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Case Report

Merve Emecen Sanli*, Hacer Ilbilge Ertoy Karagol, Ayse Kilic, Ekin Aktasoglu, Asli Inci, Ilyas Okur, Fatih Ezgu and Leyla Tumer

First successful concomitant therapy of immune tolerance induction therapy and desensitization in a CRIM-negative infantile Pompe patient

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Abstract

Objectives: Enzyme replacement therapy (ERT) with alglucosidase alfa (rhGAA) has changed the fatal course of infantile Pompe disease, however, development of anti rhGAA antibodies and infusion-associated reactions (IAR) restrict the tolerability and effectiveness of the treatment.

Case presentation: We describe a successful concomitant immune tolerance induction (ITI) and desensitization protocols in a cross-reactive immunologic material (CRIM) negative 7-month-old male patient. At the age of 5 months and eighth dose of the ERT, the patient developed IAR and his rhGAA specific IgE was negative however, his rhGAA specific IgG titer was as high as 12,800. ITI therapy to suppress antibody formation and a desensitization protocol was devised to be given concomitantly. At the end of 5-week therapy, his fatigue and weakness improved profoundly and a control antidrug antibody level decreased at 800. At the time of the patient's follow up, he was still on ERT with desensitization at the age of 15 months without any reactions.

Conclusions: This is the first report in the literature applying concomitant ITI and desensitization protocols in a CRIM negative infantile-onset Pompe disease patient successfully, hence the importance of the case.

Introduction

Pompe disease (PD) is a rare autosomal recessive lysosomal storage condition linked to acid alpha-glucosidase deficiency. It is a neuromuscular disorder in which an accumulation of glycogen occurs in the cardiac, skeletal, and smooth muscles. The condition has been classified into classic infantile-onset Pompe disease (IPD) and late-onset Pompe disease (LOPD). In classic IPD disease, skeletal and cardiac myopathy develops, and untreated infants usually die within the first year of life secondary to cardiorespiratory failure. The fatal course of IPD has been altered with the development of enzyme replacement therapy (ERT) with recombinant alglucosidase alfa (rhGAA) [1] which improves the cardiomyopathy, muscular weakness, and survival of patients [2].

ERT response is affected by cross-reactive immunologic material (CRIM) status and antidrug antibody development to rhGAA. CRIM negative status is related to a lack of residual enzyme activity and poor prognosis in IPD patients on ERT. Patients who are CRIM negative are more likely to mount a devastating immune response to ERT with developing IgG type antidrug antibody [3]. Elevated IgG antibody titers to rhGAA not only decrease the efficacy of the ERT but also are associated with infusion-associated reactions (IAR), including anaphylaxis [4].

Immune tolerance induction (ITI) therapy has been used on patients with ERT-naïve settings to prevent the development of antibodies to rhGAA, or on ERT patients who are CRIM-negative and/or anti rhGAA IgG positive, to eliminate the antibodies to rhGAA [1]. Here we report a concomitant therapy of desensitization and ITI in a patient with CRIM-negative IPD who developed IgG antibodies to rhGAA and infusion-associated anaphylaxis (IAA).

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Case presentation

A 7-month-old male patient with PD who developed IAR during ERT administration at an external center was referred to our clinic. He had been diagnosed at the age of 1 month with PD and was the second child of consanguineous parents who was born after an uncomplicated antenatal course. The diagnosis was suspected on the basis of a previously affected sibling. Echocardiography revealed mild hypertrophic cardiomyopathy with normal cardiac function. Leukocyte acid alpha-glucosidase activity showed low levels of the enzyme. The genotyping of the patient revealed homozygosity for the deletion of the 1–4 exons of the GAA gene. No sample appropriate for CRIM analysis could be collected before the first ERT, however, this mutation was predicted to be associated with a negative CRIM status based on a previously described method in literature [5]. Enzyme replacement therapy with Myozyme® (40 mg/kg/dose) every other week was started at the age of 1 month (Figure 1).

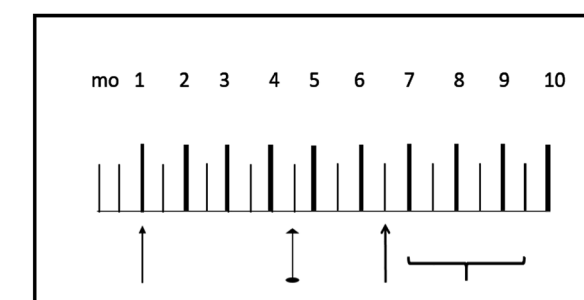
At the age of 5 months at the time of the eighth dose at a local hospital, the patient developed IAR (irritability, tachypnea with 54/min, desaturations until 92% of arterial saturation of oxygen, fever, and rash) within the first hour of the infusion, delivered at the rate of 1 mg/kg/h. He developed similar reactions twice more, despite administration at a slower rate, and so was referred to our center for a more detailed evaluation. He was admitted to our hospital at the age of 7 months when a physical examination revealed general hypotonia (he could not hold his head up or sit up straight), fatigue, tachypnea, tachycardia, and fever. Laboratory tests showed increased acute-phase reactants, and echocardiography disclosed a normal ejection fraction rate (70%) with interventricular septal hypertrophy (intraventricular septal thickness end diastole 0.7 cm, intraventricular septal thickness end systole 0.5 cm, z-score 2.8). An empiric antibiotherapy was initiated and arranged based on blood culture results. After the infection

resolved, ERT was planned to be given routinely to investigate the reaction. The patient was monitored under the supervision of the pediatric allergy department during the infusion. ERT was initiated at a dose of 0.25 mg/kg/h, and the rate was planned to be increased by 0.25 mg/kg/h every 30 min to a maximum of 4 mg/kg/h. At the third hour when the infusion rate was 1.5 mg/kg/h, the patient developed a generalized urticarial rash, pruritus, angioedema on the ears, cyanosis, irritability, tachypnea, and sibilant rhonchi without fever. The infusion was stopped immediately, and 0.01 mg/kg adrenaline was injected intramuscularly, after which all of the symptoms resolved immediately. The IAR was duly evaluated as anaphylaxis associated with the infusion.

To identify whether the IAA was an IgE-mediated or non-IgE-mediated reaction, serum titers of specific IgE and IgG type antidrug antibodies of rhGAA were analyzed. A skin prick test and intradermal test were negative. While rhGAA-specific IgE was negative, rhGAA specific IgG titer was 12,800, which is classified as low-sustained rhGAA IgG antibody titers [3].

ITI therapy and desensitization protocol

A modified ITI therapy was initiated based on the protocol described by Mendelsohn et al. [5] (Figure 2). The patient received one cycle of ITI therapy with rituximab, methotrexate, and IVIG treatments. Unlike in the original protocol, IVIG was administered every other week rather than once a month. Since the patient had a pre-diagnosis of Kartegener Syndrome, cotrimaxazole treatment was applied every other day as infection prophylaxis. During the ITI therapy, ERT was given with desensitization – the desensitization protocol being constructed with four different enzyme concentrations (Tables 1 and 2). As the reaction that occurred in the patient was severe, the starting dose was determined as 1/500,000 of the target dose.



→ 1 st ERT dose, ● → 1 st IAR, → admission to our center, — ITI therapy

Figure 1: Timeline of patient's history by age.

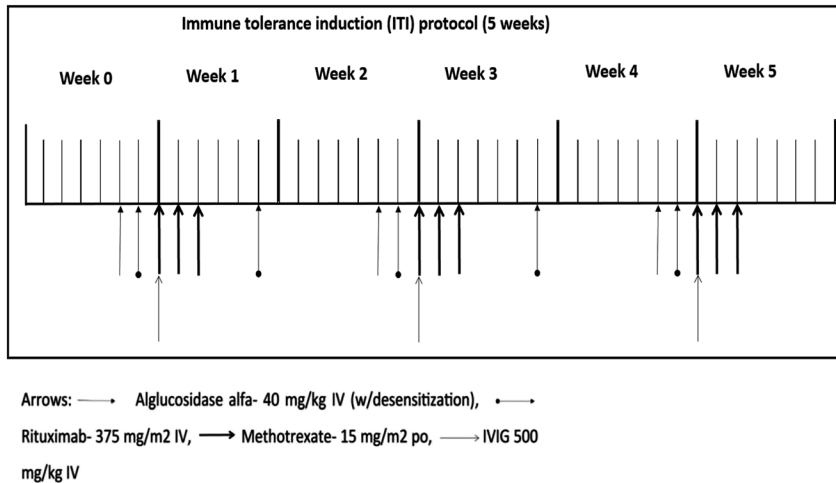


Figure 2: Immune tolerance induction (ITI) protocol (5 weeks).

Table 1: Alglucosidase alfa concentrations used to create desensitization protocol.

Solution type	Solution content	Concentration
A	10 mL solution B + 90 mL 0.9% NaCl	0.00096 mg/mL (1/1,000)
B	10 mL solution C + 90 mL 0.9% NaCl	0.0096 mg/mL (1/100)
C	10 mL solution D + 90 mL 0.9% NaCl	0.096 mg/mL (1/10)
D	48 mL drug ^a + 202 mL 0.9% NaCl	0.96 mg/mL (1/1)

NaCl, sodium chloride. ^aAlglucosidase alfa (Myozyme) = 50 mg = 10 mL.

Each step took 15 min, and the dose was increased 2–2.5-fold. A premedication treatment was given before desensitization to diminish the risk of breakthrough reactions. During the 5-week ITI therapy and ERT with desensitization, the patient developed no complications or breakthrough reactions, and despite the immune suppressive effect of ITI therapy, the patient did not develop any infections. In addition to improving his fatigue and weakness, the control antidrug antibody level decreased at 800 at the end of 5-week ITI therapy. At the time of the patient's most recent follow-up, he was still on ERT with desensitization, but was off all the ITI therapy medications, including IVIG, by the age of 15 months, without any reactions, and complete B cell recovery was achieved.

Table 2: Intravenous desensitization protocol of alglucosidase alfa.

Step	Solution type	Rate, mL/h	Infusion duration, min	Volume infused per step, mL	Dose administered with this step	Cumulative dose, mg
1	A	2	15	0.5	0.00048	0.00048
2	A	4	15	1	0.00096	0.00144
3	A	8	15	2	0.00192	0.00336
4	A	16	15	4	0.00384	0.0072
5	B	4	15	1	0.0096	0.0168
6	B	8	15	2	0.0192	0.036
7	B	16	15	4	0.0384	0.0744
8	B	32	15	8	0.0768	0.1512
9	C	6	15	1.5	0.153	0.3
10	C	12	15	3	0.3	0.6
11	C	24	15	6	0.6	1.2
12	C	48	15	12	1.2	2.4
13	D	10	15	2.5	2.4	4.8
14	D	20	15	5	4.8	9.6
15	D	20	696	232	230.4	240

Dose: 40 mg/kg/day; the patient's weight: 6 kg; total time: 15.1 h; total volume: 285.5 mL; premedication: 1 mg/kg IV methylprednisolon: 13, 7, 1 h before ERT, 1 mg/kg IV phenylamine and 1 mg/kg IV ranitidine: 1 h before ERT.

Discussion

ERT is the only life-saving treatment option in PD, although it can be challenging, particularly in patients with a profound deficiency in GAA activity. CRIM status is the most critical predictive value in terms of developing antibodies to ERT. Patients with profound GAA activity deficiency are more likely to be CRIM negative, and CRIM-negative patients are more likely to develop the high-titer antibody responses that neutralize enzyme uptake into the cells, resulting in a poor outcome.

Overall, approximately 95% of patients treated with rhGAA develop IgG antibodies, 52% experience IAR [2], and among them, type-I hypersensitivity reactions occur in 1% and severe allergic reactions in 14% [6]. Accordingly, ITI therapy in CRIM-negative patients is a clear requirement.

The immunologic mechanisms responsible for IARs are not clearly understood. Arguments include IgE mediated mechanisms and non-IgE mediated mechanisms consist of IgG antibodies induces complement activation and cytokine release, or direct mast cell stimulation. Premedication with antihistamines, antipyretics and/or corticosteroids, short interruptions to the infusion, and slower infusion rates are general approaches to the prevention of IARs [6], although desensitization is indicated when these measures fail to prevent anaphylaxis, and in cases where the drug is vital for the patient and there is no other effective or safe alternative treatment option. Regardless of whether or not the reaction is IgE-mediated, desensitization is indicated for those who develop anaphylaxis. The literature contains reports on four CRIM positive patients on desensitization protocols [6–9], while to the best of our knowledge, the case presented here is the first CRIM-negative IPD patient to be placed on a desensitization protocol. In some desensitization protocols in literature, patients were initially given lower doses (10 mg/kg) of ERT rather than the standard dose (20 mg/kg) [7, 9] and dose escalation was performed gradually. For the present case, we started with a routine dose (40 mg/kg) at the time of first application with a lower enzyme concentration (1/500,000), as the patient developed severe IAAs.

ITI therapy is applied to prevent or reduce the formation of antidrug antibodies and to increase the ERT effectiveness. Literature suggests various ITI therapy protocols, however, we decided to apply the protocol of Mendelsohn et al. since our center had experienced complication-free success in three patients using this protocol [5]. The protocol involves the administration of rituximab in weekly doses intravenously for the selective depletion of mature CD20+ B-cells, methotrexate in three doses a week within

the first three ERT infusions subcutaneously/orally for the inactivation of rapidly multiplying B- and T-cells, and IVIG monthly to compensate for the B-cell suppression induced by rituximab. We made a small modification to this protocol with the administration of IVIG biweekly to enhance the decrease of antidrug antibody titers, and the addition of cotrimaxazole treatment three days a week as infection prophylaxis.

Our CRIM negative patient could not undergo ITI therapy before the initiation of ERT and developed IAR at the age of 5 months which was probably associated with the high blood titers of IgG type antidrug antibodies. Consequently, ITI therapy was started to suppress antibody formation and to increase ERT effectiveness, and a desensitization protocol for the continuation of ERT was devised, to be given concomitantly.

Conclusions

There have been many reports assessing ITI therapy and desensitization protocols in Pompe patients, although no combination therapy of ITI therapy and ERT desensitization has been applied to date. This is the first report in literature describing the successful application of concomitant ITI therapy (with biweekly IVIG administration and cotrimaxazole prophylaxis) and desensitization (without enzyme dose reduction) protocols in a CRIM-negative IPD patient.

Learning points

Antidrug antibodies can cause IARs and reduce the effectiveness of the ERT. Concomitant desensitization and immunomodulation therapy decreased the antidrug antibody level, resolved the IARs, and improved the clinical findings of our patient.

What's new?

This is the first study in the literature to describe a CRIM-negative IPD patient who underwent successful concomitant desensitization and immunomodulation treatment.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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