Rapid Desensitization for Immediate Hypersensitivity to Galsulfase Therapy in Patients with MPS VI

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Abstract Mucopolysaccharidosis type VI (MPS VI) is a progressive, chronic, and multisystem lysosomal storage disease. Enzyme replacement therapy (ERT) with the recombinant human arylsulfatase B enzyme (galsulfase [Naglazyme]) is recommended as first-line therapy. It is generally reported as safe and well tolerated. Frequently observed mild to moderate infusion-related reactions which can be easily handled by reducing or interrupting the infusion and/or administering additional antihistamines, antipyretics, and corticosteroids are mostly mediated by non-IgE mechanisms. Here we report two children with MPS VI who experienced IgE-mediated reactions with galsulfase at the second year of the therapy. One child had anaphylaxis and the other had urticarial eruptions. They could receive ERT after successful rapid desensitization. To our knowledge, this is the second report on galsulfase allergy with IgE-mediated reaction. It is important to recognize IgE-mediated reactions since they can be life-threatening and do not respond to the standard therapies.

We recommend allergy skin tests in the evaluation of infusion-related reactions unresponsive to standard therapies, so that continuation of ERT will be feasible after successful desensitization.

Abbreviations

BWH	Brigham and Women's Hospital
ERT	Enzyme replacement therapy
GAG	Glycosaminoglycan
MPS VI	Mucopolysaccharidosis type VI
N-acetylgalactosamine -4-sulfatase	Arylsulfatase B

Introduction

Mucopolysaccharidosis type VI (MPS VI or Maroteaux-Lamy syndrome; OMIM 253200) is a lysosomal storage disorder caused by deficient activity of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B or ASB; EC 3.1.6.12), which catabolizes the glycosaminoglycan (GAG) dermatan sulfate. Accumulation of GAG in lysosomes in a wide range of tissues causes progressive multisystem involvement with physical and functional impairment and shortened lifespan (Valayannopoulos et al. 2010). ERT is recommended as first-line therapy for MPS VI with the approval of the recombinant human arylsulfatase B enzyme (galsulfase [Naglazyme]) by the US Food and Drug Administration and the European Medicines Agency. The recommended dose of Naglazyme is 1 mg/kg body weight administered once weekly as an intravenous infusion over a duration of 4 h (Harmatz et al. 2013). It is generally reported as safe and well tolerated. Infusion-related reactions

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were described in several studies and case reports, but probable IgE-mediated allergy has been reported only in one patient. Frequently observed reactions were mild to moderate infusion-related reactions, which were easily resolved by slowing or temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and corticosteroids (Harmatz et al. 2006; Horovitz et al. 2013). Here we report two children with MPS VI who experienced IgE-mediated hypersensitivity reactions with galsulfase and could receive ERT after successful rapid desensitization.

Case 1

A 9-year-old male child had been diagnosed with MPS VI when he was 12 months old with facial coarsening, hepatosplenomegaly, chest deformity, and high urinary GAG levels. Diagnosis had been confirmed with enzyme studies [lymphocyte arylsulfatase B (ARSB) 3.8 μ kat/kg protein (control range 27.4; 17–40.8 μ kat/kg protein; Sahlgrenska University)] at the age of 2.5 years, and ERT (1 mg/kg galsulfase solution, intravenous and weekly) had been initiated at the age of 7 years. According to the standard institutional practice, galsulfase solution had been diluted with sterile 0.9% sodium chloride solution to 100 ml. After parenteral pheniramine maleate (1 mg/kg) premedication, approximately 3% of the total solution had been infused during the first hour and the remaining volume in 3 h. The patient had no adverse reactions during weekly galsulfase infusions for the first 2 years of ERT. In the following 6 months, he had some mild itching and urticarial eruptions during infusions, but these reactions were controlled by elongation of the duration of infusion therapy. He was referred to the Allergy Outpatient Clinic after an anaphylaxis with generalized urticaria, angioedema of the lips and the face, stridor, and wheezing during a galsulfase therapy.

Allergy skin tests were performed with galsulfase solution using standard methods. Skin prick tests with 1:1,000, 1:100, and 1:10 dilution and full concentration (1 mg/ml) and intradermal tests with 1:100 and 1:10 dilution were performed. Although the patient's skin prick tests were negative, intradermal test with 1:100 dilution showed positive reaction (Fig. 1). The allergy skin prick tests were performed in additional eight children with MPS VI who were already receiving galsulfase therapy, and all were negative.

A modified version of the standardized desensitization protocol of Brigham and Women's Hospital (BWH) Desensitization Program was used (Castells 2006a, b; Castells et al. 2012). The patient was premedicated with intravenous pheniramine maleate (1 mg/kg), ranitidine (1 mg/kg), and methylprednisolone (1 mg/kg) 20 min before the desensitization procedure. The 20-step standard

Fig. 1 Positive intradermal skin prick test of case 1

protocol with five solutions containing 1:10,000, 1:1,000, 1:100, 1:10, and full dose of galsulfase was administered sequentially. Each solution was administered gradually in four different steps with 15 min intervals (Table 1). Generalized urticarial rash, angioedema of the lips, stridor, and wheezing occurred at the beginning of third solution (1:100 dilution). The infusion was paused, and initially intravenous pheniramine maleate, ranitidine, and inhaled adrenaline were administered. Salbutamol was also administered because of refractory lower respiratory symptoms. On resolution of the reaction, the protocol was restarted from the same step. Urticarial rash reoccurred at the end of the last step of the final fifth solution. The infusion was paused again and 5 mg montelukast, a leukotriene receptor antagonist, was given orally. When the reaction resolved, the infusion was restarted and completed.

One day before the next desensitization procedure, a week later, the patient was premedicated with oral H1-antihistamine (cetirizine) and H2-antihistamine (ranitidine). The patient completed the desensitization procedure without further reactions. The following four desensitizations were uneventful; therefore, premedication with methylprednisolone and the first two dilutions were omitted. Twelve-step protocol with three solutions was applied uneventfully for 5 months (Table 2). ERT had to be stopped for 2 months because of drug unavailability. With the start of treatment, 20-step desensitization protocol was restarted with premedication. During the infusion, urticarial eruptions and mild wheezing occurred at the beginning of the last solution. The infusion was paused, symptomatic treatment with H1 antihistamine and inhaled salbutamol was given, and the infusion was restarted after the reaction had resolved. The infusion rate could not be increased due to urticarial eruptions and stopped at the 16th step. To resolve this problem, oral montelukast was added to the premedication given the night before the desensitization day. On the

Table 1 20-Step, five-bag desensitization protocol for case 1

Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose administered (mg)	Cumulative dose (mg)
1	1	1	15	0.25	0.000005	0.000005
2	1	2	15	0.50	0.00001	0.000015
3	1	4	15	1.00	0.00002	0.000035
4	1	8	15	2.00	0.00004	0.000075
5	2	2	15	0.50	0.0001	0.000175
6	2	5	15	1.25	0.00025	0.000425
7	2	10	15	2.50	0.0005	0.000925
8	2	20	15	5.00	0.001	0.001925
9	3	1	15	0.25	0.0005	0.002425
10	3	2	15	0.50	0.001	0.003425
11	3	4	15	1.00	0.002	0.005425
12	3	8	15	2.00	0.004	0.009425
13	4	2	15	0.50	0.001	0.010425
14	4	5	15	1.25	0.025	0.035425
15	4	10	15	2.50	0.05	0.085425
16	4	20	15	5.00	0.10	0.185425
17	5	5	15	1.25	0.25	0.435425
18	5	10	15	2.50	0.5	0.935425
19	5	20	15	5.00	1.0	1.935425
20	5	39	100.4	65.25	18.064575	20.000000
<i>Total time (min)=</i>				385.4 = 6.4 h		

Solution 1 (1/10,000): 100 ml; 0.00002 mg/ml

Solution 2 (1/1,000): 100 ml; 0.0002 mg/ml

Solution 3 (1/100): 100 ml; 0.002 mg/ml

Solution 4 (1/10): 50 ml; 0.02 mg/ml

Solution 5 (1/1): 100 ml; 0.2 mg/ml

Table 2 12-Step, three-bag desensitization protocol for case 1

Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose administered (mg)	Cumulative dose (mg)
1	1	1	15	0.25	0.0005	0.0005
2	1	2	15	0.5	0.001	0.0015
3	1	4	15	1	0.002	0.0035
4	1	8	15	2	0.004	0.0075
5	2	2	15	0.5	0.01	0.0175
6	2	5	15	1.25	0.025	0.0425
7	2	10	15	2.5	0.05	0.0925
8	2	20	15	5	0.10	0.1925
9	3	5	15	1.25	0.25	0.4425
10	3	10	15	2.5	0.50	0.9425
11	3	20	15	5	1.00	1.9425
12	3	39	120.4	78.25	18.0575	20.0000
<i>Total time (min)=</i>			285.4 = 4.75 h			

Solution 1 (1/100): 100 ml; 0.002 mg/ml

Solution 2 (1/10): 50 ml; 0.02 mg/ml

Solution 3 (1/1): 100 ml; 0.2 mg/ml

desensitization day, premedication with H1 and H2 antihistamine was given before the 16th step. No more reactions occurred during therapy after four desensitizations. The desensitization protocol was shifted from 20-step to 12-step. The patient continues to receive galsulfase therapy uneventfully, on weekly basis since 10 months.

Case 2

A 4-year-old male child had been diagnosed as MPS VI with coarse facial appearance, macrocephaly, and pectus carinatum when he was 11 months old. The diagnosis had been confirmed with enzyme assays [leukocyte ARSB 0.00 $\mu\text{mol/g/h}$ (control 12.6 $\mu\text{mol/g/h}$, Willink Laboratory, Genetic Medicine, St Mary's Hospital)], and ERT (1 mg/kg galsulfase solution, intravenous and weekly) was initiated. The therapy was well tolerated for 26 months until the patient started to have recurrent urticarial eruptions during the last three galsulfase therapies. He was referred to the Allergy Outpatient Clinic for further evaluation.

The history revealed that this child had been tested for allergic reaction to galsulfase as our first patient's control case. His skin prick and intradermal tests were negative 10 months before the beginning of the allergic reactions. The repeated allergy skin tests revealed positive reaction with intradermal skin test at a dilution of 1:100. The same premedication and the 20-step standard protocol were administered sequentially. The desensitization protocol was shifted from 20-step to 12-step after four uneventful desensitizations. The patient continues to receive galsulfase therapy on weekly basis, without any adverse reactions since 5 months.

Discussion

Rapid desensitization is the induction of temporary clinical tolerance to a drug, thereby allowing the patient to be treated with the medication, which had caused hypersensitivity reaction (Brennan et al. 2009; Castells 2006a, b; Castells et al. 2012; Liu et al. 2011). Rapid desensitization targets mast cells so that it can be used for IgE-mediated anaphylactic or (non-IgE-mediated) anaphylactoid immediate type reactions (Liu et al. 2011). Here, we report two MPS VI cases with IgE-mediated hypersensitivity to galsulfase solution confirmed by positive intradermal tests and successful rapid desensitizations.

We used a modified version of BWH Desensitization Program, a universal protocol for drug-induced immediate type of hypersensitivity reactions, developed by Castells (2006a, b) and Castells et al. (2012). This protocol is a 12-

to 20-step standard protocol, in which tolerance was achieved by delivering double doses of antigen at fixed time intervals. We initially used the 20-step protocol in both cases and continued with the 12-step standard protocol.

Reported infusion-related reactions to ERT ranged from 3% to 36% (Harmatz et al. 2008; Miebach 2009). Miebach reported hypersensitivity reactions in 28 (36%) out of 77 patients with MPS type I, type II, and type VI, all of which were controlled by reducing the infusion rate and/or administering antihistamines, antipyretics, and low-dose corticosteroids (2009). Horovitz et al. reported infusion-related reactions in eight (24%) out of 34 patients with MPS VI, and none of them were severe reactions (2013). Intervention and/or premedication with antihistamines, steroids, and antipyretics and decreasing the rate of infusion were sufficient to overcome the reactions.

Kim et al. reported severe anaphylactoid reactions to galsulfase infusion in a 3.5-year-old patient with MPS VI during the fourth and fifth weeks of the therapy (2008). The patient could not receive all of the galsulfase infusion in spite of interruption of the infusion and intervention with antihistamines and steroids. They were able to prevent reactions with oral prednisolone the day before each infusion, intravenous methylprednisolone, and diphenhydramine 1 h before each infusion and decreasing the rate of infusion. The first case with probable IgE-mediated allergic reactions was reported by Begin et al. (2013). A 10-year-old girl with MPS VI had presented with urticarial eruptions, severe conjunctivitis, and lip angioedema during galsulfase therapy after an uneventful duration of ERT for 1 year. Intradermal skin test at a dilution of 1:10 (0.1 mg/ml) was positive, and they also successfully desensitized the patient with a different rapid desensitization protocol (Begin et al. 2013).

We confirmed that IgE-mediated reactions to galsulfase can occur in patients with MPS VI. Case 1 had presented with anaphylaxis and case 2 had presented only with urticarial eruptions. In both cases, there was an interval of 2 years with the beginning of the ERT and IgE-mediated reactions. The case with probable IgE-mediated allergy reported by Begin et al. also had one uneventful year before the onset of the first allergic reaction (2013). We suggest that frequently observed mild to moderate infusion-related reactions which can be easily handled by reducing or interrupting the infusion and/or administering additional antihistamines, antipyretics, and corticosteroids are mostly mediated by non-IgE mechanisms. However, it is important to recognize late-appearing IgE-mediated reactions since they can be life-threatening and do not respond to the standard therapies. IgE-mediated reactions occur after an

interval during which the host is sensitized with the offending allergen.

Non-IgE-mediated infusion-related reactions are mostly observed at the earlier phases of ERT, whereas IgE-mediated reactions are more common during the later stages since a time interval for sensitization is necessary. We recommend allergy skin tests in the evaluation of infusion-related reactions unresponsive to the standard therapies, so that continuation of ERT will be feasible after successful desensitization.

Take-Home Message

Allergy skin tests should be performed in the evaluation of infusion-related reactions unresponsive to standard therapies, so that continuation of ERT will be feasible after successful desensitization.

Compliance with Ethics Guidelines

Conflict of Interest

Zeynep Tamay, Gulden Gökçay, Fatih Dilek, Mehmet C Balci, Deniz Ozceker, Mubeccel Demirkol, and Nermin Guler declare that they have no conflict of interest.

Competing Interests

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

This article does not contain any animal subjects performed by the any of the authors.

Details of the Contributions of Individual Authors

Zeynep Tamay designed and reported the cases; Fatih Dilek, Mehmet C Balci, and Deniz Ozceker conducted the rapid desensitization procedures; Gulden Gokcay revised

the language and also revised the intellectual content with Mubeccel Demirkol and Nermin Guler.

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