

# Safety and Efficacy of Febuxostat Treatment in Subjects with Gout and Severe Allopurinol Adverse Reactions

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**ABSTRACT.** *Objective.* Allopurinol, a purine base analog inhibitor of xanthine oxidase (XO) activity, remains the standard for pharmacologic urate-lowering management of gout. Allopurinol is efficacious and safe in most patients, but intolerance is estimated to occur in up to 10% of treated patients. Severe or life-threatening allopurinol adverse reactions (AE) occur much less frequently, and include severe cutaneous allopurinol reactions, vasculitis, and/or a multisystem allopurinol hypersensitivity syndrome. During clinical development of febuxostat (FEB), a recently approved non-purine analog inhibitor of XO, subjects with severe allopurinol intolerance were excluded from randomized double-blind FEB/allopurinol comparative trials.

*Methods.* In this retrospective study, safety and urate-lowering efficacy of FEB was assessed in 13 successively encountered gout patients with prior documented severe allopurinol reactions.

*Results.* FEB was well tolerated in 12 of 13 patients, each of whom remains on treatment. One patient previously hospitalized with documented exfoliative erythroderma during allopurinol treatment, developed biopsy-confirmed cutaneous leukocytoclastic vasculitis. None of the other 12 patients treated with FEB showed rash, worsening hepatic function, blood cytopenia or eosinophilia.

*Conclusion.* In 12 of our 13 gout patients with previously documented severe allopurinol AE, FEB treatment was safe. However, the development of a hypersensitivity type cutaneous vasculitis (likely but not definitively FEB-related) early in treatment mandates caution, careful dose escalation, and close monitoring when FEB urate-lowering therapy of allopurinol-intolerant patients is considered. (J Rheumatol First Release July 1 2011; doi:10.3899/jrheum.110092)

## Key Indexing Terms:

GOUT

ALLOPURINOL

FEBUXOSTAT

Gout is a metabolic disorder manifested by hyperuricemia and resultant deposition of monosodium urate crystals in joints, soft tissue, and kidneys. Major advances in the treatment of gout have been made in the past 5 years. Allopurinol, a purine base analog inhibitor of xanthine oxidase activity, remains the standard for pharmacologic urate-lowering management of gout. Allopurinol is efficacious and safe in most patients, but intolerance is estimated to occur in up to 10% of treated patients<sup>1</sup>. Severe or life-threatening allopurinol adverse reactions precluding re-challenge with the drug occur much less frequently (~0.1 to 0.4% of treated patients), and include severe cutaneous reactions, vasculitis, and/or a multisystem allopurinol hypersensitivity syndrome (AHS)<sup>2</sup>. Febuxostat, a structurally distinct non-purine inhibitor of xanthine oxidase, was approved by the US Food and Drug Administration (FDA) for the treatment of the hyperuricemia of gout in 2009, the first alternate urate lowering therapeutic in gouty arthritis treatment in 40 years. During clinical development of febuxostat, subjects with severe allopurinol intolerance were excluded from the 3 randomized double-blind febuxostat/allopurinol comparative trials. We describe here our initial

experience with regard to the safety and efficacy of febuxostat treatment in a small group of patients with documented allopurinol intolerance.

## MATERIALS AND METHODS

Patients followed longitudinally in our Gout Clinic were identified as having experienced severe allopurinol adverse events. All patients fulfilled American Rheumatism Association preliminary criteria for the diagnosis of gout<sup>3</sup>. Institutional Review Board approval was obtained and all participants provided written approved consent before review of relevant materials, including medical charts and laboratory results. In this retrospective study, safety and urate lowering efficacy of febuxostat were assessed in 13 successively encountered gout patients (8 men, 5 women; age range, 52 to 85 yrs) with prior documented severe allopurinol reactions: severe cutaneous allopurinol reactions only, 10 patients; multisystem involvement, 3 patients, including skin (2 patients), acute or acute on chronic renal insufficiency (3), hepatitis (1) and/or hematologic abnormalities (2). All patients had impaired baseline renal function: estimated creatinine clearance and creatinine clearance (eCLcr) 60–89 ml/min, 4; 30–59 ml/min, 5; 15–29 ml/min, 4 (Table 1). Febuxostat is FDA approved at doses of 40 and 80 mg/day in the United States. Treatment was initiated at 40 mg/day in 12 patients and 20 mg/day in 1 patient. Febuxostat dose was titrated, where permitted by safety and renal function monitoring, to achieve and maintain serum urate levels < 6.0 mg/dl.

## RESULTS

All 13 patients were hyperuricemic (range: serum urate level 7.5 to 14 mg/dl) prior to febuxostat therapy. Febuxostat was well tolerated in 12 patients, each of whom remains on treatment (mean febuxostat exposure 10 mo; range 1.5 to 15 mo). Serum urate levels decreased 25% to 59% in these 12 patients:

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Table 1. Characteristics of study patients.

Age	Gender	Adverse Event	Allopurinol Starting Dose (mg)	Febuxostat Starting Dose (mg)	Febuxostat Current Dose, mg	SUA Initial, mg/dl	SUA Post, mg/dl	Percentage SUA Reduction	Duration on Drug (mo)	Estimated Cr CI (ml/min)
85	F	Exfoliative erythroderma requiring hospitalization	40	40	0	10.9	Unknown	xxx	0.25	33.7
52	F	Full body rash with desquamation	40	40	80	14	9.5	32	15	60.0
74	F	Dyspnea, likely acute renal failure	40	40	40	11.3	6.9	39	12	56.2
83	M	Full body rash	40	40	80	9.8	4.7	52	13	52.3
66	M	Rash	40	40	60	10.2	4.6	55	12	65.1
70	M	Acute renal failure, eosinophilia and vasculitis on bx	20	20	20	11	5.9	46	7	27.4
71	M	Desquamating skin rash	40	40	40	9.9	Unknown	xxx	1.5	50.6
60	M	Desquamating skin rash of mouth	40	40	80	13.7	5.6	59	9	91.2
75	F	Rash	40	40	40	10.3	4.8	53	3	18.3
71	M	Severe cutaneous reaction	40	40	100	8.8	5	43	13	57.6
62	M	Diffuse rash	40	40	40	8.7	5.7	34	16	29.2
80	F	Diffuse cutaneous reaction on worsening chronic kidney diagnosis	40	40	40	10.2	4.9	52	13	14.7
75	M	Rash and eosinophilia	40	40	40	7.5	5.6	25	6	81.0

SUA: serum uric acid; eCLcr: estimated creatinine clearance.

6 remain on the initial febuxostat dose (20 mg/day, 1 patient; 40 mg/day, 5 patients), and 10 patients have maintained serum urate level < 6.0 mg/dl on febuxostat doses from 20 to 80 mg/day. In 2 patients, serum urate level remains > 6.0 mg/dl despite 32% and 38% serum urate level reductions from baseline, respectively, on febuxostat 40 mg/day and 80 mg/day.

One patient, an 85-year-old woman, previously hospitalized with documented exfoliative erythroderma during allopurinol treatment, developed biopsy-confirmed cutaneous leukocytoclastic vasculitis after 4 days exposure to febuxostat

40 mg/day (Figures 1 and 2). No evidence for other organ system involvement was detected, and the rash resolved promptly after febuxostat withdrawal and a 6 day corticosteroid taper. This patient had also received seasonal influenza vaccination on day 1 of febuxostat treatment. She did receive another dose of seasonal influenza vaccination compounded with H1N1 virus one year later with no adverse events.

None of the other 12 patients treated with febuxostat



Figure 1. Possible drug eruption with extensive petechiae.

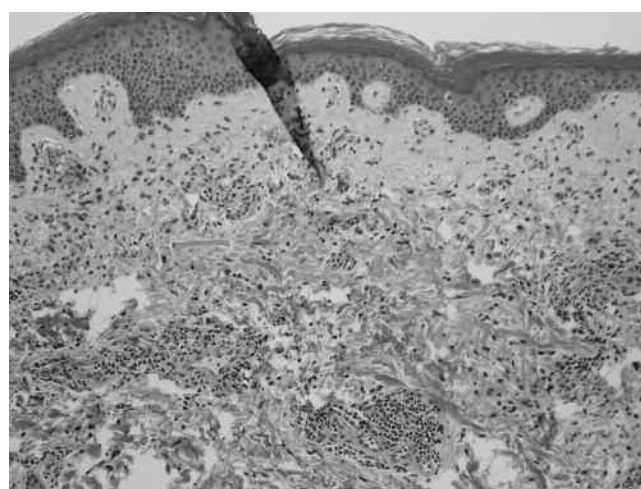


Figure 2. Skin biopsy shows perivascular infiltrate of neutrophils, karyorrhectic debris, eosinophils and erythrocytes, consistent with leukocytoclastic vasculitis.

showed rash, worsening hepatic function, blood cytopenia, or eosinophilia. One patient with baseline moderate chronic kidney disease progressed to severe chronic kidney disease; renal biopsy showed focal segmental glomerulosclerosis.

## DISCUSSION

The allopurinol hypersensitivity syndrome is poorly understood and the exact pathophysiology is unclear. Some have suggested that accumulation of oxypurinol metabolites, the byproduct of purine metabolism, and hypersensitivity to oxypurinol account for the toxic effects of allopurinol<sup>4</sup>. Risk factors include chronic kidney disease, use of thiazide diuretics and recent institution of allopurinol therapy. Recent genetic studies have identified the presence of the HLA-B\*5801 allele in the Han Chinese as also increasing the risk for severe cutaneous allopurinol reactions<sup>5</sup>. Symptoms of AHS include dermatologic manifestations of maculopapular rash, toxic epidermal necrolysis or Stevens Johnson syndrome, fever, bone marrow suppression, hepatitis, and renal involvement. While the incidence of AHS is estimated at 1–4/1000 allopurinol treated patients, it is quite rare and close monitoring in high risk patients with renal insufficiency should be employed<sup>2</sup>. Mortality from AHS has been reported to be 25%, most frequently from renal and hepatic failure<sup>4,6,7</sup>.

Allopurinol dosing in patients with renal impairment remains controversial. Multiple studies have recently shown that the renal based allopurinol dosing guidelines may not be appropriate, as patients often do not reach goal serum urate levels when the guidelines are followed<sup>4,8,9</sup>. Additionally, no study has shown that dose reduction of allopurinol in renal disease mitigates the risk of AHS<sup>9,10</sup>.

Febuxostat is a thiazolecarboxylic acid derivative that inhibits xanthine oxidase by a noncompetitive mechanism of inhibition rather than as with allopurinol. Unlike allopurinol, febuxostat and its metabolites appear not to interfere with pyrimidine metabolism and are not reincorporated into purine nucleosides<sup>11</sup>. While both allopurinol and febuxostat are hepatically metabolized, only allopurinol's main metabolite, oxypurinol, is renally excreted. There have been 3 large studies comparing efficacy and safety of febuxostat with allopurinol<sup>12,13,14</sup>. As all studies were double blinded, patients with known allopurinol reactions were excluded from the study. Our cohort of patients presented a unique opportunity to evaluate tolerability of febuxostat in an allopurinol sensitive population, in which several patients had life or organ threatening AHS. We have been able to demonstrate efficacy of febuxostat in this population as well as almost universal tolerability of the drug in a uniquely ill population.

In conclusion, in 12 of our 13 gout patients with previously documented severe allopurinol adverse events, febuxostat treatment was safe; in 10, goal range serum urate level was achieved and maintained over a mean treatment period of 10 months. However, the development of a hypersensitivity type

cutaneous vasculitis (likely but not definitively febuxostat-related) early in treatment mandates caution, careful dose escalation, and close monitoring when febuxostat urate lowering therapy is considered in allopurinol-intolerant patients.

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