

Successful sebelipase alfa desensitization in a pediatric patient

Ilknur Kulhas Celik, MD^a, Aynur Kucukcongar Yavas, MD^b, Ozlem Unal Uzun, MD^b, Betul Siyah Bilgin, MD^c, Emine Dibek Misirlioglu, MD^a, and Mehmet Gunduz, MD^b



Clinical Implications

- Sebelipase alfa has recently been used as an enzyme replacement therapy in patients with Wolman disease. Data from the clinical trials revealed good tolerability of sebelipase alfa. This report presents a case of sebelipase alfa–induced anaphylaxis and successful desensitization.

TO THE EDITOR:

Lysosomal acid lipase (LAL) deficiency is a rare multisystem autosomal recessive storage disease caused by the absence or deficiency of LAL, an enzyme that hydrolyzes cholesteryl esters and triglycerides. The infantile form of the disease (frequently called Wolman disease) presents as rapid progression and death before 1 year of age.¹ Sebelipase alfa, a recombinant human LAL, is an enzyme produced via targeted gene expression in the egg white of transgenic *Gallus gallus domesticus* hens.^{2,3} Data from clinical trials in humans revealed good tolerability of sebelipase alfa.⁴⁻⁸ In clinical trials, 3 (3%) of 106 patients treated with sebelipase alfa experienced signs and symptoms consistent with anaphylaxis. These 3 patients included an infant, a child, and an adult, all of whom developed anaphylaxis during infusion a year after initial treatment.⁹ Here we present a case of sebelipase alfa–induced anaphylaxis and successful desensitization.

A 3-month-old boy was diagnosed with Wolman disease in our pediatric metabolic disease clinic and developed a hypersensitivity reaction to sebelipase alfa (Kanuma). He received 3 weekly doses of sebelipase alfa by intravenous (IV) infusion

without premedication. However, 60 minutes after initiating the fourth sebelipase alfa infusion (again without premedication), the patient experienced generalized rash without systemic symptoms. Sebelipase alfa was stopped, and the patient was treated with 1 mg/kg of hydroxyzine and 1 mg/kg of methylprednisolone. Seven days after this reaction, skin tests were performed to demonstrate the patient's hypersensitivity. Skin prick test with undiluted sebelipase alfa and intradermal test with 1:100 and 1:10 dilution were negative. Skin prick test with hen's egg was also negative. Two days after the reaction, the patient was premedicated with 1 mg/kg IV methylprednisolone 1 hour before sebelipase alfa infusion and the infusion rate was decreased. He received the enzyme for 2 weeks with premedication without any reaction. However, in the seventh week of treatment, the patient experienced generalized urticaria, cyanosis of the lips, shortness of breath, and tachycardia within 10 minutes of starting the sebelipase alfa infusion. Pulse oximetry indicated 70% oxygen saturation. The infusion was immediately stopped, and the patient was treated with 0.01 mg/kg intramuscular epinephrine and 1 mg/kg prednisolone. Because our patient required sebelipase alfa therapy, we decided to attempt desensitization.

A 12-step desensitization protocol was performed using 3 different solutions of sebelipase alfa. Based on the normal therapeutic dose required by the patient, solutions of 0.0024, 0.024, and 0.24 mg/mL were prepared (Table I). Each solution was used for 4 steps, with the entire 12-step protocol completed in 6.5 hours (Table I). Infusion was initiated 1 hour after the administration of 1 mg/kg hydroxyzine and 1 mg/kg methylprednisolone as premedication. No adverse reaction was observed during the infusion, and desensitization was completed successfully. After undergoing desensitization, the patient has continued weekly sebelipase alfa therapy with no further adverse reactions. To date, the patient has received sebelipase alfa 3 times with premedication and 4 times without premedication with no complications.

Sebelipase alfa (Kanuma) was developed for long-term enzyme replacement therapy in patients with LAL deficiency. IV sebelipase alfa is generally well tolerated. No serious adverse reactions

TABLE I. Intravenous desensitization protocol of sebelipase alfa

Step	Solution type	Rate, mL/h	Infusion duration, min	Volume infused per step, mL	Dose administered with this step, mg	Cumulative dose, mg
1	A	2	30	1	0.0024	0.0024
2	A	5	30	2.5	0.006	0.0084
3	A	10	30	5	0.012	0.0204
4	A	20	30	10	0.024	0.0444
5	B	4	30	2	0.048	0.0924
6	B	8	30	4	0.096	0.1884
7	B	16	30	8	0.192	0.3804
8	B	40	30	20	0.48	0.8604
9	C	8	30	4	0.96	1.8204
10	C	16	30	8	1.92	3.7404
11	C	32	30	16	3.84	7.5804
12	C	68.40	60	68.40	16.4196	24

Solution A is 3 mL of B solution + 27 mL of 0.9% NaCl (concentration, 0.0024 mg/mL). Solution B is 4.5 mL of C solution + 40.5 mL of 0.9% NaCl (concentration, 0.024 mg/mL). Solution C is 12 mL (24 mg) of drug + 88 mL of 0.9% NaCl (concentration, 0.24 mg/mL).

were reported in the first-in-human phase I/II clinical trial of sebelipase alfa.⁴ A phase III clinical trial of sebelipase alfa reported 2 serious infusion-related adverse reactions during the study period. One of these patients had an atypical reaction (8.5 hours after infusion) that resolved rapidly after a single dose of oral diphenhydramine, and the other patient did not complete the double-blind period because dosing was paused pending further investigation of an infusion-associated reaction.⁵

Skin tests are important for the diagnostic evaluation of drug hypersensitivity reactions. Immediate reactions (onset usually <1 hour after drug exposure) can be assessed by immediate-reading skin tests. However, there are various technical and nontechnical reasons that may cause an absence of skin test reactivity.¹⁰ The fact that our patient's skin tests were negative may be linked to the absence of the standard test dose of the drug and the short time period between the development of the reaction and the time of testing.

There is no reported case of successful desensitization to sebelipase alfa in an infant. To the best of our knowledge, this is the first case in the literature to describe successful desensitization to sebelipase alfa using the 12-step protocol.

^aDivision of Pediatric Allergy and Immunology, University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

^bDivision of Pediatric Metabolism, University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

^cDivision of Neonatology, University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 1, 2018; revised June 19, 2018; accepted for publication July 10, 2018.

Available online July 24, 2018.

Corresponding author: Ilknur Kulhas Celik, MD, Division of Pediatric Allergy and Immunology, University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, 6080 Altindag, Ankara, Turkey. E-mail: dr.ilknur-46@windowslive.com.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.07.012>

REFERENCES

1. Grabowski GA, Charnas L, Du H. Lysosomal acid lipase deficiencies: the Wolman disease/cholesteryl ester storage disease spectrum. In: Valle SD, Beaudet AL, Vogelstein B, et al., editors. *The Online Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York: McGraw-Hill; 2012.
2. Anderson RA, Sando GN. Cloning and expression of cDNA encoding human lysosomal acid lipase/cholesteryl ester hydrolase. Similarities to gastric and lingual lipases. *J Biol Chem* 1991;266:22479-84.
3. Quinn AG, Leavitt M, Hu W, Hollingsworth KG, Thoma C, Trenell MI, et al. SBC-102, a recombinant enzyme replacement therapy corrects clinically relevant phenotypic abnormalities in a rat model of lysosomal acid lipase deficiency. *Metabol Mol Genet* 2011;102:37.
4. Balwani M, Breen C, Enns GM, Deegan PB, Honzik T, Jones S, et al. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. *Hepatology* 2013;58:950-7.
5. Burton BK, Balwani M, Feillet F, Barić I, Burrow TA, Camarena Grande C, et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. *N Engl J Med* 2015;373:1010-20.
6. Valayannopoulos V, Malinova V, Honzik T, Balwani M, Breen C, Deegan PB, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. *J Hepatol* 2014;61:1135-42.
7. Jones SA, Plantaz D, Vara R, Eckert S, Le Quan Sang KH, Brassier A, et al. Effect of sebelipase alfa on survival and liver function in infants with rapidly progressive lysosomal acid lipase deficiency. *Mol Genet Metab* 2015;114:59.
8. Jones SA, Brassier A, Hughes J, Plantaz D, Vara R, Breen C, et al. Effect of sebelipase alfa on survival and liver function in infants with rapidly progressive lysosomal acid lipase deficiency: 2-year follow-up data. *Mol Genet Metab* 2016;117:63.
9. Su K, Donaldson E, Sharma R. Novel treatment options for lysosomal acid lipase deficiency: critical appraisal of sebelipase alfa. *Appl Clin Genet* 2016;9:157-67.
10. Kränke B, Aberer W. Skin testing for IgE-mediated drug allergy. *Immunol Allergy Clin North Am* 2009;29:503-16.