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Anaphylaxis after *Elosulfase A* infusion: Omalizumab as coadjuvant for enzyme replacement therapy desensitization

To the editor:

Type IV A mucopolysaccharidosis (MPS IV A) is a lysosomal storage disease caused by an autosomal recessive mutation in the gene encoding the enzyme galactosamine-6-sulfatase, which catalyses the degradation of glycosaminoglycans (GAGs). It leads to the accumulation of GAG keratan sulfate. Symptoms include skeletal dysplasia, atlanto-axial instability, pectus carinatum, short stature, laxity of joints, cervical spinal cord compression, cardiac and pulmonary complications, corneal opacity, impaired hearing but normal cognitive development. These patients have a shorter life expectancy, requiring physical management, palliative care, and treatment of complications.¹

Enzyme replacement therapy (ERT) with *Elosulfase A* (recombinant human GALNS BMN 110; Vimizim®; BioMarin Pharmaceutical Inc, Novato, CA, USA) is the only approved therapy for these patients. It has shown to be effective, at a dose of 2 mg/kg/week, slowing down disease's progression for at least 2 years measured as absence of deterioration in endurance and lung function tests.

According to manufacturers' instructions, *elosulfase* should be administered in 4-hour long infusion periods, with antihistamines and/or non-steroid anti-inflammatory drugs (NSAID) 30-60 minutes prior to enzyme infusion. Reported adverse reactions (AR)² to *elosulfase* include "infusion reactions" (IR) (headache, fever, chills, stomachache) and allergic reactions, with an overall incidence of 25%.^{1,2} Severe allergic reactions to *elosulfase* may appear in 10% of the patients.^{1,2}

We report a 5-year-old child, affected by MPS IV A, who developed 2 allergic reactions during *elosulfase* infusion. He had received ERT (24 mg/week) for 21 weeks without incidences. At 22nd, he developed acute urticaria at the end of the infusion. The following week, *elosulfase* was administered in an 8-hour long infusion (0.2 mL/min) with dexchlorpheniramine (0.15 mg/kg), desloratadine (1.25 mg), methylprednisolone (10 mg), and acetaminophen (0.15 mg/kg) and he developed an anaphylaxis (urticaria, wheezing, and hypoxia) at the end of the infusion (tryptase determinations: 5.91 mcg/L (75 minutes after urticaria onset); baseline: 4.2 mcg/L; normal tryptase values: <11.4 mcg/L [*ImmunoCAP Tryptase ThermoFisher Scientific, Uppsala, Sweden*]).

Allergy workup was performed 4 weeks later, consisting of skin prick tests (1/10 and undiluted *elosulfase* (1 mg/mL)) and intradermal (1/10 and 1/100 diluted) tests, according to other ERT hypersensitivity reports³ and ENDA/EAACI recommendations.⁴ Five healthy children were also tested. A basophil activation test (BAT) using CD63

as marker for activated basophils (FACSCanto, BD Biosciences, San José, California, USA)⁵ was performed with five serial dilutions of *elosulfase* with patient's blood sample and three atopic controls (Table 1).

Prick test was positive with the undiluted enzyme. Intradermal tests were not performed. Controls had negative prick and intradermal tests. BAT results are described in Table 1.

Symptoms were consistent with anaphylaxis. Skin and BAT results suggested an IgE-mediated mechanism. There are several evaluation strategies to assess BAT results, including a cutoff point of activated basophils of 5%⁵ or if elicitor's exposure doubles baseline figures⁵. There are no previous data on BAT accuracy in ERT hypersensitivity. In this case, activation observed at two dilutions was considered positive, opposed to control results. A desensitization was proposed due to the lack of alternative treatments.

A procedure with four serial dilutions of *elosulfase* (initial dose: 0.0144 micrograms) with desloratadine, dexchlorpheniramine, montelukast (4 mg), and acetaminophen was prepared, adapting a previous report⁶ and following ENDA/EAACI recommendations on rapid drug allergy desensitization⁷ (Table 2). Desensitization was performed weekly for 10 weeks following this procedure. The patient developed several breakthrough reactions⁷ (urticaria episodes at 20th step) requiring additional antihistamines and steroids. Additional modifications for the following weeks included, separately, modifications in the infusion rate and additional antihistamines at 19th step, without success (Figure 1). Procedure's duration ranked between 10 and 34 hours. Omalizumab (patient's weight: 11 kg; total IgE: 55 UI/mL; dose: 75 mg/4 weeks) was added to the desensitization protocol at 11th week, 4 days prior to the following desensitization. The patient developed one urticaria during the desensitization performed after the initial dose. Five weeks after, due to good tolerance, 1:10 000 dilution was ceased, without incidences. At 22nd, 1:1000 dilution was stopped. Urticaria reappeared at the first attempt of 1:100 dilution cessation, at 28th week. The 1:100 and 1:10 dilutions were eliminated at 40th and 50th, respectively. *Elosulfase* has been successfully administered in non-desensitization regime for 22 weeks so far.

Adverse reactions conditions ERT administration in long infusion periods and the need of premedication. Involved mechanisms include IgE-mediated reactions, cell-mediated immune reactions, and cytokine release, among others. Infections increase the risk of an AR through immune system cell stimulation. Management of IR includes infusion rate modifications and premedication, usually

Abbreviations: AR, adverse reactions; BAT, basophil activation test; ENDA, European network for drug Allergy/EAACI interest group on drug hypersensitivity; ERT, enzyme replacement therapy; GAG, glycosaminoglycans; IR, infusion reactions; MPS, mucopolysaccharidosis; NSAID, non-steroidal anti-inflammatory drugs.

TABLE 1 Allergy workup

Allergy workup			Results
Skin tests	Prick (elosulfase 1mg/ml)	1:10	Negative
		1:1	3 x 3
		Saline	Negative
	Intradermal	Histamine dichloride	3 x 3
		1:1000	Not performed
		1:100	Not performed
Basophil activation test	a	-	-
		Negative control	0.4% activation
		Positive control	54.3% activation
		1:1	5.6%
		1:10	13%
		1:100	4.7%
		1:1000	1%
		1:10 000	0.3%
	b	-	-

Skin tests: results expressed as wheal diameter (mm).

Basophil activation test: results expressed in % of basophil activation.

^aFive controls had negative prick and intradermal skin tests.

^bThe test was also carried out in parallel in three atopic controls.

NSAID, antihistamines, and/or steroids. Desensitization may be the option for patients with IgE-mediated reactions, non-responsive to premedication.

Several desensitization protocols have been published in other ERT hypersensitivity cases.^{3,6} In most cases, desensitization includes premedication (antihistamines, montelukast, or steroids). Reported tolerance varies depending on patients' initial manifestations, including anaphylaxis episodes.⁶

There are no common recommendations about the management of breakthrough reactions during desensitization procedures.⁷ We tried several of the proposed options⁷: treatment of the episodes without modifying our protocol, changes in the infusion rate, and the addition of premedication during intermediate steps. Episodes of acute urticaria yielded with additional antihistamines and steroids, changes in the infusion rate worsened the symptoms, and antihistamine addition in intermediate step had no effect. Omalizumab was added instead of weekly doses of systemic steroids due to the foreseeable risk of bone tissue adverse effects in addition to the underlying disease.⁸

Omalizumab had been previously used as a coadjuvant for desensitization in a toddler affected by Pompe disease⁹ and a child affected by MPS VI and breakthrough reactions during galsulfase desensitization¹⁰. Data on the duration and doses of omalizumab for its use in drug allergy desensitization are limited. The discontinuation of omalizumab may condition symptoms' reappearance. Cessation of elosulfase administration in our patient does not seem foreseeable in short term, which would allow suspending omalizumab. We have opted for dose reduction by increasing dose intervals, with good response so far.

This is the 2nd report of allergy to *Elosulfase A*. Symptoms were consistent with anaphylaxis. Modifications in ERT administration

performed after the first urticaria did not prevent anaphylaxis appearance. Skin and BAT results suggested an IgE-mediated mechanism. BAT was a valuable tool in this case due to the limited data on skin test reliability for this drug.

Recently,¹¹ the 1st case of successful desensitization to elosulfase was published. However, we explored different approaches due to the persistence of breakthrough reactions during desensitization. Omalizumab binds to free IgE, blocking its interaction with basophils' and mast cells' IgE receptors, preventing mediator's release. Desensitization mechanisms have been not fully elucidated yet, but mast cells and basophils appear to be involved in tolerance induction. We considered omalizumab might replace the desensitization instead of the premedication, but we opted for ceasing desensitization steps progressively. The reappearance of urticaria at the 1st 1:100 dilution bag cease suggested the need of both procedures in this patient. Omalizumab allowed us to control breakthrough reactions and to continue ERT administration. In long term, it allowed us to cease the desensitization itself and to continue treatment under normal conditions. Desensitization procedures must be tailored to each patient and drug, not without risks. MPSs are infrequent conditions and so are ERT allergy cases, compared to other drug allergies. Information regarding cases with different treatment approaches and different evolution can facilitate the management of future patients.

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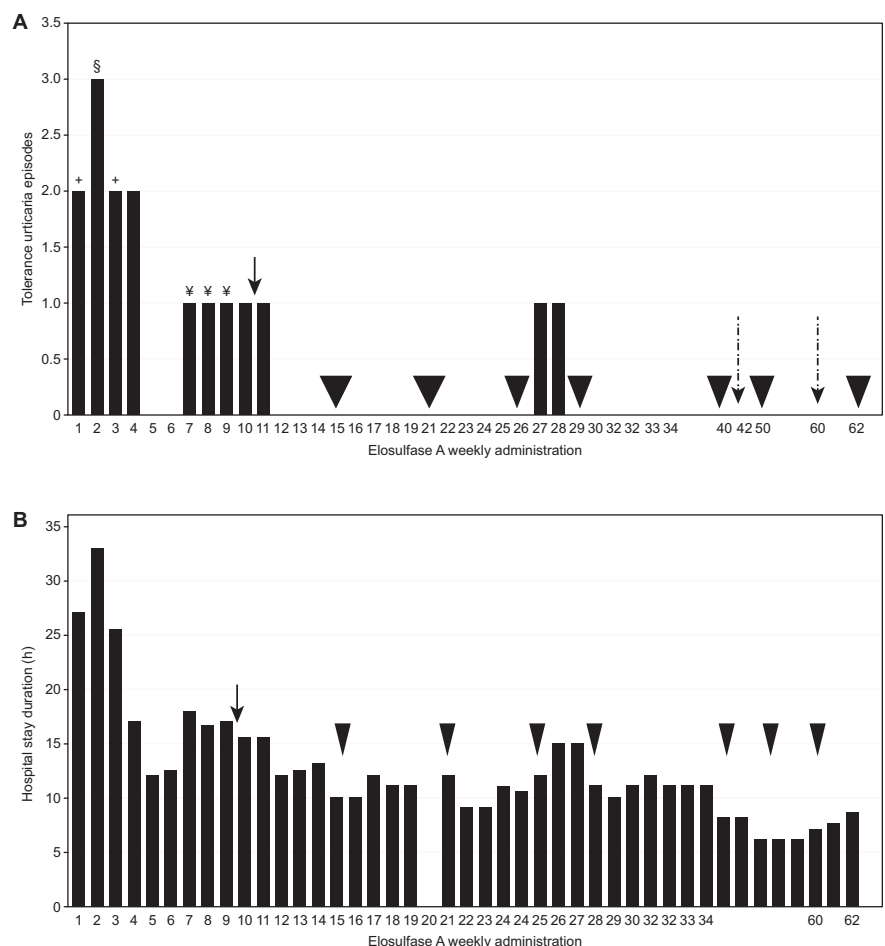
Patient's and controls' parents provided written consent for this report's publication. Complejo Hospitalario de Navarra's Medical

TABLE 2 Desensitization procedure

Step	Dilutions	Solution (mcg/mL)	mL	Infusion rate (mL/h)	Minutes	Dose (mcg)	Accumulated dose (mcg)
1	1 mL of B solution in 9 mL of Saline (A)	0.024 (A)	0.6	2.5	15	0.0144	0.0144
2		0.024 (A)	1.2	5	15	0.0288	0.0432
3		0.024 (A)	2.5	10	15	0.06	0.1032
4		0.024 (A)	5	20	15	0.12	0.2232
5	1 mL of C solution in 9 mL of Saline (B)	0.24 (B)	0.6	2.5	15	0.144	0.3672
6		0.24 (B)	1.2	5	15	0.288	0.6552
7		0.24 (B)	2.5	10	15	0.6	1.2552
8		0.24 (B)	5	20	15	1.2	2.4552
9	1 mL of D solution in 9 mL of Saline C	2.4 (C)	0.6	2.5	15	1.44	3.9552
10		2.4 (C)	1.2	5	15	2.88	6.8352
11		2.4 (C)	2.5	10	15	6	12.8352
12		2.4 (C)	5	20	15	12	24.8352
13	1 mL of E solution in 9 mL of Saline (D)	24 (D)	0.6	2.5	15	14.4	39.23
14		24 (D)	1.2	5	15	28.8	68.03
15		24 (D)	2.5	10	15	60	128.03
16		24 (D)	5	20	15	120	248.03
17	24 mg of Elosulfase A in 74 mL of Saline (E)	240 (E)	0.6	2.5	15	144	392.03
18		240 (E)	1.2	5	15	288	680.03
19		240 (E)	5	10	15	1200	1880.03
20		240 (E)	93	20	300	22120	24000.03

Elosulfase dose: 2mg/kg/week; patient's weight: 11 kg

FIGURE 1 A, Elosulfase administration and tolerance. Columns: number of urticaria episodes. B, Elosulfase administration and duration of patient's stay at the hospital. Management of breakthrough reactions: + Treatment of urticaria with dexchlorpheniramine (0.15 mg/kg/dose) and methylprednisolone (1 mg/kg). § Reduction of infusion rate after urticaria appearance plus additional antihistamines. Repeated urticaria episodes were treated with antihistamines (dexchlorpheniramine, ranitidine) and additional infusion rate modifications. ¥ Additional antihistamine dose (hydroxyzine 1 mg/kg) added at 19th step. Arrow: Omalizumab addition; discontinuous arrow: modifications in omalizumab administration frequency. Triangle: Desensitization steps cease. Sixty-second week: elosulfase infusion according to drugs' leaflet



Board authorized omalizumab's off-label use as coadjuvant for the desensitization procedure in this patient. We thank the nursing staff of the Outpatient Clinic and the staff of the Paediatric Emergency Unit of Complejo Hospitalario de Navarra for their co-operation during the acute management and monitorization of this patient.

CONFLICTS OF INTEREST

The authors do not declare any competing interests.

ORCID

Esozia Arroabarren  <https://orcid.org/0000-0001-7191-3390>

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Esozia Arroabarren¹ 
Elena Aznal²
Marta Anda¹
Felix Sanchez-Valverde²

¹Department of Allergy, Complejo Hospitalario de Navarra, Pamplona, Spain

²Department of Pediatrics, Complejo Hospitalario de Navarra, Pamplona, Spain
Email: esoziaa@yahoo.es

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