



Letter

Successful desensitization in a type VI mucopolysaccharidosis patient with probable IgE-mediated allergy to galsulfase [Naglazyme]

Type VI mucopolysaccharidosis, also known as Maroteaux-Lamy syndrome, is caused by mutations in the gene encoding arylsulfatase B, located on chromosome 5q14.1. These mutations are responsible for accumulation of the glycoaminoglycan dermatan sulfate, in numerous tissues.¹ Weekly enzyme replacement therapy (ERT) with recombinant human arylsulfatase B (galsulfase [Naglazyme, BioMarin Pharmaceutical Inc, Novato, California]) is the only available treatment.² Infusion reactions are relatively frequent with ERT, occurring at a rate of 16% in clinical trials.³ Here we describe a simple rapid desensitization protocol to desensitize patients with probable IgE-mediated allergy to galsulfase and subsequent evolution of a case over 2 years.

The case is a young girl who was diagnosed with mucopolysaccharidosis (MPS) VI at 10 years of age. Galsulfase therapy was initiated using standard infusion protocol (1 mg/mL over 4 hours, with oral acetaminophen and intravenous diphenhydramine premedication). Therapy was well tolerated for 1 year, until the patient started to present with generalized urticaria toward the end of each treatment. Clinical tolerance was temporarily reestablished by increasing the total perfusion time to 8 hours and adding an oral dose of diphenhydramine 1 hour before the end of the perfusion. Urticarial reactions returned after 4 weeks with concomitant severe conjunctivitis and lip angioedema. She was then referred to the allergy clinic.

Allergy skin tests were performed with galsulfase solution using standard methods.⁴ Both skin prick at a concentration of 1 mg/mL and intradermal injection with a 1:100 dilution (0.01 mg/mL) were negative. An intradermal skin test at a dilution of 1:10 (0.1 mg/mL) induced a wheal of 10 mm and an erythema of 25 mm. Ten healthy controls were tested negative at this dilution.

Enzyme replacement therapy was resumed, using the rapid desensitization protocol described in Table 1. The patient received intravenous diphenhydramine premedication and, because of urticarial reaction with last perfusion rates, a second intravenous diphenhydramine dose was added 1 hour before the end. Protocol was administered weekly and well tolerated. Intradermal skin tests were repeated and were still positive at a dilution of 0.1 mg/mL at 1 and 2 years, with wheals of 9 mm and 8 mm and erythemas of 25 and 22 mm, respectively. Despite persistently positive skin tests, drug provocation challenge was performed to verify induction of tolerance after 2 years of weekly desensitization. Desensitization protocol was progressively stepped down over 3 weeks without any adverse event. Treatment has since been received normally and has been well tolerated now for 4 months.

To the best of our knowledge, this is the first report on galsulfase allergy to document a probable immunoglobulin E (IgE)

mechanism. IgE-mediated reactions have been well described with ERT given for MPS I and MPS II, and development of IgE against galsulfase had been observed in preliminary animal studies.^{5–7} Infusion reactions occur in up to 16% of patients with MPS VI.³ These reactions were assumed to be non-IgE-mediated, but an IgE-mediated mechanism was not ruled out.^{3,8} Hence, true IgE-mediated reactions may be much more frequent than previously assessed and may represent the dominant mode of reaction in MPS VI.

The standard approach to “anaphylactoid” reactions as recommended by the monograph and previous publications has been to premedicate with antihistamine and prolong perfusion time up to 20 hours.^{2,7} However, some patients reacted despite these precautions.⁸ Another approach is to further add 2 doses of prednisone the day before and 1 dose of methylprednisolone 1 hour before the slowed infusion. Although reported to be successful, this approach carries the major caveat of chronic exposure to relatively high-dose corticosteroids, because ERT must be received every week.

Our rapid desensitization protocol has the advantage of being steroid-sparing, relatively rapid, and easy to perform, and it is shown here to be effective for IgE-mediated reactions. Given the short half-life of the enzyme (26 minutes), desensitization must be repeated with every treatment every week. Return to a normal perfusion was tolerated in our patient after 2 years of weekly

Table 1
Rapid desensitization protocol

Infusion volume (mL)	Duration of infusion (min)	Administered dose (mg)
Bag #1 (0.0069 mg/mL)		
0.6	15	0.004
0.9	15	0.006
1.7	15	0.012
2.6	15	0.018
4.3	15	0.030
6.9	15	0.047
11.7	15	0.081
19.1	15	0.132
Bag #2 (0.38 mg/mL)		
0.6	15	0.228
0.9	15	0.342
1.7	15	0.646
2.6	15	0.988
4.3	15	1.634
6.9	15	2.622
11.7	30	4.446
19.1	60	7.258
Total	5 h	18.495^a

^aTotal dose calculated for a weight of 18.5 kg (1 mg/kg).

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desensitization, suggesting induction of permanent clinical tolerance. However, this could also represent the natural evolution of galsulfase allergy; previous series of MPS VI patients with “anaphylactoid” reactions also showed that perfusion rates could usually be increased back to normal after many weeks of very slow ERT perfusion. As with *Hymenoptera* venom immunotherapy, persisting positive skin tests do not rule out achievement of clinical tolerance. Regardless of underlying mechanism, stepwise provocation challenge should be attempted after many weeks of treatment to reassess the need for weekly desensitization.

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