

CORRESPONDENCE

Laronidase hypersensitivity and desensitization in type I mucopolysaccharidosis

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To the Editor,

Mucopolysaccharidosis-I (MPS-I) is a lysosomal storage disorder, resulting from the deficiency of lysosomal alpha-L-iduronidase enzyme. It is a rare disorder, with an estimated prevalence ranging from 0.69 to 3.8 per 100,000 live births (1). The disorder affects independently the central nervous, skeletal, digestive, cardiac, upper and lower respiratory systems at different grades of severity (1).

Untreated patients with MPS-I have a lower life expectancy and higher morbidity. The enzyme replacement therapy (ERT) with laronidase has been approved for MPS-I treatment since 2003 in the United States and 2005 in Brazil (2). We describe the first case of a MPS-I patient with hypersensitivity to laronidase, who was successfully treated with a three bags, 12 steps rapid desensitization protocol.

Case report

An 11-yr-old female subject was referred to our allergy outpatient clinic for evaluation of hypersensitivity reactions during ERT with laronidase. The patient had a history of multiple surgeries and was diagnosed with MPS-I when she was 9 yr old. In January 2012, she started ERT with laronidase (20.3 mg/wk). She received four uneventful infusions and, during the fifth infusion, 90 min after starting the procedure (infusion rate 80 ml/h), she experienced hives in ears, neck, and back, lip swelling, increase in corporal body temperature (37.3°C) without respiratory, digestive, or cardiovascular symptoms. The infusion was stopped, and the patient was treated with hydroxyzine 0.5 mg/kg and methylprednisolone 2 mg/kg. The symptoms improved, and the infusion was restarted 1 h later (20 ml/h). After 3 min, she experienced a new episode of widespread hives, and the infusion was discontinued.

Three weeks after the reaction, laronidase-specific IgG antibodies were detected (enzyme immunoassay/radioimmuno-precipitation test; Genzyme, Cambridge, MA, USA).

On the other hand, *in vitro* specific IgE to laronidase (enzyme-linked immunosorbent assay – ELISA; Genzyme) was not found. A skin prick test with undiluted laronidase (0.58 mg/ml) was positive with a 3 mm-diameter wheal and flare as compared with the negative control. The test was negative in 10 disease-free controls and in one patient with MPS-I on ERT.

Because laronidase was considered first line therapy, a three bags, 12-step laronidase desensitization protocol was elaborated based on previous chemotherapy protocols (3) (Tables 1 and 2), and informed consent was obtained.

The patient was pre-medicated with ranitidine 35 mg, loratadine 10 mg, and montelukast 10 mg, 20 min before the

procedure, and loratadine 10 mg and montelukast 10 mg before the 3rd bag. The desensitization was done in the intensive care unit, and no reaction occurred while the target dose of 20.3 mg was reached successfully.

The patient was treated for 8 months weekly without any reactions. During 28th desensitization, after a dose adjustment for her weight, she experienced widespread urticaria at step 12. The protocol was amended by adding cetirizine 10 mg before step 9. The patient has been tolerating weekly infusions of laronidase adjusted to her weight for the last 2 months using the amended protocol without any reactions.

Discussion

Treatment with laronidase is the single best therapeutic option for patients over 18 months of age with MPS-I, and hypersensitivity reactions may prevent their continued treatment. Although the most frequent adverse events associated with ERT are mild and infusion-related (flushing, arthralgia, and headache), severe anaphylactic hypersensitivity reactions, requiring discontinuation of therapy, were described in 1/45 patients in a phase III clinical trial to evaluate the efficacy and safety of laronidase in the treatment of MPS-I (4). Our patient showed a mild (urticaria and angioedema) immediate hypersensitivity reaction during laronidase infusion. Due to the lack of any other factor or concomitant drugs that could account for the reaction observed, and the recurrence of symptoms when restarting the infusion, laronidase was considered the primary suspect drug.

Immediate hypersensitivity reactions to drugs are those occurring up to 1 h after exposure, and, in most cases, are caused by IgE-mediated mechanism, that is, mainly urticaria, angioedema, bronchoconstriction, rhinitis, and anaphylactic shock. As the symptoms were suggestive of IgE-mediated reaction, prick testing with undiluted laronidase was done with positive results. Because the predictive value and the potential for non-specific irritation were unknown, 10 controls and one

Table 1 Desensitization protocol for laronidase IV (20.3 mg): solution preparation

	Volume (ml)	Concentration (mg/ml)	Total amount of drug in each solution (mg)
Solution 1	250	0.000812	0.2030
Solution 2	250	0.00812	2.0300
Solution 3	250	0.08056	20.1403

Table 2 Desensitization protocol for laronidase IV (20.3 mg): protocol for administration

Step no.	Solution no.	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0004	0.0004
2	1	5.0	15	1.25	0.0010	0.0014
3	1	10.0	15	2.50	0.0020	0.0035
4	1	20.0	15	5.00	0.0041	0.0075
5	2	5.0	15	1.25	0.0102	0.0177
6	2	10.0	15	2.50	0.0203	0.0380
7	2	20.0	15	5.00	0.0406	0.0786
8	2	40.0	15	10.00	0.0812	0.1598
9	3	10.0	15	2.50	0.2014	0.3612
10	3	20.0	15	5.00	0.4028	0.7640
11	3	40.0	15	10.00	0.8056	1.5696
12	3	80.0	174.375	232.50	18.7305	20.300

Total time = 340 min (5.6 h).

patient on laronidase treatment were tested with negative results (5).

In vitro IgG antibodies were found but not IgE. IgG levels in non-reactors vary and are present in 93%. The clinical significance of antibodies to laronidase is not known, including the potential for product neutralization. Although the levels of IgG antibodies do not seem to correlate with the incidence of infusion associated reactions, it was observed by Clarke et al. that most reactions occurred just after soroconversion.

A negative IgE to laronidase does not exclude the possibility of an IgE mechanism to this reaction as the ELISA method is not standardized for this drug, and its sensitivity and specificity are unknown.

After establishing the nature of the immediate hypersensitivity reaction to laronidase, desensitization was indicated, as the patient was in need of the medication, and there was high risk for anaphylaxis during subsequent exposures. Protocols for desensitization vary according to the nature of the reaction, the drug involved, and the route of administration (6).

Patients with lysosomal storage disorders have successfully undergone desensitizations to alglusidase alfa and

idursulfase (7, 8); however, no previous report was found of laronidase desensitization. Based on other protocols, we elaborated a new successful laronidase protocol with three bags and 12 steps which provided temporary clinical tolerance at full therapeutic doses (3) and protected against severe reactions. After 8 months, the patient's laronidase dose was adjusted to her weight, and she presented a minor urticarial reaction that was less intense, easily treated, and did not require infusion interruption. This new protocol could be provided to patients with immediate hypersensitivity reactions to laronidase.

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