease is one of the rare progressive myopathies for which there is an efficient treatment. Infusions must be regularly maintained to induce a clinical benefit. There is no alternative therapy. In a recent study on PD treatment, 52% of the patients experienced infusion-associated reactions, 1% of the patients developed anaphylactic shock and/or cardiac arrest during alglucosidase alfa infusion, and 5–14% of patients treated with alglucosidase alfa have developed significant allergic reactions [1,5] (*safety Myozyme* www.myozyme.com). Despite previous anaphylaxis, our simplified desensitization to alglucosidase alfa protocol allowed to continue ERT at full doses for our 2 patients with only minor reactions, enabling ERT benefits and disease stabilization.

During ERT infusion, two different kinds of immune reactions were reported. The first type was a drug hypersensitivity reaction (DHR), which leads to an anaphylactic reaction against ERT. It can occur with or without IgE mediation. It has been reported in more than 60% of treated patients in some studies [1,6]. The second type of immune reaction is the development of immunoglobulin G (IgG) against the ERT, which reduces treatment efficiency without

Table 1
Simplified desensitization protocol for enzymotherapy in adult Pompe disease. Solution concentration 2 mg/ml calculated on the standard dose of 20 mg/kg (1000 mg in 500 ml for our patient).

Step	Time	Flow	Rate (ml/H)	Administrated dose (mg)	Cumulative dose (mg)
1	H0	1 drop		50 µl = 0,1 mg	0,1
2	0H10	3 drops in 10 min		150 µl = 0,33 mg	0,43
3	0H20	10 drops in 10 min		500 µl = 1 mg	1,43
4	0H30	1 ml in 10 min	14 ml/H	2 mg	3,43
5	0H40	2 ml in 10 min	14 ml/H	4 mg	7,43
6	0H50	3 ml in 15 min	14 ml/H	6 mg	13,43
7	1H05	4 ml in 15 min	20 ml/H	8 mg	21,43
8	1H20	5 ml in 15 min	20 ml/H	10 mg	31,43
9	1H35	15 ml in 30 min	30 ml/H	30 mg	61,43
10	2H05	20 ml in 30 min	40 ml/H	40 mg	101,43
11	2H35	35 ml in 30 min	70 ml/H	70 mg	171,43
12	3H05	370 ml in 30 min (infusion 3H20)	110 ml/H	740 mg	911,43

H: hours; min: minutes.