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Asfotase Alfa hypersensitivity: an outpatient 8-steps desensitization protocol

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Background

Hypophosphatasia (HPP) is a rare inherited disorder of bone and mineral metabolism, caused by a number of loss-of-function mutations in the ALPL (alkaline phosphatase liver type) gene, with generalized reduction of activity of the tissue-non-specific (liver/bone/kidney) isoenzyme of ALP (TNSALP) [1].

The main clinical signs are related to defective bone and teeth mineralization (rickets, osteomalacia, fractures, teeth loss), but other systemic manifestations can be present in the severe forms (seizures, respiratory and kidney problems, chronic pain, weakness, etc.) [2].

Since 2015, Asfotase Alfa has been authorized by the European Medicine Agency (EMA) for treatment of severe forms of perinatal, infantile, and childhood HPP [3].

Asfotase Alfa was generally well-tolerated, with most adverse events being mild-to-moderate. The most frequently observed adverse reactions in clinical studies were injection-site reactions (approximately 73%) such as pain, erythema, pruritus, swelling, papule, nodule atrophy, and lipohypertrophy in the injection site. Other adverse events reported are increased serum levels of parathyroid hormone and calcium, ectopic calcification, craniosynostosis, and disproportionate weight gain [4].

Injection site rotation and proper injection techniques are crucial to minimize such problems.

Hypersensitivity reactions, signs, and symptoms of anaphylaxis within minutes after subcutaneous administration

of Asfotase Alfa have been reported and can occur also in patients who have received treatment for more than 1 year.

These symptoms included difficulty in breathing, a choking sensation, periorbital edema, and dizziness. Reactions occurred within minutes of subcutaneous administration. Other hypersensitivity reactions included vomiting, nausea, fever, headache, flushing, irritability, chills, rash, pruritus, and oral hypoesthesia.

Once a patient experiences a severe infusion reaction, current opinion is that these patients should not be treated with Asfotase Alfa again, thus exposing the patient to the recurrence of hypophosphatasia [5].

Drug desensitization is a procedure by which patients can tolerate medications that previously induced hypersensitivity reactions; this procedure is usually performed through the administration of a series of very gradual drug dose increments such that the sum total dose equals the original target dose of the drug.

Usually, premedications that antagonize the effect of mediators of Type-1 hypersensitivity (histamine, leukotrienes, prostaglandins) are often given to lessen the risk of breakthrough symptoms which may occur during the course of a desensitization procedure.

Two types of protocols are usually distinguished: rapid desensitization, that is usually performed in a time frame of a few hours or a few days, and slow sensitization, that is performed over several weeks. Rapid drug desensitization (RDD) protocols address Type-1 reactions with mast cell/basophils/IgE involvement, and slow drug desensitization protocols address delayed type IV reactions with T-cell involvement.

Mixed reactions are seen with increasing frequency, with patients presenting urticarial rashes in a delayed fashion, and RDD protocols have been used for delayed reactions with great success, changing the paradigm of the segregation and use of RDD versus slow drug desensitization [6, 7].

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Case presentation

We report a 29-year-old Caucasian woman affected by early infancy-onset of HPP (hypophosphatasia) bearing a homozygous ALPL gene mutation (p.Asp109Glu mutation; exon 5: c.327C > A).

Since diagnosis, she had a rickets-like skeletal involvement characterized by reduced bone mineralization and pathological fractures with abnormal consolidation time and several deformities.

Her clinical conditions improved with the enzymatic therapy, even if the patient's intake was initially discontinuous; she performed four cycles of 6-month therapy over 3 years (from 2016 to 2019).

Thanks to the therapy with Asfotase Alfa, she was able to regain full weight bearing on his right leg with a 50% shorter consolidation time than the previous similar fracture.

The patient came to our attention in February 2020, referring that she had stopped Asfotase Alfa because of an episode of dyspnea and bronchospasm occurred several minutes after the drug administration in August 2019.

Therapy was suspended after this episode.

Considering the importance of the therapy with Asfotase Alfa and the absence of drug alternatives, we

decided to proceed with rapid desensitization protocol (RDD) in 2 days.

The desensitization was successfully performed without any adverse reactions.

The patient was then able to resume the three-weekly subcutaneous administration of the drug without presenting further adverse reactions.

This represents the first reported case of desensitization to Asfotase Alfa.

Treatment

We used a custom-designed rapid desensitization protocol, performed using an outpatient 8-steps protocol over 2 days, with the administration of incremental doses of the drug until her cumulative dose was reached (Table 1).

The main difficulty of the procedure was in the parcelling of the cumulative dose of the drug, due both to the extremely low volumes and the non-diluibility of the drug, and for the reduced physical and chemical stability [8].

Before performing the desensitization, she underwent a spirometric examination that showed a severe restrictive pattern in association to a mild obstructive deficit. Preliminary laboratory tests showed a basal serum tryptase of 4.53 µg/ml.

Table 1 The 8-steps protocol for Asfotase Alfa described in this report

Asfotase Alfa — Strensiq®					
Target dose (mg)			80 mg		
Standard volume per vial (ml)			0.8		
Calculated target concentration (mg/ml)			100 mg/ml		
Drug desensitization protocol					
Day 1					
Time 0		Premedication		Chlorphenamine maleate 10 mg/ml	
Step	Time	Dose administrated with the step (mg)	Volume administrated per step (ml)	% of target dose	% of cumulative dose
1	30	5	0.05	6.25	6.25%
2	60	8	0.08	10	16.25%
3	90	10	0.1	12.5	28.75%
4	120	18	0.18	22.5	51.25%
Day 2					
Step	Time	Dose administrated with the step (mg)	Volume administrated per step (ml)	% of target dose	% of cumulative dose
5	0	8	0.08	10	10%
6	30	10	0.1	12.5	22.50%
7	60	18	0.18	22.5	45%
8	90	44	0.44	55	100%
Day 3					
Step	Time	Dose administrated with the step (mg)	Volume administrated per step (ml)	% of target dose	% of cumulative dose
	0	80	0.8	100	100%

The first day the patient received a premedication with Montelukast 10 mg and a intramuscular injection of chlorphenamine maleate 10 mg/ml; after 30 min we started injecting incremental doses of Asfotase Alfa over 2 h. We did not observe local or systemic reactions.

The second day she reached the 100% of the total drug dose (80 mg) without adverse manifestations. Every single injection was done in different parts of the body in order to prevent local adverse reactions and with a dose interval of 30 min, monitoring all vital signs.

Outcome and follow-up

The patient came for a third day in which received the 100% of the drug without premedication and she was evaluated for any immediate or delayed reactions.

Since that day she has resumed the therapy according to the previous treatment scheme in the absence of adverse reactions.

Discussion

In the past decade, biological agents and novel agents have proved to be very effective treatments for many diseases, including rare or ultra-rare diseases.

The advent of biological therapies and their proven effectiveness could be undermined by hypersensitivity reactions that could lead to the discontinuation of therapy; hence, drug desensitizations have increasingly been used.

Drug desensitization is a useful and important tool in case of hypersensitivity to several life-saving therapies or drugs used in the second or third level after therapeutic failures with other classes. Of note, it is highly effective in treating immediate hypersensitivity reactions regardless of whether the reaction is IgE or non-IgE mediated; furthermore, an increase in patient's life expectancy and quality of life has also been demonstrated [7, 9, 10].

This is the first reported case of a patient successfully undergoing desensitization after hypersensitivity reaction to Asfotase Alfa, and emphasizes the role of the allergist in a multidisciplinary setting.

Although more data and further evaluation of the results obtained would be needed, this protocol potentially

represents a significant step forward in patients with hypophosphatasia who have experienced hypersensitivity reactions to this drug.

The role of the Allergist in an increasing interdisciplinary setting can be an additional resource for the patient's health.

Declarations

Conflict of interest The authors declare no competing interests.

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