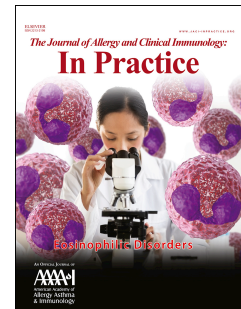


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HYPERSENSITIVITY REACTIONS AND ENZYME REPLACEMENT THERAPY: OUTCOMES AND SAFETY OF RAPID DESENSITIZATION IN 1,008 INFUSIONS

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PII: S2213-2198(21)01242-3

DOI: <https://doi.org/10.1016/j.jaip.2021.10.052>

Reference: JAIP 3936

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 14 December 2020

Revised Date: 15 October 2021

Accepted Date: 18 October 2021

Please cite this article as: Aranda CS, Aun MV, Souza CFMd, Pinto LLdC, Porras-Hurtado GL, Salgado OFS, Arantes RR, Martins AM, Solé D, HYPERSENSITIVITY REACTIONS AND ENZYME REPLACEMENT THERAPY: OUTCOMES AND SAFETY OF RAPID DESENSITIZATION IN 1,008 INFUSIONS, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.10.052>.

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**HYPERSENSITIVITY REACTIONS AND ENZYME REPLACEMENT
THERAPY: OUTCOMES AND SAFETY OF RAPID DESENSITIZATION IN
1,008 INFUSIONS**

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Conflict of Interest Statement

CSA has received honoraria for presentations and travel grants from BioMarin.
LLCP has received honoraria for presentations for BioMarin, Sanofi, Takeda and
PTC as well as travel grants from BioMarin, Sanofi, Takeda, PTC and Janssen.
GLPH has speaker fees and travel grants from BioMarin. AMM has received
honoraria for presentations for Alexion, BioMarin, Leditant, Sanofi and Takeda as
well as travel grants from BioMarin and Sanofi. MVA, CFMS, OSS, RRA, DS have
no conflicts of interest to declare.

Funding

Financial support has been provided to support medical writing of the manuscript by BioMarin Brasil Farmacêutica Ltda., but the publication was developed independently by the authors who are entirely responsible for the scientific content of the manuscript.

Word count

Main text: 1129

CLINICAL IMPLICATIONS

Enzyme replacement therapy (ERT) discontinuation significantly worsens visceromegaly, respiratory function and walking capacity in patients with mucopolysaccharidoses. As ERT is the only possible therapeutic alternative for almost patients, but hypersensitivity reactions are a cause of early treatment discontinuation. Patients experiencing hypersensitivity reactions to ERT can benefit from rapid desensitization to receive their treatment safely.

Keywords: MPS, infusion-related reaction; MPS VI; MPS IVA, desensitization, anaphylaxis, adverse events management.

CLINICAL COMMUNICATION

Patients with mucopolysaccharidoses (MPS) display deficient lysosomal enzymes leading to the accumulation of glycosaminoglycan (GAG) in a myriad of cells and tissues. Multiple organs malfunction and abnormalities in growth and development have been described in these patients (1).

Enzyme replacement therapy (ERT) is the most important therapeutic strategy for MPS patients, slowing the disease progression, ameliorating the symptoms and improving health-related quality of life (1). Specific enzymatic treatment is available for patients with MPS I, II, IVA, VI and VII (1). Except for vestronidase alfa-vjbk (which is biweekly administered), the recombinant enzymes are administered in weekly intravenous infusions.

Enzyme infusion-related immediate hypersensitivity reactions (IHR) are infrequent and they can be mild to moderate, including cutaneous, gastrointestinal and respiratory symptoms (1).

RDD (rapid drug desensitization) is a therapeutic technique that modifies the immune response of allergic patients to those drugs they are allergic to. RDD induces a temporary tolerance that can only be maintained whilst drug serum levels are maintained, and the temporary tolerance is lost as soon as the drug is eliminated (2). Based on *in vivo* and *in vitro* evidence, RDD protocols follow specific methodology, namely, starting at very low doses that are subthreshold for anaphylaxis, with doses doubling every 15-30 min at each increment until the target dose is attained. In previous experience with platins, RDD has shown to be cost-effective and to not to affect the efficacy of the drug (3). RDD is the only hope to continue life-saving treatment in patients who react to first-line therapies and have no equally-efficacious treatment alternatives. ERT is vital in patients

with MPS. We evaluated the efficacy and the safety of RDD in Latin American patients with MPS IVA and VI who experienced infusion-induced IHR.

We conducted a multicentric retrospective observational study between July 2012 and September 2020 including patients from Brazil (São Paulo, Belo Horizonte, Florianópolis and Porto Alegre) and Colombia (Bogota) diagnosed with MPS IVA or VI receiving elosulfase alfa or galsulfase who presented with IHR regardless of severity. There were no exclusion criteria or sample size calculation because of the rarity of the condition. The study was approved by the Institutional Ethic Committee and informed consent was obtained from all patients (or their parents, when legally obliged) prior to inclusion in the study.

A survey containing questions about demographic data, biochemical and genetic diagnosis, ERT initiation and the information regarding the IHR and the RDD protocol was sent to the physicians who retrieved data from the medical records of the participants.

Immediate readings for skin prick (SPT) and intradermal (IDT) tests were used as *in vivo* biomarkers for IgE-mediated sensitization (4). The SPT was performed using an undiluted aliquot of the enzyme. IDT were performed with diluted (1/100 and 1/10) and pure concentrations according to our previous data showing this is not irritant (5). Both tests were performed and interpreted according to the European guidelines (4).

As per standard guidance (2), we decided to offer RDD for patients with a confirmed hypersensitivity reaction with no equally-effective therapeutic alternative. Since all patients had positive skin tests and were in need of ERT, all patients were offered RDD. Therefore, the RDD consisted in administering elosulfase alfa (MPS IVA) or galsulfase (MPS VI) in a 12-step or in a 16-step

protocol as proposed by Castells and co-authors (2, 6). The choice between both protocols was performed based on risk stratification, according to the severity of the initial reaction, as previously described by Sloane and colleagues (3). All protocols were performed in settings in which resuscitation personnel and resources were readily available (2).

All the enzyme infusions were only conducted if patients were considered healthy. Additionally, the patient could not have any infections or being under antibiotics in 72 h prior to the infusion.

Of the six enrolled patients, three patients (50%) were diagnosed with MPS IVA and three patients (50%) had MPS VI. Only one patient was male (with MPS VI). The median age of the patients was 11.3y [standard deviation (SD): 10.8] and they started receiving ERT at the median age of 5.2y (SD: 11.14). ERT-induced IHR onset occurred after 1.1y of treatment (SD: 1.7). Demographic data are detailed in the Table E1.

The severity of the reactions was classified using the grading system of the World Allergy Organization (7). The initial anaphylactic reactions included: skin manifestations (83%, 5/6), gastrointestinal symptoms (67%, 4/6) and tachycardia (33%, 2/6). One MPS IVA patient displayed reduced SpO₂ associated with vomiting during infusion and the IHR was deemed as grade 3 (accordingly to the WAO consensus document (7)) (Table 1).

All patients underwent the 12-step or the 16-step RDD protocols (Table 1) and 1,008 RDD were conducted (Figure 1). All patients received antihistamines before the infusion even though it is not preconized that ERT should be preceded by premedication (Table E2). Due to breakthrough reactions, three patients (#1, #4 and #5) also received steroids. The rate of breakthrough reactions was 1.5%

(15/1,008 in three patients). Two patients (#1 and #4) displayed cutaneous symptoms and nausea that were successfully treated, and the subsequent infusion was performed under the 16-step protocol. Patient #5 had a total of 12 breakthrough reactions. After the first reaction, the patient was switched to a 16-step RDD protocol and higher doses of premedication were also administered but unsuccessfully prevented another IHR. Omalizumab, an anti-IgE drug, was thus (a monthly dose of 150 mg) added-on as previously described (8) and the patient stopped to react during ERT (Table 1).

Our data demonstrated that RDD is safe and efficacious in maintaining ERT for individuals with MPS IVA and VI and enzyme-induced IHR. 50% of the patients experienced at least one breakthrough reaction during RDD. However, all patients achieved uneventful tolerance after adjustments to their RDD protocols, as per standard recommendations (2).

Ensina and co-workers (9) demonstrated that the RDD was effective in controlling a laronidase-induced IHR in a MPS I patient, indicating that such a protocol could be extended to patients with lysosomal storage disorders. This conjecture was confirmed by Aranda et al. (5), who employed this protocol to manage IHR to ERT in patients with Pompe, Gaucher, Fabry and MPS.

The positive skin tests results suggest an involvement of specific IgE activating mast cells or basophils. These results corroborate the hypothesis that ERT can induce a specific immune response. Notably, omalizumab administration led to a complete control of breakthrough reactions, thus indicating a pathogenic role of IgE in the development of those allergic reactions.

RDD, using validated protocols by Castells et al., was safe and efficacious in maintaining ERT for individuals with MPS IVA and VI and enzyme-induced IHR

169 (5, 6). These findings demonstrate an important strategy for maintaining specific
170 therapies in these patients, thus contributing to delay disease progression and
171 avoid the reduction of their health-related quality of life.

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DECLARATIONS*Acknowledgments*

The authors would like to thank Tatiana Magalhaes, MD and Debora Mesojedovas, PharmD of BioMarin Latin America for contributions and BioMarin Brasil Farmacêutica Ltda., which sponsored the preparation of this article and reviewed the article for medical and scientific accuracy. A special thanks to Camilla Patti Hissamura who was the medical writer of this manuscript.

Authors' contribution

CSA, MVA, AMM and DS conceived the manuscript. CSA, CFMS, LL, GLP, OSS and RRA collected the data. All authors critically revised the text and approved the final manuscript.

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219 **FIGURE LEGEND**

220 **Figure 1** – Flow chart of enrolled participants. MPS: mucopolysaccharidosis, n: number
221 of patients; SPT: skin prick test; IDT: intradermal test; NA: not available/not assessed;
222 RDD: rapid drug desensitization.

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TABLE

Table 1 – Characterization of the IRR and the breakthrough reactions presented by the enrolled patients before and after the RDD

Patient ID	ERT-induced IHR	Brown's classification of IHR	SPT	IDT	Breakthrough reactions during the RDD	Breakthrough reactions clinical features	Breakthrough reactions [†]	Management of future RDDs
1	Flushing (erythema and/or warmth), pruritus, urticaria and nausea	Grade 2	Positive	Positive	Yes Step #12 (twice)	Flushing (erythema and/or warmth), pruritus	Grade 1	Change from 12-step to 16-step protocol
2	Vomiting and SpO ₂ <92% at any stage	Grade 3	NA	Positive	No	No	NA	Change from 16-step to 12-step protocol
3	Flushing (erythema and/or warmth), pruritus, urticaria and tachycardia	Grade 1	Positive	Positive	No	No	NA	NA
4	Flushing (erythema and/or warmth), pruritus, urticaria, tachycardia and vomiting	Grade 2	Positive	NA	Yes Step #12	Urticaria	Grade 1	Change from 12-step to 16-step protocol
5	Flushing (erythema and/or warmth), pruritus, urticaria and vomiting	Grade 2	Positive	Positive	Yes Various steps*	Pruritus, urticaria and nausea	Grade 2	Change from 12-step to 16-step protocol and administration of omalizumab
6	Flushing (erythema and/or warmth), pruritus, urticaria	Grade 1	Positive	Positive	No	No	NA	NA

RDD: rapid drug desensitization; ERT: enzyme replacement therapy; IHR: immediate hypersensitivity reactions; SPT: skin prick test; NA: not available/not assessed; IDT: intradermal test. *The patient #5 presented with 12 breakthrough reactions. Three of those reactions occurred during the 10th and 12th steps of the 12-step RDD protocol and the remaining ones were observed during the last step of the 16-step protocol. •The severity of the reactions was classified using the grading system of the World Allergy Organization.

