

Desensitization to febuxostat: report of two cases

Camilla Di Paolo, MD^a, Stefano Minetti, MD^b,
Michela Mineni, MD^b, Silvia Inverardi, MD^b,
Fabio Lodi Rizzini, MD^b, Massimo Cinquini, MD^a, and
Cinzia Tosoni, MD^a

Clinical Implications

- Febuxostat has been recently introduced in the market as an alternative urate-lowering drug. Its allergenic profile has not been fully outlined and the clinical management of hypersensitivity reactions is not standardized. We report 2 cases of hypersensitivity reactions to febuxostat and present a desensitization protocol.

TO THE EDITOR:

Adverse reactions to allopurinol are frequently observed and potentially severe, which occur in up to 10% of treated patients, ranging from urticaria and angioedema, fixed drug eruption, maculopapular exanthema to Stevens Johnson syndrome (SJS), toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms.¹ Allopurinol hypersensitivity has been associated with the presence of the allele HLA-B 5801, which appears to increase the risk of developing severe adverse reactions.²

Febuxostat (Uloric) is a recently approved nonpurine selective xanthine-oxidase inhibitor and is the treatment of choice for urate-lowering in patients who developed severe reactions to allopurinol and/or were found to be HLA-B 5801 positive.³

Overall safety in clinical trials showed that febuxostat is generally well tolerated. Adverse reactions to febuxostat were found to be less frequent and severe compared with those caused by allopurinol. However, over the past few years, adverse reactions to febuxostat have been reported to the Food and Drug Administration (FDA) or described in the literature, some even resulting in severe systemic involvement.⁴

In patients who develop adverse reactions to both allopurinol and febuxostat, but still require urate-lowering therapy, drug desensitization is the only clinical option. Drug desensitization is a medical procedure that induces temporary unresponsiveness toward drug antigens responsible for the hypersensitivity reaction. It is based on a gradual reintroduction of incremental amounts of the drug up to the full therapeutic dose. It is used both in IgE-mediated and non-IgE-mediated, or delayed hypersensitivity reactions.⁵ Whereas allopurinol desensitization has been widely studied and attempted, only one desensitization protocol has been proposed so far for febuxostat and no reports of its safety and efficacy are available.

Two cases of successful desensitization to febuxostat performed in the Allergy Service of Spedali Civili di Brescia are presented in this article. To our knowledge no reports of safe and successful desensitization to febuxostat have yet been published.

In both cases, desensitization was successful and patients were able to continue their treatment without further adverse reactions.

TABLE I. Patient 1 desensitization protocol

Day	Time (h)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Daily dose (mg)
1	0.00	0.01	10	0.1	0.1
	0.45	0.05	5	0.25	0.35
	0.90	0.05	10	0.5	0.85
	1.35	0.2	5	1	1.85
	1.70	0.2	10	2	3.85
2	0.00	22	23	4	4
	0.45			6	10
3	0.00	2	5	10	10
	0.45	2	10	20	30
4	0.00	4	5	20	20
	0.45	4	10	40	60
5	0.00	8	1	80	80
	0.45				(Target dose)

CASE REPORT 1

A 79-year-old man was diagnosed with renal cell carcinoma and was treated with conservative surgery. He subsequently developed moderate renal failure, hyperuricemia, and gout. He was prescribed allopurinol, initially 150 mg every other day and then increased to 150 mg daily. After 5 months of daily allopurinol treatment, the patient developed a generalized pruritic, scaly, maculopapular rash and was referred to our Allergy Service. After having ruled out other causes, an adverse reaction to allopurinol was diagnosed and the treatment was discontinued.

The patient was given intravenous and topical corticosteroid and antihistamine with resolution of skin lesions, although 2 relapses were observed 2 and 5 weeks later, which required short steroid and antihistamine courses.

Six months later, due to persistently elevated blood urate levels, the patient was started on febuxostat 40 mg daily. At that time no skin lesions had recurred for months and both corticosteroid and antihistamine had long been discontinued. After 3 days of febuxostat treatment, the patient developed diffuse multiform erythematous scaly patches. Febuxostat was discontinued, and after a short course of prednisone and topical antibiotic, resolution of skin lesions was achieved.

Given the need to lower urate levels (8 mg/dL), the patient required desensitization to febuxostat, which was carried out as indicated in Table I. Because no standardized allergy tests are available for febuxostat and because the patient had not developed clearly IgE-mediated anaphylactic symptoms, no prior skin tests were performed.

The desensitization was well tolerated, no adverse effects were observed, and the patient regularly continued to take febuxostat 80 mg daily without further adverse reactions.

CASE REPORT 2

A 65-year-old man, suffering from chronic gout for 10 years, was treated with diclofenac, colchicine, and allopurinol. He was diagnosed with pneumonia and admitted to hospital where he was prescribed paracetamol, amoxicillin, and clorfenamine. After 7 days

TABLE II. Patient 2 desensitization protocol after failure of protocol 1

Day	Time (h)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Day	Time (h)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Day	Time (h)	Concentration (mg/mL)	Volume (mL)	Dose (mg)
1	0.00	0.01	1	0.01	10	0.00	4	4	16	19	0.00	4	4	16
	0.45	0.05	5	0.25		0.45	4	4	16		0.45	4	4	16
	0.90	0.05	10	0.5		0.90	4	7	28		0.90	4	7	28
	1.35	0.2	5	1										
	1.70	0.2	10	2										
2	0.00	0.04	5	2	11	0.00	4	5	20	20	0.00	4	4	16
	0.45	0.04	5	2		0.45	4	5	20		0.45	4	4	16
						0.90	4	10	40		0.90	4	7	28
									(Target dose)					
3*	0.00	2	1	2	12†	0.00	4	10	40	21	0.00	4	4	16
	0.45	2	1	2		0.45	4	10	40		0.45	4	4	16
	0.90	2	1	2					(Target dose)		0.90	4	7	28
4	0.00	2	1	2	13	0.00	1	40	40	22	0.00	4	4	16
	0.45	2	1	2							0.45	4	4	16
	0.90	2	2	4							0.90	4	7	28
5	0.00	2	1	2	14	0.00	1	40	40	23	0.00	4	4	16
	0.45	2	1	2							0.45	4	4	16
	0.90	2	3	6							0.90	4	9.05	38
6	0.00	2	5	10	15	0.00	4	3	12	24	0.00	4	8	32
							4	3	12		0.45	4	9.05	38
							4	4	16					
7	0.00	2	5	10	16	0.00	4	4	16	25	0.00	4	10	40
						0.45	4	4	16		0.45	4	10	40
						0.90	4	7	28					(Target dose)
8	0.00	4	2	8	17	0.00	4	4	16	26	0.00	1	80	80
	0.45	4	3	12		0.45	4	4	16					(Target dose)
						0.90	4	7	28					
9	0.00	4	3	12	18	0.00	4	4	16	27	0.00	1	80	80
	0.45	4	3	12		0.45	4	4	16					(Target dose)
	0.90	4	4	16		0.90	4	7	28					

*On day 3, the patient develops an erythematous rash on both legs.

†On day 12, diffuse erythema appears and febusostat dosage is again lowered to 40 mg.

of treatment, he developed an extensive bullous eruption, was diagnosed with Lyell syndrome, and was transferred to the intensive care unit. HLA-B5801 genotyping was performed and resulted positive, which indicated a possible causative role of allopurinol in the hypersensitivity reaction and it was then discontinued. Colchicine was safely reintroduced, whereas diclofenac caused a fixed drug eruption that required drug discontinuation.

Two months later, when skin lesions steadily resolved, he was started on febuxostat 80 mg daily. However, on the fourth day of treatment, he developed a maculopapular erythematous rash that required febuxostat discontinuation and a short course of topical steroid. Although no standardized skin tests are available, the patch test with febuxostat in 3% petrolatum was performed and resulted negative.

Given the severity of the previous adverse reactions and the presence of HLA-B 5801, allopurinol reintroduction was contraindicated. Therefore, the patient underwent desensitization to febuxostat, performed as outlined in Table I.

However, on the third day of desensitization, the patient developed delayed urticaria, 3 hours after the last administration, and febuxostat administration was interrupted.

After cutaneous lesions healed, desensitization was restarted, this time performed following a slower 12 days' scheme as shown in Table II. Despite more gradual dosage increases, the patient still developed a mild erythema on both legs, but the procedure was not suspended. After reaching the target dose of 80 mg on days 11 and 12, a more diffused pruritic erythema appeared. The patient was then treated with oral antihistamine and topical steroid, and the febuxostat dose was lowered again to 40 mg but not discontinued.

Skin lesions rapidly cleared and 16 more days of controlled febuxostat administration was planned. The patient was able to tolerate 60 mg of febuxostat into 3 divided doses for 8 days. Because no skin lesions relapsed, on day 23 the dose was increased to 70 mg and on day 25 the target dose of 80 mg was reached. From then on the patient steadily tolerated febuxostat without developing further skin eruption and urate blood levels rapidly decreased within the normal range.

DISCUSSION

Allopurinol, febuxostat, and rasburicase are so far the FDA approved drugs for urate-lowering management of gout. Allopurinol and febuxostat are available for oral administration and are therefore widely used, whereas rasburicase is only available for intravenous infusion for the treatment of acute hyperuricemia in tumoral lysis syndrome and has more restricted indications. Allopurinol has often been associated with a wide range of adverse reactions, potentially severe. Pathogenetic mechanisms underlying allopurinol hypersensitivity are not fully understood. Among these, the accumulation of oxypurinol metabolites and byproducts of purine metabolism, and hypersensitivity to oxypurinol have been suggested. Risk factors include chronic kidney failure, use of thiazide diuretics, recent introduction of allopurinol treatment, and the presence of HLA-B5801.⁶

Febuxostat has been more recently introduced to the market. It has a different mechanism of action, which represents an alternative urate-lowering therapy for patients with allopurinol hypersensitivity or renal failure, and has so far been related to a low incidence of hypersensitivity reactions. Given the different

chemical structure, the probability of developing adverse reactions to both allopurinol and febuxostat is theoretically low. Interestingly, clinical trials published so far on febuxostat have not reported severe cutaneous reactions as frequently as with allopurinol; however, the incidence of mild cutaneous rash associated with febuxostat was 2%, similar to that of allopurinol.⁷

Premarketing clinical trials estimated an incidence of 0.5% and 1.6% of cutaneous rash in patients treated with febuxostat 40 mg and 80 mg daily, respectively.⁸ From 2009 to November 2012, the FDA received spontaneous reports of febuxostat hypersensitivity reactions, with a few cases of severe reactions such as SJS and anaphylactic shock, generally occurring within the first month of treatment.⁹ Postmarketing surveillance studies estimate the frequency of SJS to be equal to or greater than 1/10,000 to less than 1/1,000.⁸ In the literature, on the other hand, the first case of febuxostat hypersensitivity reaction was only recently described in a 69-year-old woman with multiple comorbidities including gout and renal failure.¹⁰

In the next few years, as febuxostat becomes more widely available, more cases of adverse events might be reported helping to determine its actual safety profile in comparison with that of allopurinol and outlining potential risk factors for the development of hypersensitivity reactions.

In the 2 cases described in this report, both patients developed cutaneous reactions associated with febuxostat, similar to those observed in allopurinol hypersensitivity. It is unclear whether allopurinol and febuxostat hypersensitivity might share the same risk factors or if a previous allopurinol adverse reaction might have a role in the subsequent development of hypersensitivity to other drugs including febuxostat. Interestingly, patients with previous hypersensitivity reactions to allopurinol were excluded from febuxostat phase III studies; hence, more data on patients with previous allopurinol hypersensitivity treated with febuxostat are required to understand the safety profile of febuxostat in this subgroup.

So far, febuxostat hypersensitivity reactions have seldom been described in the literature and no successful desensitization procedures have been reported. In 2009, Sullivan elaborated the first febuxostat desensitization protocol.¹¹ However, no details are available on the number of treated patients, type of previous adverse reactions treated patients had developed, and whether the desensitization protocol was safe and effective. Because no previous clinical experience on febuxostat desensitization was available in the literature, we modified the Sullivan protocol to achieve tolerance induction to the full therapeutic dose (80 mg) within the first week of administration, starting from a dose of 0.1 mg and administering multiple increasing doses each day under medical supervision. This approach was effective in patient 1 but not in patient 2, who required a much slower build-up phase with a more gradual dosage increase.

Because the clinical manifestations of the 2 patients suggested a delayed, cell-mediated pathogenesis, a slow desensitization protocol was preferred. This slow protocol was well tolerated, perhaps due to enhanced metabolic adaptation, which eventually resulted in a more rapid and efficient clearance of reactive drug metabolites that might stimulate the immune response underlying allergic reactions.⁵

The 2 reports demonstrate that oral desensitization with febuxostat can be successfully performed ensuring an alternative treatment to patients with previous severe adverse reactions to both allopurinol and febuxostat who still require urate-lowering therapy.

^aStruttura Semplice Valenza Dipartimentale Allergologia, Spedali Civili di Brescia, Brescia, Italy

^bStruttura Semplice Valenza Dipartimentale Allergologia, Università del studi di Brescia, Brescia, Italy

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication October 2, 2014; revised January 29, 2015; accepted for publication January 30, 2015.

Available online March 7, 2015.

Corresponding author: Stefano Minetti, MD, SSVD Allergologia, Spedali Civili di Brescia, P.le Spedali Civili 1, 20125 Brescia, Italy. E-mail: Steminetti@libero.it. 2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.01.022>

REFERENCES

1. Lee HY, et al. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? *Singapore Med J* 2008;49:384-8.
2. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011;12:118.
3. Bardin T. Current management of gout in patients unresponsive or allergic to allopurinol. *Joint Bone Spine* 2004;71:481-5.
4. Chohan S, Becker M. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. *J Rheumatol* 2011;38:1957-9.
5. Fam AG, Dunne SM, Iazzetta J, Paton TW. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001;44:231-8.
6. Ryu H, Song R, Kim HW, Kim JH, Lee EY, Lee YJ, et al. Clinical risk factors for adverse events in allopurinol users. *J Clin Pharmacol* 2012;53:211-6.
7. Dubchak N, Falasca G. New and improved strategies for the treatment of gout. *Int J Nephrol. Renovasc. Dis* 2010;3:145-66.
8. Garcia-Valladares I, Khan T, Espinoza LR. Efficacy and safety of febuxostat in patients with hyperuricemia and gout. *Ther Adv Musculoskel Dis* 2011;3:245-53.
9. www.accessdata.fda.gov. Accessed February 17, 2015.
10. Abeles AM. Febuxostat hypersensitivity. *J Rheumatol* 2012;39:659.
11. Sullivan T. Protocols for rapid and slow drug allergy desensitization, 1st ed., November 2009. Available from: <http://www.scribd.com/doc/22062135/Protocols-for-Drug-Allergy-Desensitization>. Accessed February 17, 2015.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.