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A new strategy of desensitization in mucopolysaccharidosis type II disease treated with idursulfase therapy: A case report and review of the literature

Vincenza Gragnaniello [a], Silvia Carraro [b], Laura Rubert [a], Daniela Gueraldi [a], Chiara Cazzorla [a], Pamela Massa [a], Stefania Zanconato [b], Alberto B. Burlina [a,*]

[a] Division of Inherited Metabolic Diseases, Department of Diagnostic Services, University Hospital, Padua, Italy
[b] Women's and Children's Health Department, Padua University Hospital, Padua, Italy

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ABSTRACT

Mucopolysaccharidosis type II (MPS II) is a multisystemic lysosomal storage disorder caused by deficiency of the iduronate 2-sulfatase enzyme. Currently, enzyme replacement therapy (ERT) with recombinant idursulfase is the main treatment available to decrease morbidity and improve quality of life. However, infusion-associated reactions (IARs) are reported and may limit access to treatment. When premedication or infusion rate reductions are ineffective for preventing IARs, desensitization can be applied. To date, only two MPS II patients are reported to have undergone desensitization. We report a pediatric patient with recurrent IARs during infusion successfully managed with gradual desensitization. Our protocol started at 50% of the standard dosage infused at concentrations from 0.0006 to 0.06 mg/ml on weeks 1 and 2, followed by 75% of the standard dosage infused at concentrations from 0.0009 to 0.09 mg/ml on weeks 3 and 4, and full standard dosage thereafter, infused at progressively increasing concentrations until the standard infusion conditions were reached at 3 months. Our experience can be used in the management of MPS II patients presenting IARs to idursulfase infusion, even when general preventive measures are already administered.

1. Introduction

Mucopolysaccharidosis type II (MPS II; Hunter syndrome; OMIM 309900) is an X-linked lysosomal storage disorder caused by deficiency of the iduronate 2-sulfatase enzyme (I2S) [1]. Recently, the incidence estimated by newborn screening is 1 in 162,000 live male births [2]. Decreased I2S activity results in intracellular and extracellular accumulation of the glycosaminoglycans (GAGs) heparan sulfate (HS) and dermatan sulfate (DS), with impaired cellular functions and multiple organ damage.

Patients with MPS II present with coarse facial features, dysostosis multiplex, short stature, joint stiffness, hepatosplenomegaly, inguinal and umbilical hernias, thickening of heart valves and of the upper airway tissues, resulting in frequent respiratory tract infections. The severe phenotype also presents central nervous system involvement and high risk of early mortality [3].

MPS II is diagnosed by an abnormal qualitative and quantitative pattern of GAGs (elevated DS and HS) in urine or dried blood spots, and reduced I2S activity in leukocytes, fibroblasts, dried blood spots, free plasma, or serum. Molecular genetic testing is the confirmatory test [4–6].

Enzyme replacement therapy (ERT) with idursulfase and hematopoietic stem cell transplantation (HSCT) are the two treatments proposed for the disease [7]. ERT is administered once weekly via the intravenous route with improvement of somatic symptoms. Although ERT does not cross the blood-brain barrier, it is currently the main available therapy to decrease morbidity and improves quality of life in patients with MPS II [3,8–10]. New strategies with enzymes able to cross the blood-brain barrier (e.g., pabinafusp) or intraventricular ERT are in development [11,12].

After HSCT, stem cells can potentially cross the blood-brain barrier and improve neurological symptoms, but studies are still limited and performed very early, before onset of irreversible clinical manifestations [13–16].

Abbreviations: DS, dermatan sulfate; ERT, enzyme replacement therapy; GAGs, glycosaminoglycans; HS, heparan sulfate; HSCT, hematopoietic stem cell transplantation; I2S, iduronate 2-sulfatase enzyme; IARs, infusion-associated reactions; IDS, iduronate 2-sulfatase gene; IgE, immunoglobulin E; IgG, immunoglobulin G; MPS II, mucopolysaccharidosis type II; MRI, magnetic resonance imaging; MS/MS spectrometry, tandem mass spectrometry; SPTs, skin prick tests.

* Corresponding author at: Division of Inherited Metabolic Diseases, Department of Diagnostic Services, University Hospital, via Oris 2B, 35129 Padua, Italy.
E-mail address: alberto.burlina@unipd.it (A.B. Burlina).

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ERTs for mucopolysaccharidoses are generally well tolerated, but infusion-associated reactions (IARs), including rash, urticaria, angioedema, bronchoconstriction, rhinitis, pyrexia, nausea, vomiting, and rare life-threatening anaphylaxis have been reported, especially with idursulfase ERT [17]. Most IARs are hypersensitivity reactions that can be either allergic (IgE- or non-IgE-mediated) reactions, or nonallergic reactions in which an immunologic pathogenic mechanism is not demonstrated [18].

IgE-mediated reactions are usually immediate. The main clinical presentations include cutaneous, respiratory, gastrointestinal, and systemic (anaphylaxis) manifestations [19–21]. Non-IgE-mediated reactions (formerly called "anaphylactoid" reactions) can present with the same symptoms as IgE-mediated reactions. Other non-IgE-mediated reactions are delayed, occurring more than 1 h after drug administration (typically within 12–24 h) [22]. Some of these reactions are mediated by T cells [23]. Clinical manifestations include skin reactions (more frequently maculopapular exanthems) and sometimes systemic symptoms [24]. For others an immunologic pathogenic mechanism has not been demonstrated, but may be related to mechanisms of complement activation, immunocomplex deposition, cytokine release and direct mast cell stimulation [18].

They are generally resolved by interrupting or reducing the infusion rate and/or by the administration of antihistamines, antipyretics and/or corticosteroids [25]. The diagnostic workup consists of a precise clinical history, skin tests and laboratory tests (i.e., IgE antibodies, if available). A drug provocation test to confirm/exclude hypersensitivity may be considered only when the clinical suspicion of drug allergy is low [26]. For ERT, the temporal relationship, recurrence and the absence of alternative causes is usually sufficient to raise strong suspicion.

In patients with recurrent IARs, despite slowing infusion rate and premedication, desensitization can be considered [17]. However, specific guidelines are lacking and recurrent IARs may restrict access to treatment.

Here, we report our successful experience treating a patient with MPS II who experienced recurrent IARs during ERT infusion, and propose a desensitization protocol that allows treatment to continue.

2. Patient and methods

Our patient is an Italian male who presented at age 2 years with a history of recurrent upper airway infections, coarse facial features with enlarged skull, hepatosplenomegaly, umbilical and inguinal hernias, joint contractures with claw hand deformity. The patient presented with psychomotor delay (total intelligence quotient 79 based on the WPPSI-III score), hyperactivity, and attention difficulties. Despite the symptoms, diagnosis was delayed until age 4 years, when the patient came to our attention. At that time, instrumental assessments showed dysostosis multiplex (whole-body radiography), enlargement of perivascular spaces (brain MRI) and aortic and mitral stenosis (echocardiography). Biochemical analyses showed elevated urinary GAGs, with total urinary GAGs 95.8 mg/mmol creatinine (nv < 26.8), HS 47.8 mg/mmol creatinine (nv < 1.2), DS 32 mg/mmol creatinine (nv < 11.4) (MS/MS spectrometry) [27,28]. I2S activity in dried blood spots was low at 0.5 umol/h, 4.1% daily mean activity (MS/MS spectrometry seven-plex kit-PerkinElmer®) [6]. Molecular analysis revealed a pathogenic hemizygous *IDS* variant c.1295G > A (p.Cys432Tyr), confirming the diagnosis of MPS II. This variant is reported to have a severe phenotype [29]. Weekly ERT with intravenous idursulfase (Elaprase®, Takeda) at the standard dosage (0.5 mg/kg, total dose 12 mg) was promptly initiated. Following manufacturer's recommendations [30], 12 mg (6 ml) were diluted in 94 ml of normal saline (total volume 100 ml, concentration 0.12 mg/ml) and administered over 3.5 h with incremental infusion rate of 7 ml/h for 30 min, 14 ml/h for 30 min, 25 ml/h for 30 min, 40 ml/h until finished. Despite this therapeutical regimen, several symptoms raised the suspicion of IARs. About 18 h after the first infusion, the patient experienced fever and vomiting for 2 days. These symptoms were initially attributed to a concurrent viral infection and therapy was not stopped. At infusion 3, after the first 10 min, the patient presented with cough and hoarse voice. The infusion was immediately stopped, and the patient was successfully treated with iv chlorphenamine (0.25 mg/kg) and methylprednisolone (1 mg/kg) with rapid resolution of symptoms. The infusion was resumed at a reduced rate and completed. At subsequent infusions, the patient was premedicated with iv chlorphenamine (0.25 mg/kg) and methylprednisolone (1 mg/kg). The therapy proceeded regularly until infusion 8, when, 1 h after the end of the infusion, the patient presented with mild facial maculopapular rash, that resolved spontaneously within 12 h; this symptom was more severe at the next infusion (Fig. 1). Antihistamine was given with rapid improvement and resolution of the rash after about 12 h. Idursulfase skin prick tests (SPT; idursulfase 2 mg/ml) and intradermal tests (dilution 1:1000, 1:100, 1:10 of idursulfase 2 mg/ml) were negative (Fig. 2). Tryptase levels at the time of the reaction and anti-idursulfase IgE antibodies were also negative, but non-neutralizing anti-idursulfase IgG antibodies were positive.

These results suggested that the reaction was not IgE-mediated. Thus, at the next infusion the patient was premedicated with iv chlorphenamine (0.25 mg/kg), methylprednisolone (1 mg/kg), inhaled salbutamol (2.5 mg) and oral acetaminophen (15 mg/kg). The enzyme infusion was changed to: 50 ml of 1:100 idursulfase dilution (0.0012 mg/ml) administered in 2 h 10 min, followed by 50 ml of 1:10 idursulfase dilution (0.012 mg/ml) in 2 h 10 min, finally 94.5 ml of standard idursulfase dilution (0.12 mg/ml), corresponding to 94.5% of total dose, in 3 h 20 min. The total infusion time was 7 h 40 min. Despite that protocol, 4 h after the end of the infusion, the patient presented with fever, cough, and bronchospasms, which were treated with iv acetaminophen (15 mg/kg), inhaled salbutamol (2.5 mg) and budesonide (0.5 mg). A nasopharyngeal swab revealed the presence of a rhinovirus. However, we could not exclude that the symptoms were due to an IAR; therefore, at the next infusion, we gave half the total dose without changing the total volume and infusion rate (Table 1). No symptoms occurred after the infusion. We then progressively increased the dosage, reaching the target dose after 1.5 months. Simultaneously, the concentration of infused drug was progressively increased (from 0.6 μg/ml to the standard dilution of 0.12 mg/ml at infusion 11, see Table 1), so that the target total ERT dose was administered in 3.5 h according to standard protocol without adverse reactions after 3 months. Two months after desensitization was finished, premedication was still used as a precaution and clinically the patient had a reduction of hepatosplenomegaly and of the frequency of the upper airway infections/otitis; urinary GAGs were also reduced (Fig. 3). Brain MRI and total intelligence quotient were unchanged from baseline. Despite the presence of anti-ERT antibodies and the reduction of the dosage during the first steps of the desensitization protocol, ERT improved the organomegaly and reduced GAGs levels.

3. Discussion

IARs are defined as adverse events occurring during or within 24 h of an infusion and for which there is evidence of a causal relationship.

They are quite frequent in MPS II disease and can be IgE- or non-IgE-mediated. In the Hunter Outcome Survey database, 65 IARs (2 severe) were identified during the first year of follow up in 33 patients out of 597 (5.5%). Most IARs occurred within the first 3 months of therapy. Anti-idursulfase antibodies were evaluated in 7 patients, of which 6 tested positive for IgG (2 neutralizing); none were positive for IgE [31].

In a cohort of 34 patients initiating ERT with recombinant human idursulfase for MPS II, 3 patients experienced anaphylaxis (8.8%), and four other patients exhibited urticaria/angioedema following infusion (total 20.6%). The mean time to onset of IAR was 67 ± 46 weeks (range 3–109 weeks) after the first dose of idursulfase. Four patients (including all patients who experienced anaphylaxis) had positive SPTs and two had negative SPTs but positive intradermal tests. All patients who

Fig. 1. Facial maculopapular exanthema (2 h after the end of idursulfase infusion 9).

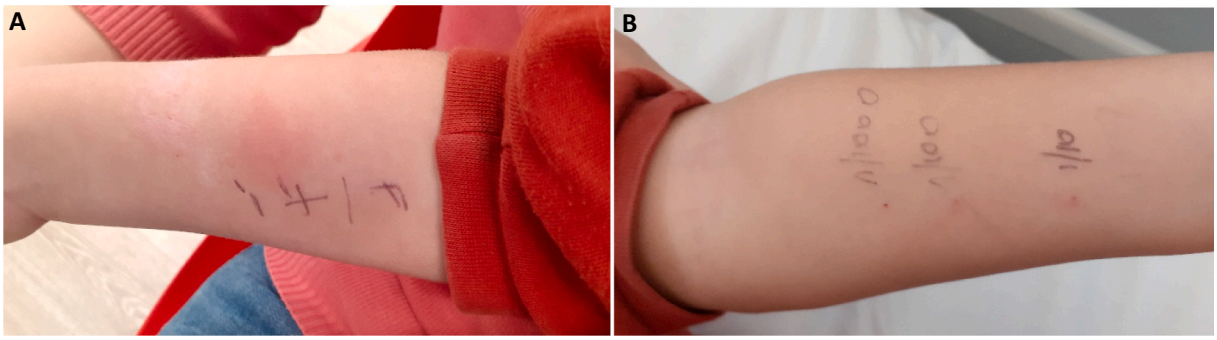

Fig. 2. Skin prick tests (A) and intradermal tests (B).
A. + positive control (histamine),
- negative control (normal saline),
mn F: idursulfase (2 mg/ml).
B. Intradermal tests: dilution 1:1000 (0.002 mg/ml), 1:100 (0.02 mg/ml), 1:10 (0.2 mg/ml).

Table 1
Desensitization protocol.

Infusion(s)	Total dose	Concentrations mg/ml	Preparation	Total volume	Infusion rate	Duration
1–2	6 mg (50%)	0.0006	0.5 ml of D3 in 49.5 ml of NS	50 ml	For each dilution:	7 h 40 min
		0.006	5 ml of D3 in 45 ml of NS	50 ml	7 ml/h for 30 min	
		0.06	D3: 6 mg (3 ml) in 97 ml of NS	94.5 ml	14 ml/h for 30 min	
3–4	9 mg (75%)	0.0009	0.5 ml of D2 in 49.5 ml of NS	50 ml	25 ml/h for 30 min	7 h 40 min
		0.009	5 ml of D2 in 45 ml of NS	50 ml	40 ml/h until the end	
		0.09	D2: 9 mg (4.5 ml) in 95.5 ml of NS	94.5 ml		
5–6	12 mg (100%)	0.0012	0.5 ml of SD in 49.5 ml of NS	50 ml		7 h 40 min
		0.012	5 ml of SD in 45 ml of NS	50 ml		
		0.12	SD: 12 mg (6 ml) in 94 ml of NS	94.5 ml		
7–8	12 mg (100%)	0.0024	1 ml of SD in 49 ml of NS	50 ml		7 h 40 min
		0.012	5 ml of SD in 45 ml of NS	50 ml		
		0.12	SD: 12 mg (6 ml) in 94 ml of NS	94 ml		
9–10	12 mg (100%)	0.012	5 ml of SD in 45 ml of NS	50 ml		4 h 30 min
		0.12	SD: 12 mg (6 ml) in 94 ml of NS	95 ml		
11···	12 mg (100%)	0.12	SD: 12 mg (6 ml) in 94 ml of NS	100 ml		3 h 30 min

Patient's body weight 24 kg, target dosage 12 mg. SD (standard dilution): 0.12 mg/ml; D2 (dilution 2): 0.09 mg/ml; D3 (dilution 3): 0.06 mg/ml; NS: normal saline.

experienced allergic reactions had increased serum levels of IgE and IgG against idursulfase [32].

Of note, about 50% of treated MPS II patients develop anti-idursulfase IgG and about 50% of these develop neutralizing antibodies [30]. The role of antibody in ERT tolerance and effectiveness is not well defined [17,33]. The incidence of hypersensitivity reactions appears to be higher in patients positive for ERT-specific IgG [34,35]. Moreover, antibody positivity and hypersensitivity reactions are more frequent in younger patients and in patients with severe *IDS* gene pathogenic variants (complete deletion/large rearrangement, nonsense or frameshift variants) compared with patients with missense pathogenic variants [30,35,36]. Our patient had a severe phenotype; he was

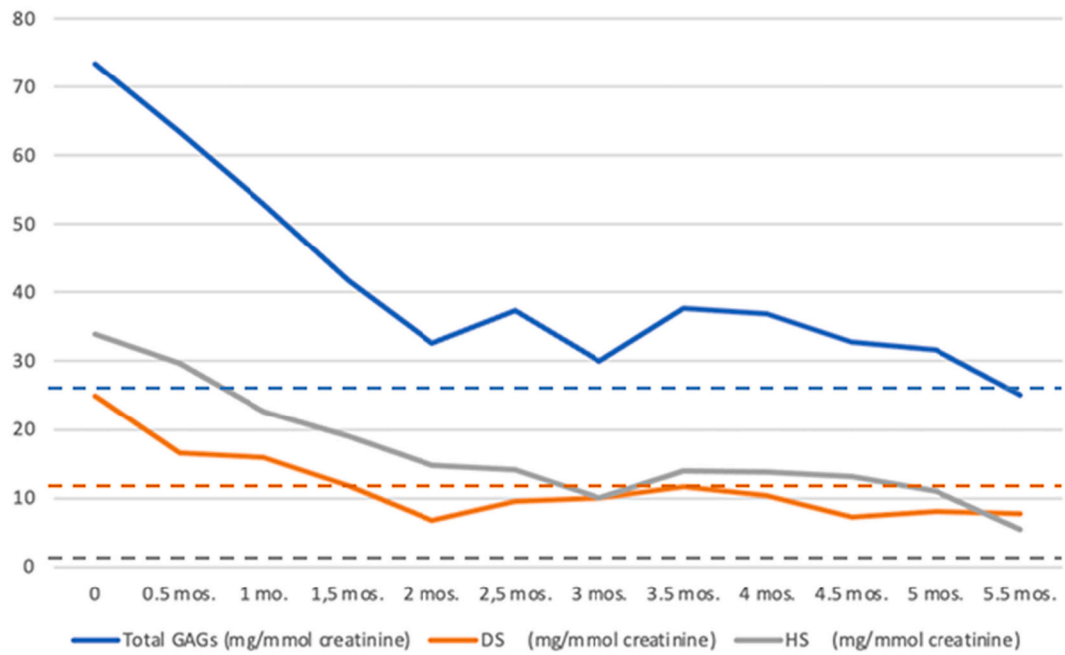

Fig. 3. Urinary GAGs trend from the start of Idursulfase therapy.
Upper limits of normality for age (dashed lines): total GAGs 26.8 mg/mmol creatinine (blue), DS 11.4 mg/mmol creatinine (orange), HS 1.2 mg/mmol creatinine (grey).

still young and had positive anti-idursulfase IgG when he developed hypersensitivity reactions. Because of the lack of alternative idursulfase therapy, general preventive measures should be adopted after an IAR, including premedication with corticosteroids, acetaminophen, and antihistamines, and reduction of the infusion rate [17,25]. When these measures are ineffective, desensitization can be performed. In the proper setting, it is safe and effective for both immediate and (non-severe) nonimmediate reactions [37,38].

Drug desensitization is defined as the induction of a state of unresponsiveness to a compound that provokes a hypersensitivity reaction. It is performed by administering increasing doses of the medication over a short period of time (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated. As there are risks associated with the procedure, its use is reserved for patients lacking effective alternatives after a positive risk/benefit analysis [37]. General rules for drug desensitization are indicated in position papers from the European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology on immediate reactions [37], and delayed reactions [38]. The starting dose should range from 1/10000 to 1/100 of the full therapeutic dose and can be doubled every 15–20 min over the course of several hours until the therapeutic dose is reached [37]. There is no consensus on the value of premedication prior to desensitization, because it could mask early reactions (especially antihistamines in immediate-type reactions) but can also prevent mild reactions [38].

In general, it is preferable to use protocols that have been validated in >10 patients, but this may not be possible in rare diseases [37]. Many protocols are personalized for each patient and each drug [38]. To date, two cases of desensitization to idursulfase have been reported [39,40].

In the first patient, the index IAR was generalized urticaria that occurred 1 h after starting the 6th infusion. SPT and anti-idursulfase IgE were negative. The patient was premedicated with clemastine and treated with an 8-h desensitization protocol, starting from an initial dilution of 1:10000 (0.00012 mg/ml). This protocol was well-tolerated and was still ongoing at the time of publication (after 16 weeks) [39].

In the second patient, IARs presented after 4 years of treatment as two episodes of anaphylaxis during the infusion. SPTs were negative, but the intradermal reaction was positive at 1:10 dilution (0.2 mg/ml). Premedication with corticosteroids and antihistamines was ineffective, and a 12-step (3-concentration) desensitization protocol was performed, starting with a 1:100 dilution (0.0006 mg/ml, total volume 200 ml) and increasing the dose every 15 min [40].

Our patient had both immediate and delayed reactions that affected the respiratory system and the skin, respectively. He had negative results on SPT, anti-idursulfase IgE and tryptase, but positive anti-idursulfase IgG, suggesting a non-IgE-mediated hypersensitivity reaction. Reactions recurred despite premedication with antihistamines and corticosteroids, so initially we applied a desensitization protocol based on published data [37–40]. This is the youngest reported patient with MPS II to undergo idursulfase desensitization, to date.

Despite our protocol, the patient experienced a breakthrough hypersensitivity reaction, i.e., a hypersensitivity reaction that occur despite the desensitization procedure. Breakthrough reactions are more frequent during the first course of desensitization, and there is no consensus on further management. Approaches include continuing to treat through reactions without modifying the protocol, or modifying the protocol by introducing intermediate dosing steps, going back one or two steps, or re-starting at the stopping point using a lower dose [37]. Our approach was to halve the starting total dose to 6 mg (0.25 mg/kg), followed by progressively increasing it to reaching the full dose at week 5. We used lower than standard idursulfase concentrations, and progressively increased the concentration to achieve the standard infusion regimen for this 24 kg patient (12 mg in 100 ml infused over 3.5 h) after 3 months of desensitization. No further adverse reactions were observed. Administration of a reduced dose of ERT during the first steps of desensitization could be a concern. Despite that limitation, the clinical and biochemical improvements support the efficacy of this protocol.

4. Conclusion

This report shows the usefulness of a gradual desensitization protocol for idursulfase therapy in MPS II. Our protocol was safe and effective in this patient, and we propose its use in patients with MPS II who develop hypersensitivity reactions during idursulfase replacement therapy to

promote their return to effective therapy and minimize disease progression.

Declaration of interest statement

The authors declare no conflict of interest.

Informed consent statement

Informed consent was obtained from parents of the patient.

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CRediT authorship contribution statement

Vincenza Gragnaniello: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Silvia Carraro:** Methodology, Formal analysis, Investigation, Writing – review & editing. **Laura Rubert:** Conceptualization, Methodology, Formal analysis, Investigation. **Daniela Gueraldi:** Conceptualization, Methodology, Formal analysis, Investigation. **Chiara Cazzorla:** Formal analysis, Investigation. **Pamela Massa:** Formal analysis, Investigation. **Stefania Zanconato:** Methodology, Formal analysis, Investigation, Writing – review & editing. **Alberto B. Burlina:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

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