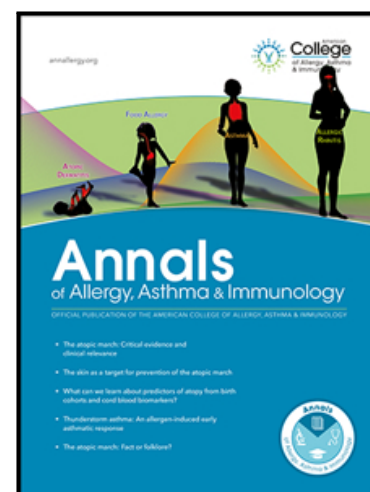


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Shortened desensitization leading to two years of enzyme replacement therapy with elosulfase-alfa

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Short Title: Shortened desensitization with elosulfase-alfa

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Abbreviations:

ERT: Enzyme replacement Therapy

HSR: Hypersensitivity Reactions

IDT: Intradermal Test

Morquio Syndrome (mucopolysaccharidosis-type-IV) is an autosomal-recessive lysosomal storage disease causing bone and joint disorders, respiratory and cardiac disease, spinal cord compression, impaired vision, hearing loss, and dental problems.¹ The only treatment is enzyme-replacement-therapy (ERT) with elosulfase-alfa (recombinant human n-acetyl-galactosamine-6-sulfatase-110; Vimizim®(5mg/5ml); BioMarin, Pharmaceutical Inc., Europe Lt, UK) and hypersensitivity reactions (HSR) may occur during elosulfase-alfa infusion like the other ERTs.² In case of severe HSR, drug desensitization is required³ and there is limited data on elosulfase-alfa desensitization.

This report presents a five-and-a-half-year-old female patient who developed anaphylaxis with elosulfase-alfa. The patient was diagnosed with Morquio Syndrome at the age of three years and started to receive elosulfase-alfa at a weekly dose of 2mg/kg. At the eighth week of treatment, within a few minutes of the initiation of the infusion, the patient suddenly exhibited facial flushing and emesis. The infusion was terminated suddenly. However in a few minutes, she developed a feeling of itching in her throat, angioedema of her lips, cyanosis, hypotension (systolic blood pressure was 50 mmHg), reduced heart rate of 40/min and a decrease in oxygen saturation (70%). The patient was treated with intramuscular adrenaline, intravenous methylprednisolone, and pheniramine immediately, and all symptoms resolved. During patient evaluation, a skin-prick test with undiluted commercial form of elosulfase-alfa and an initial intradermal test (IDT) with 1/1000 diluted form were performed. Both of the tests revealed negative results. Subsequently the IDT performed with 1/100 dilution resulted in a positive reaction with an endurance of 9 x 8 mm with a surrounding erythema. These test concentrations were used in previous studies and

skin tests were performed following published reports and guidelines.^{4,5} To exclude false positivity, IDTs with elosulfase-alfa at 1/100 dilution were performed on six healthy children, and all of them revealed negative results. Since the patient had no other treatment options, elosulfase-alfa was administered via desensitization.

Four different concentrations of elosulfase-alfa were prepared (Table 1a). A desensitization protocol was designed, starting with 2.5/100000 of the total required dose, calculated based on the weight of the patient, (Table 1a). Elosulfase-alfa was administered successfully with a premedication of methyl-prednisolone (1mg/kg) an hour before the desensitization procedure, in addition to acetaminophen (10mg/kg) and cetirizine (5mg), which were routinely recommended before the infusion following the manufacturers' instructions. The patient did not experience any HSRs then, methyl-prednisolone was terminated at the end of 12 weeks of desensitization. The four-bottle desensitization protocol was applied for an additional four weeks without any complications. Afterwards, the enzyme was administered following a 12 step protocol at three different concentrations, starting from bottle B (Table 1a) for 68 weeks. Subsequently, an additional modification was introduced in the desensitization protocol, starting from bottle B, and the duration for each step was shortened, reaching a final desensitization period of 153 minutes (Table 1b). As a result the desensitization period was shortened by half. A total of 96 successful desensitizations were performed during the two-year follow-up period, with eight weeks of missed treatment due to drug unavailability or respiratory-tract infection in the patient. A written informed consent was obtained from the parents for this report's publication.

Life-threatening HSRs such as cough, dyspnea, and hypotension, together with flushing, urticaria and/or angioedema, might be induced by elosulfase-alfa and other ERTs.⁵ The rate of HSRs associated with elosulfase-alfa and the rate of serious

elosulfase-alfa-induced anaphylaxis has have been reported as varying from 18.7% to 25%, and 7.7% to 10%,^{2,6} respectively. Premedication with antihistamines, montelukast, corticosteroids or prolonged infusion are useful methods in the management of mild reactions. However, desensitization is required in severe cases, and when the patient has no alternative treatment.^{3,5} Considering the benefit of elosulfase-alfa for these patients, desensitization is preferred.^{7,8}

There are only two case reports in the literature presenting desensitization protocols with elosulfase-alfa. In one of these, antipyretics and antihistamines were administered before a 16-step desensitization protocol was initiated. However the patient experienced urticaria in the sixth step. The patient was treated with methyl-prednisolone, followed by successful administration of elosulfase-alfa during subsequent desensitizations.⁷ Our patient was initially premedicated with methyl-prednisolone but it was stopped after 12-weeks of treatment. Cases with severe or breakthrough reactions require continuous weekly administration of methyl-prednisolone.⁵ However, since ERT for Morquio Syndrome is implemented weekly or biweekly, suppression of hypothalamic-pituitary-adrenal-axis is not expected with an intermittent low dose of methyl-prednisolone (1mg/kg).⁹ In the other case, reported by Arroabarren et al., elosulfase-alfa was administered via desensitization for 10 weeks, with a premedication of desloratadine, dexchlorpheniramine, montelukast, and acetaminophen, but the patient developed several breakthrough reactions and required additional steroids and antihistamines.⁸ Further modifications for the following 10 weeks included, using a more diluted elosulfase-alfa solution additionally and decreasing the infusion rate, and adding extra antihistamine doses, which were unsuccessful attempts. After initiation of omalizumab injection every four-weeks prior to desensitization, HSRs ceased, and tolerance was achieved. During subsequent

infusions, the number of dilutions and the desensitization steps were decreased, eventually reaching to an ordinary administration regimen at the end of an additional 11-week period.⁸ In our case, we gradually decreased the number of premedication agents first, followed by the number of steps and the desensitization period. Huffaker et al. reported on three patients with a history of sebelipase-alfa induced anaphylaxis. After a certain period of subsequent desensitizations using several serial solutions and prolonged infusions, the authors administered the ERT uneventfully in shorter periods, starting with 10 to 25 times higher concentrations even without premedication.¹⁰ Our patient treated with a shortened desensitization protocol and reduced premedication was the longest followed case for 104 weeks without any breakthrough reactions with elosulfase-alfa. We aimed to move forward by starting to the desensitization at 1/10 dilution, but there were missed doses during the follow-up period. Since the half-life of the drug was short, as expressed in minutes (8-36 minutes), we predicted that there might be a decrease in the tolerance gained due to the missed doses. Hence we decided to shorten the period for each step, which was successfully achieved.

In conclusion, desensitization protocols should be evaluated on a “patient specific” basis. Our patient tolerated a shortened infusion protocol of elosulfase-alfa with reduced premedication, despite having a history of severe anaphylaxis. We believe that the protocol followed for our patient can be used for the management of similar cases in the future.

Table 1a : Initial intravenous elosulfase-alfa* desensitization protocol

Step	Bottle	Elofulfase- alfa Concentration of the Bottle	Solution Content of the Bottle	Rate (mL/h)	Time of Infusion(min)	Volume of infusion(mL)	Dose of the step(μ g)	Cumulative dose (μ g)
1	A	0.2 μ g/mL (1/1000)	10 mL B solution + 90 mL SF	4	15	1	0.2	0.2
2	A			8	15	2	0.4	0.6
3	A			16	15	4	0.8	1.4
4	A			32	15	8	1.6	3
5	B	2 μ g/mL (1/100)	10 mL C solution + 90 mL SF	8	15	2	4	7
6	B			16	15	4	8	15
7	B			32	15	8	16	31
8	B			64	15	16	32	63
9	C	20 μ g/mL (1/10)	10 mL D solution + 90 mL SF	16	15	4	80	143
10	C			32	15	8	160	303
11	C			64	15	16	320	623
12	C			128	15	32	640	1263
13	D	200 μ g/mL (1/1)	40 mL elosulfas e alfa + 160 ml SF	24	15	6	1200	2463
14	D			48	15	12	2400	4863
15	D			96	15	24	4800	9663
16	D			120	76	150	30400	40000

Elosulfase-alfa (Vimizim®): 5 mg/5 mL. *Total required dose: 40 mg (2mg/kg, weight of the patient is 20 kg)
SF: Serum physiologic

Table 1b: Final shortened intravenous elosulfase-alfa desensitization protocol

Step	Bottle	Rate (mL/h)	Time of infusion (min)	Volume of infusion(mL)	Dose of the step (µg)	Cumulative dose (µg)
1	B	12	10	2	4	4
2	B	24	10	4	8	12
3	B	48	10	8	16	28
4	B	96	10	16	32	60
5	C	24	10	4	80	140
6	C	48	10	8	160	300
7	C	96	10	16	320	620
8	C	192	10	32	640	1260
9	D	36	10	6	1200	2460
10	D	72	10	12	2400	4860
11	D	144	10	24	4800	9660
12	D	180	53	158	30340	40000

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