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CASE REPORT

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Type 1 hypersensitivity reaction with elosulfase alpha treated with desensitisation

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Keywords

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ABSTRACT • Elosulfase alpha is an recombinant enzyme used to treat patients with mucopolysaccharidosis type 4A (MPS 4A). A patient diagnosed with mucopolysaccharidosis type 4A had 13 doses of elosulfase alpha with 2 mg/kg per dose weekly. The patient developed urticaria, angioedema of the lips and dyspnea, maculopapular and urticarial rash over the foot and also he had fever. The patient then was consulted to pediatric allergy and intradermal test with elosulfase alpha 1/100 dilution was found positive with 6x6 mm enduration surrounding erythema. Total enzyme amount was calculated and desensitisation with dilutions of 1/100, 1/10 and whole concentration were performed within six hours. No complications or reactions were seen. The patient has taken 40 doses of enzyme within about 10 months with desensitisation protocol. Elosulfase is currently the only approved medication to be used in mucopolysaccharidosis type 4A patients. Desensitisation seems to be an effective method to overcome type I hypersensitivity reaction.

INTRODUCTION

Allergic reactions to many drugs range widely in clinical severity from mild pruritus to anaphylaxis (1). Number of hypersensitivity reactions those were reported in literature is increasing with the use of biological agents like cytokines, monoclonal antibodies and enzymes (2-4). Mucopolysaccharidosis (MPS) type IVA (Morqiuo A syndrome) is a rare, autosomal recesessive, progressive degenerative lysosomal disease (5). Typically patients have skeletal and joint anomalies (short stature, knee and joint dysplasia, genu valgum, pectus carinatum, joint hypermobility and spinal anomalies), ophthalmologic, sensorial, digestive, cardiovascular and/or respiratory anomalies, but intelligence is not effected (6-8). Recently, intravenous elosulfase alfa has been approved for the treatment of MPS type 4A disease. Although hypersensitivity reactions with this enzyme are mentioned in an phase 3 study (9), reports about desensitisation are lacking in the literature. We present the first case of a successful elosulfase alfa desensitisation, who developed a type 1 hypersensitivity (15).

CASE REPORT

The patient was diagnosed with MPS type 4A (Morquio disease) at 4 years of age with complaints of growth retardation, thorax deformities and also recurrent otitis media. He was born 2100 gr with normal vaginal delivery. The patient's neuromotor development was normal. He was referred

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to department of pediatric metabolic disorders due to coarse face, short neck, pectus carinatum, kyphosis, scoliosis, hepatomegaly and splenomegaly when he was at four years of age. Haemogram and biochemical investigations were normal. Enzyme analysis of N-acetylgalactosamine 6 sulfatase (GALNS) for mucopolysaccharidosis type 4A was 82 pmol/g/h (normal level 400-2000). Since enzyme level was significantly decreased with other sulfatases being normal, he had been diagnosed with mucopolysaccaridosis type 4A. Treatment with elosulfase alfa (Vimizim®) was started at a dose of 2mg/kg/week. On the 13th week of the treatment the patient developed urticaria, fever at the second hour of infusion and generalized itching at the first hour of treatment on the 14th week. At the 15th week during the 45th minute, the patient developed urticaria, angioedema of the lips and dyspnea which was treated by stopping the infusion, providing nasal oxygen and injecting 1/1000 adrenaline with a dose of 0.001 mg/kg, intramuscular and oral antihistaminics (2). As the clinical situation was compatible with type 1 hypersensitivity reaction, prick to prick epidermal test was performed by using elosulfase alpha at concentration of 5 mg/5 ml. The test was negative. Then intradermal tests with elosulfase alfa were performed in order of 1/1000, 1/100 dilutions of 5 mg/5 ml of the enzyme. The intradermal test with 1/100 dilution was found positive with 6x6 mm enduration with surrounding erythema. The patient had no alternative, effective treatment and the enzyme was vital for his disease. Therefore desensitisation with elosulfase alfa was decided. Cumulative enzyme dose was calculated and a general rapid desensitisation protocol recommended by Castells et al (1) (Table 1). Standard premedication with antihistaminic, and antipyretics plus H_2 receptor antagonist ranitidine 1 mg/kg were given to the patient 1 hour prior to desensitisation. The patient received

Table 1 Elosulfase alfa desensitisation protocol

Dilution					Cumulative drug dose	
Dilution 1 (1. bottle): 1/100 Dilution		250 cc SF			0,32 mg	
Dilution 2 (2. bottle): 1/10 Dilution		250 cc SF			3,2	
Dilution 3 (3. bottle): Full Dilution		250 cc SF			28,48 mg	
Level dose	**Dilution**	**Infusion rate (ml/hour)**	**Time (minute)**	**Volume (ml)**	**Dose (mg)**	**Cumulative**
1	1	2.5	15	0,625	0,0008	0,0008
2	1	5	15	1,25	0,0016	0,0024
3	1	10	15	2,5	0,0032	0,0056
4	1	20	15	5	0,0064	0,0120
5	2	5	15	1.25	0,016	0,0136
6	2	10	15	2.5	0,032	0,0168
7	2	20	15	5	0,064	0,023
8	2	40	15	10	0,128	0,036
9	3	10	15	2.5	0,282	0,064
10	3	20	15	5	0,565	0,120
11	3	40	15	10	1,13	1,2507
12	3	80	180	232,5	30,75	32

Cumulative drug dose: 32 mg/100 ml (Elosulfase alfa, 2 mg/kg), weight of the patient: 16 kg

the enzyme treatment 40 times without any complication following the same desensitisation protocol instructions for about 10 months.

DISCUSSION

Elosulfase alfa is the first and the only treatment for MPS type 4A today. In the literature, there is only one study about safety of elosulfase alfa treatment which is a a placebo-controlled randomized, double-blinded phase 3 study that was conducted at 33 centers from 17 countries between 2011-2012. One hundred and seventy-six patients diagnosed as Morquio A syndrome with mean age 11.9 years were included. Immunogenicity profile of elosulfase alfa besides efficacy and safety were investigated. All patients developed elosulfase alfa anti-drug antibodies, majority of which were neutralizing antibodies capable of interfering with cation-independent mannose-6- phosphate receptor binding in vitro. Less than 10 % of patients tested positive for drug-specific IgE during the study. Serious drug-related adverse events were observed in 9 of patients treated with elosulfase alfa 2 mg/kg/week and 4 of patients treated with 2 mg/kg elosulfase alfa every other week. Three patients developed serious drug-related hypersensitivity with anaphylaxis. No correlations were detected between elosulfase alfa- specific IgE type antibody positivity or total antibody titers and increased incidence of drug-related hypersensitivity reactions like anaphylaxis and angioedema (9). Desensitisation remains one of the choices for elosulfase alfa related severe allergic hypersensitivity. This case is the first MPS type IVA patient who underwent elosulfase alfa desensitisation in the literature. In 2010, the European Network of Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI) research groups declared a consensus report compromising general considerations about desensitisation for drug hypersensitivity reactions (1). The desensitisation method by Castells et al. can be one of the choices used for rapid desensitisation (10). We applied this general protocol to our patient who received elosulfase alfa desensitisation for 40 infusions without any complications for 10 months. As a result, data about drug-specific Ig E mediated hypersensitivity reactions to elosulfase alfa in the treatment of MPS type IV A is limited and ours is the first case with successful desensitisation.

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