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Febuxostat: Successful Desensitization Protocol

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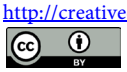

Abstract

Hyperuricemia is defined as the increase in uric acid when it exceeds its solubility limit, about 6.8 mg/dl. Persistent hyperuricemia causes diseases such as gouty arthritis, arthropathy, urolithiasis, and nephropathy. We present the clinical case of a 46-year-old patient with gout and persistent hyperuricemia; he presented cutaneous hypersensitivity to allopurinol and febuxostat and, for this reason, the patient stopped the treatment. After undergoing a 5-day new febuxostat desensitization protocol, he tolerated the drug without adverse effects. This case report highlights the importance of allergy desensitization if there's no other therapeutic option in patients with hypersensitivity to allopurinol and febuxostat.

Subject Areas

Allergy, Drug Allergy, Clinical Immunology

Keywords

Febuxostat, Drug Allergy, Hypersensitivity, Desensitization Protocol, Allergy

1. Introduction

Hyperuricemia is defined as the increase in uric acid when it exceeds its solubility limit, about 6.8 mg/dl. Persistent hyperuricemia causes diseases such as gouty arthritis, arthropathy, urolithiasis, and nephropathy [1]. Therapy to lower uric acid levels includes medications such as allopurinol, a xanthine oxidase inhibitor, whose adverse effects have been linked to polymorphisms in HLA-B*58:01 [2], and febuxostat, another non-purine xanthine oxidase inhibitor, this drug is

metabolized and oxidized in the liver [1].

Cutaneous adverse effects with febuxostat begin approximately 21 days after the start of the drug, compared with 36 days after the start of allopurinol [3]. The cutaneous adverse effects are erythema, itching, granulomatous eruptions and, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) [4].

In individuals who present adverse reactions to allopurinol, febuxostat has been an effective alternative, however, monitoring is recommended due to the risk of cutaneous hypersensitivity such as vasculitis related to febuxostat; progressive dose increase is recommended to avoid this adverse effect [5]. We present the clinical case of a patient who underwent a successful desensitization protocol to febuxostat, a medication with which he presented adverse effects.

2. Case Report

A 46-year-old male with a 4-year diagnosis of gouty arthritis and hypertension presented erythroderma in 2018 with the administration of allopurinol due to the diagnosis of hyperuricemia; by personal decision, the patient abandoned the treatment for two years. In 2020 he consulted rheumatology again for hyperuricemia; he started treatment with febuxostat 80 mg every 24 hours. Four days after taking the drug, he presented generalized erythema and discontinued the drug (**Figure 1**).

He was sent to nephrology due to a decrease in renal function, with an elevation of serum creatinine to 2 mg/dl, and glomerular filtration rate of 38.9 ml/min with hyperuricemia of 11.7 mg/dl. In July 2021 we requested basophils activation test for allopurinol 300 mg with a report of CD63+/CD123+HLA-DR- expression in 23.5% and for febuxostat 80 mg, with an expression in 41.1% (normal < 30%) (CD = Cluster of differentiation, HLA = Human Leukocyte Antigen). Due to the urgency of starting treatment, a desensitization protocol was started (**Table 1**).

The patient tolerated the febuxostat administration for 5 days without presenting any adverse effect during the protocol; after the 80 mg dose, the patient was monitored by telephone, and he did not report adverse effects. Currently, the patient is on continuous intake of febuxostat with the last control of serum uric acid of 6.7 mg/dl, a decrease in tophi size, and without progression of chronic kidney disease (**Figure 2**).

3. Discussion

There is currently no standardized protocol for desensitization to febuxostat; in 2015 di Paolo reported a 5-day desensitization protocol in two patients where the dose increase was different for each one, in this case, it was suspected that the adverse effects were late, and they were mediated by cells [6]. Sulaiman *et al.* reported another case of successful desensitization in a patient with exfoliative dermatitis, desensitization was achieved with a slower schedule for 14 days and a maximum dose of 40 mg [7].

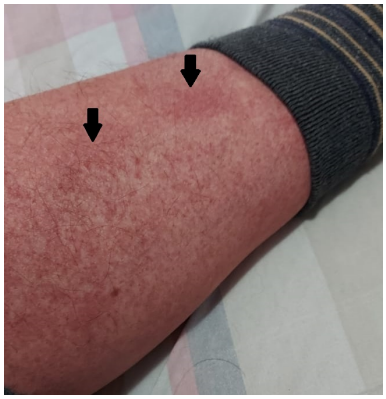

Figure 1. Dermatological lesions presented in the first 24 hours of febuxostat intake. The arrows indicate the erythema of the patient's leg.

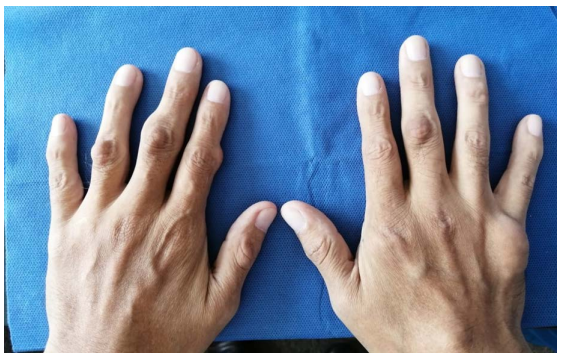

Figure 2. Tophi in the patient's joints, without inflammation after treatment with febuxostat.

Table 1. Febuxostat desensitization protocol used in the patient, drug dilutions, and surveillance time are shown. After administration of the 80 mg tablet, surveillance was maintained for 1 hour in medical office.

Febuxostat desensitization protocol					
Day	Time (minutes)	Dilution (mg/ml)	Dose (mg)	Volume (ml)	Total daily dose (mg)
1	0	1	0.1	0.1	0.1
	30	1	0.25	0.25	0.35
	60	1	0.50	0.50	0.85
	90	1	1.0	1	1.85
	120	1	2.0	2	3.85
2	0	1	4	4	4
	45	1	6	6	10
3	0	2	10	5	10
	45	2	20	10	30
4	0	2	20	10	20
	45	2	40	20	60
5	0		80 (complete tablet)		80

In the case that we present, the activation of basophils was requested due to the reaction time in which the skin reactions occurred in the patient, these being within the first 24 hours, immediate hypersensitivity was suspected, this was verified with the positivity of the activation of CD63+/CD123+HLA-DR-cells. In the literature review, we did not find reports of immediate reactions to febuxostat that could suggest the existence of humoral mechanisms against the drug, and this is suggested by the symptoms of our patient.

In a randomized, controlled study conducted in an Asian population with negative HLA-B*58:01, febuxostat did not cause any serious adverse reactions and was equally effective, making it safe for this group of patients [8]. In case reports of patients who have had this double adverse reaction, it is believed that it is unlikely that HLA has a role in the pathophysiology or even a non-immunological mechanism could be suspected [1]. We believe that if a non-immunological mechanism were involved, there would be no tolerance to febuxostat even with desensitization protocols.

For many years, febuxostat has been a good alternative for the treatment of patients with adverse reactions to allopurinol; in some studies, it is more effective in reducing the tophi area (P = 0.08 for 80 mg of febuxostat vs. allopurinol) [9]. After desensitization protocol, our patient can have the benefits of treatment for hyperuricemia.

4. Conclusion

Desensitization to febuxostat is a good alternative in patients with adverse reactions to both drugs. This option should be considered by the allergist, due to the risk of progression of chronic kidney disease without treatment.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The authors declare no conflicts of interest.

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