

Clinical Communications

Successful rapid desensitization to imiglucerase in an adult patient with Gaucher disease and documented IgE-mediated hypersensitivity

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Clinical Implications

- The authors present the first report of successful rapid desensitization (RD) to imiglucerase in an adult patient with Gaucher disease and documented IgE-mediated hypersensitivity. They used a well-standardized RD protocol the further application of which is required to provide more data to substantiate its efficacy and safety in imiglucerase-RD.

TO THE EDITOR:

Gaucher disease (GD) is an autosomal recessive genetic disease and the most common lysosomal disease. This metabolic disorder is caused by a deficiency of the lysosomal enzyme glucocerebrosidase, and as a result, the lipid substrate glucosylceramide is degraded much more slowly than in normal cells and accumulates intracellularly, primarily in cells of mononuclear phagocyte origin.¹ The glucosylceramide-laden macrophages, also known as “Gaucher cells,” are the classical hallmark of the disease. GD is classified into 3 phenotypic categories; type I, also referred to as adult or nonneuronopathic GD, is the most common type ($\geq 90\%$),² characterized by the presence of visceral involvement, bone disease, and hematologic abnormalities, and the absence of significant neurological impairment. Its prevalence worldwide is 1 in 50,000-100,000.² Although referred to as adult GD, 66% of the patients are diagnosed before the age of 20.³

We report the case of a 22-year-old woman diagnosed with type I GD at the age of 3, who was referred to our Drug Allergy Outpatient Clinic due to adverse reactions during the infusion of imiglucerase (Cerezyme, Genzyme Corporation, Cambridge, Mass). Imiglucerase is the standard of care enzyme replacement therapy for type I GD.² To our knowledge, anaphylactic/anaphylactoid reactions to imiglucerase have only been reported in 3 patients,⁴⁻⁶ and according to the corresponding international postmarketing safety surveillance program in 2007,⁷ these reactions are considered extremely rare. In the case of our patient, the enzyme replacement therapy was started at the Hematology Department of our hospital at the age of 16 and she was treated with imiglucerase, 30 U/kg, every 2 weeks. After 2.5 years on the aforementioned therapy, she experienced headache, flushing, and tachycardia in 3 consecutive, unsuccessful administrations, despite pretreatment with antihistamine and lower infusion rates. At the age of 19, the therapeutic regimen was subsequently changed to miglustat (Zavesca, Actelion Pharmaceuticals, Basel, Switzerland). This substrate reduction therapy was administered for nearly 3 years (34 months) but resulted in deterioration of hematologic (thrombocytopenia, anemia) and bone (decreased

mineral density, marrow infiltration) parameters. Aiming at a better clinicolaboratory response, the hematologists decided to reinstate imiglucerase (30 U/kg, 70 mL/h, every 2 weeks), and the patient tolerated well the first 3 therapies, without symptoms or signs of adverse reactions. But during the fourth therapy, she developed pruritus around the wrist and ankle joints, and the site of the IV catheter, flushing on the face, and periorbital angioedema 1.5 hours after the beginning of the nonpremedicated infusion (70 mL/h). In the subsequent infusion, the patient, although pretreated with IV dimetindene maleate (Fenistil (Novartis Consumer Health SA, Nyon, Switzerland), a substituted alkylamine, H1-receptor antagonist), developed pruritus in the palms, soles, and genitals, periorbital angioedema, and flushing on the face approximately 10 minutes after the beginning of imiglucerase administration (70 mL/h). The infusion was ceased and IV dimetindene maleate and methylprednisolone were administered. At a final attempt, the hematologists chose to re-administer imiglucerase by means of a desensitization protocol according to which 1500 U (30 U/kg) of the drug were meant to be delivered in 250 mL normal saline, in 4 consecutive steps of increasing administration rate as follows: 10, 30, 50, and 70 mL/h. The first 3 steps lasted 30 minutes each. Although premedication with IV dimetindene maleate was administered, 5 minutes after the final step was reached the patient reported itch in the same body areas as in the beginning of the previous infusion reaction; the administration was immediately ceased and symptoms were treated with IV dimetindene maleate. The hematologists did not obtain blood samples for the measurement of serum tryptase concentrations at any of the above-mentioned 6 infusion reactions. She was ultimately referred to us for allergy evaluation in respect to a safer and effective rapid desensitization (RD) protocol.

Following a thorough drug allergy history record at the Allergy Unit, *in vivo* testing was undertaken. The skin prick test (SPT) with imiglucerase, 200 U/5 mL, was negative. Intradermal (ID) tests were performed using in succession 0.03 mL of 1:1000, 1:100, and 1:10 dilution of the reconstituted enzyme (200 U/5 mL) in normal saline and were each evaluated in 20 minutes; 1:1000 resulted in erythema, 1:100 in a positive 8 mm wheal, and 1:10 in a positive 16 mm wheal (Figure 1). Intradermal injection with 0.03 mL normal saline (negative control) did not produce a wheal or flare reaction. Histamine (10 mg/mL) SPT (positive control) resulted in a 6 mm wheal. The same *in vivo* testing was realized in 2 separate groups of controls: the first group comprised 5 (3 male and 2 female) healthy individuals, 20-30 years old, and the second group 2 male patients with type I GD, aged 31 and 33 years, who were receiving imiglucerase uneventfully for the last 2 and 7 years, respectively. All performed tests in both control groups were negative.

Regarding serum *in vitro* testing at the time of evaluation, tryptase levels were normal (1.4 µg/L) and anti-imiglucerase IgE antibodies measured by ELISA (Genzyme Corporation, Framingham, Mass) undetectable.

On completion of the allergy workup and the patient's written informed consent, we prepared a 12-step RD protocol for the administration of 1500 U (30 U/kg) imiglucerase. It was based on a well-standardized RD protocol already proposed for other

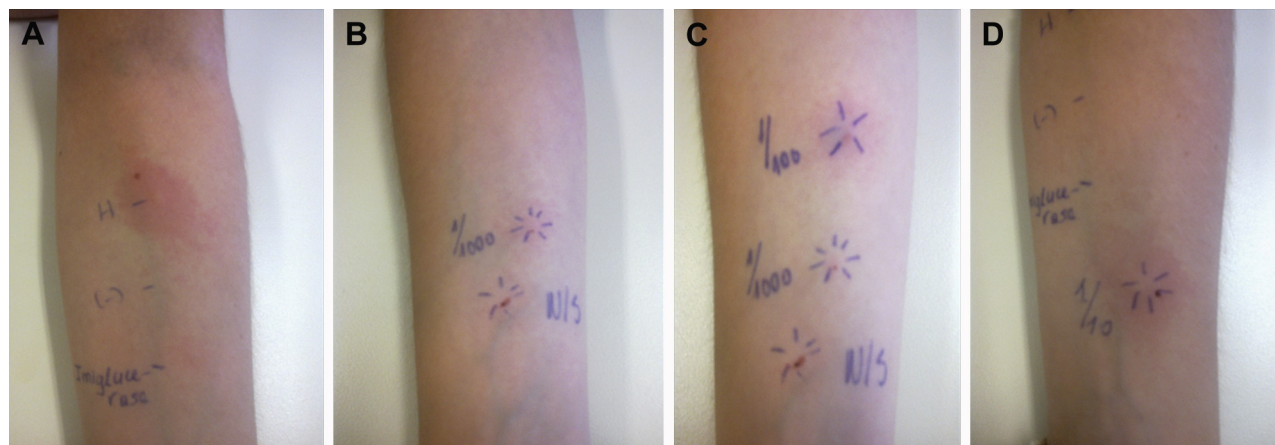


FIGURE 1. *In vivo* testing with imiglucerase; SPTs were evaluated at 15 minutes and IDs at 20 minutes. **A**, Negative imiglucerase, 200 U/5 mL, and normal saline [marked as “(-)"] SPT. Positive histamine (marked as “H”) (10 mg/mL) SPT. **B**, Erythema produced by ID with 1:1000 dilution of reconstituted imiglucerase (200 U/5 mL) in normal saline. Negative ID with normal saline (marked as “N/S”). **C**, Positive ID at 1:100 dilution of imiglucerase. **D**, Positive ID at 1:10 dilution of imiglucerase. SPT, skin prick test; ID, intradermal test.

TABLE I. Rapid desensitization protocol for intravenous administration of imiglucerase (1500 U)

Solution	Step	Rate (mL/h)	Time (min)	Dose administered with each step (U)	Cumulative dose (U)
1	1	2.0	15	0.0300	0.0300
1	2	5.0	15	0.0750	0.1050
1	3	10.0	15	0.1500	0.2550
1	4	20.0	15	0.3000	0.5550
2	5	5.0	15	0.7500	1.3050
2	6	10.0	15	1.5000	2.8050
2	7	20.0	15	3.0000	5.8050
2	8	30.0	15	4.5000	10.3050
3	9	7.0	15	10.4279	20.7329
3	10	15.0	15	22.3454	43.0783
3	11	30.0	15	44.6909	87.7691
3	12	80.0	177.75	1412.2309	1500.0000

Description: Solution 1, 0.060 U/mL; Solution 2, 0.600 U/mL; Solution 3, 5.959 U/mL. Total administration time: 5.71 h.

Premedication: dimetindine, 4 mg, administered intravenously 20 minutes before rapid desensitization.

biologicals⁸ and for chemotherapeutics.⁹ According to that, 3 solutions (each 250 mL, in normal saline) were delivered in 12 consecutive steps, each step increasing the rate of administration by 2- to 2.5-fold. Solutions 1 (steps 1-4) and 2 (steps 5-8) were a 100-fold and 10-fold dilution of the final target concentration, respectively. The concentration of solution 3 (steps 9-12) was calculated by subtracting the cumulative dose administered in steps 1 to 8 from the total target dose. Steps 1 to 11 each took 15 minutes, and step 12 was prolonged to complete the target dose (Table I). Twenty minutes before RD begun, the patient was premedicated with dimetindine maleate (4 mg, IV), which is the only IV antihistamine available in the market in Greece. The full therapeutic dose was successfully administered in less than 6 hours in an intensive care unit; almost 30 minutes after the start of the 12th step that delivers approximately 92% of the total dose of medication, the patient developed mild flushing on the face

and a few itchless wheals on the neck area, without cardiovascular or respiratory symptoms and/or signs. Nevertheless, the administration was continued and the reaction gradually resolved in 1 hour without any additional treatment.

Using the same 12-step RD protocol, the patient has been receiving imiglucerase, 1500 U/2 weeks, for the last 2 months. During the 12th step of all these subsequent administrations, the aforementioned mild cutaneous reaction has been identically present with spontaneous resolution.

To our knowledge, this is the first report of successful RD to imiglucerase in an adult patient with type I GD and documented IgE-mediated hypersensitivity to imiglucerase as suggested by the strongly positive skin testing. The clinical manifestations were in full accordance with the positive ID testing, progressively more severe, immediate-type reactions that reappeared 1.5 months after the hematologists reinitiated imiglucerase therapy. This reappearance of infusion reactions suggests that the drug-specific IgE antibodies subsided during the time the substrate reduction therapy was given and that they redeveloped after imiglucerase reexposures. The negative SPT and ID tests in both control groups (exposed and nonexposed to imiglucerase) advise the immediate immunological mechanism underlying the infusion reactions and that the positive patient wheal-and-flare result was antibody mediated and not irritant. The number of exposed controls recruited is small but should be considered on the basis that type I GD is very rare and patients who receive imiglucerase are few. To our knowledge, these are the only recorded data on SPT and ID tests with imiglucerase in exposed and/or nonexposed control subjects.

With regard to desensitization to imiglucerase, two case reports have been published so far; Erdoğan et al⁶ reported the successful desensitization of an adult patient with no proven immediate hypersensitivity as the *in vivo* test (SPT, ID), using the same dilutions of imiglucerase, was negative. Peroni et al⁵ presented the desensitization of a child with positive ID at 1:100 dilution of the enzyme. However, no skin tests in control subjects, exposed or nonexposed to imiglucerase, were performed in either of these cases. Literature on imiglucerase skin testing in

patients presenting acute infusion reactions is not available, so we cannot be aware of its sensitivity and specificity. The same stands for the serum-specific IgE determination values, which were in our case negative, but in Peroni's child patient positive.⁵

To date, these are the only recorded cases of patients with type I GD and reactions during the infusion of imiglucerase that have undergone desensitization. The therapeutic doses administered, as well as the desensitization protocols used, are different among the three cases. We treated our patient using a well-standardized and efficient 12-step RD protocol as proposed by Castells⁹ and Brennan⁸ for other drugs and hence support that it might be effective in imiglucerase as well. Of course, the further application of the suggested protocol in imiglucerase RD is required to provide more data to substantiate its efficacy and safety. Our choice to proceed with the specific RD protocol was due to the fact that its efficacy is well and widely recorded in the literature and that we have been successfully using it in our Desensitization Unit for other biologicals, chemotherapeutics, and antibiotics. On the basis that the molecular mechanisms underlying RD are unknown,⁸ it is acknowledged that all existing RD protocols are empirical. Still, taking into consideration the unsuccessful effort of the treating hematologists to administer imiglucerase to our patient by the application of another, less-standardized, RD protocol, we would strongly like to stress the importance of using already clinically well-documented and widely used protocols. When the drug concerned is irreplaceable or more effective than potential alternatives, as in our patient, and an RD is applicable, the choice of an RD protocol that is recorded to reduce the known risks associated with desensitization is crucial.

In conclusion, we present the first report of successful RD to imiglucerase in an adult patient with type I GD and documented IgE-mediated hypersensitivity. Our data suggest that the use of a well-standardized RD protocol currently applied in other biologicals and in chemotherapeutics might be effective in imiglucerase-RD but on the basis of the stringently controlled conditions of this case report. Thus, its wider application in large, ideally multicenter, controlled clinical studies would be needed to substantiate any apparent efficacy and demonstrate safety.

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