Febuxostat in Gout: Serum Urate Response in Uric Acid Overproducers and Underexcretors

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ABSTRACT. ***Objective.*** Hyperuricemia of gout can arise due to either overproduction or underexcretion of uric acid. Not all available urate-lowering therapies are equally effective and safe for use in patients with renal disease. The objective of this post-hoc analysis was to determine the effectiveness of the xanthine oxidase inhibitor febuxostat in reducing serum urate (sUA) levels in gouty patients who were either overproducers or underexcretors.

Methods. Gouty subjects 18 to 85 years of age with sUA ≥ 8.0 mg/dl at baseline were enrolled in a Phase 2, 28-day, multicenter, randomized, double-blind, placebo-controlled trial and randomized to receive febuxostat 40 mg, 80 mg, or 120 mg daily, or placebo. The primary efficacy endpoint was the proportion of subjects with sUA < 6.0 mg/dl at Day 28. Secondary efficacy endpoints included percentage reductions in sUA and urinary uric acid (uUA) from baseline to Day 28.

Results. Of the 153 subjects, 118 (77%) were underexcretors (uUA ≤ 800 mg/24 h) and 32 (21%) were overproducers (uUA > 800 mg/24 h); baseline uUA data were missing for 3 subjects. Treatment with febuxostat led to the majority of subjects achieving sUA < 6.0 mg/dl at Day 28. Treatment with any dose of febuxostat led to significantly greater percentage reductions in uUA than that observed in the placebo group, for both underexcretors and overproducers.

Conclusion. Febuxostat is a highly efficacious urate-lowering therapy in patients with gout regardless of overproduction or underexcretion status. (First Release May 15 2011; J Rheumatol 2011;38:1385–9; doi:10.3899/jrheum.101156)

Key Indexing Terms:
FEBUXOSTAT ALLOPURINOL GOUT
HYPERURICEMIA URIC ACID EXCRETION

Gout is characterized by hyperuricemia [serum urate (sUA) concentration > 6.8 mg/dl, the limit of urate solubility] and by the acute and chronic consequences of monosodium urate crystal deposition, including gout flares, tophi, arthropathy, and increased likelihood for nephrolithiasis[1,2,3]. Hyperuricemia can arise due to either overproduction (10% of patients) or underexcretion (90% of patients) of urate, or a combination of both[4].

Urate-lowering therapy (ULT) is used for achieving and maintaining subsaturated goal sUA < 6.0 mg/dl, with the aim of dissolving and eliminating urate crystal deposits and the possibility of crystal-associated inflammation[5,6,7,8]. ULT options available in the United States include the xanthine oxidase (XO) inhibitors allopurinol and febuxostat, and the uricosuric probenecid. Probenecid is not effective in gout patients with renal impairment[9] and should not be used in patients with nephrolithiasis or in those who overproduce uric acid (vs underexcretors), as therapy can lead to deposition of uric acid crystals in the renal tubules, further development of stones, and worsening of renal function[10,11]. Allopurinol, the only XO inhibitor available until recently, is efficacious in both urate overproducers and underexcretors[12].

Febuxostat is a selective nonpurine analog XO inhibitor[13] approved in the United States and European Union for the treatment of chronic hyperuricemia in patients with gout[14,15]. Data from 3 comparative randomized controlled trials[16,17,18] have demonstrated the superior efficacy of febuxostat 80 mg daily compared to both allopurinol 300 mg[19,20] and placebo. In addition, febuxostat 40 mg daily was shown to be non-inferior to allopurinol[18]. The objective of this subanalysis was to determine if febuxostat was equally efficacious in gout patients with hyperuricemia, whether caused by overproduction or underexcretion of uric acid. Given the comparable efficacy of allopurinol in these 2 populations of people with hyperuricemia, we expected that febuxostat would also be effective in both groups.

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MATERIALS AND METHODS

As described[21], subjects who met the American Rheumatology Association[22] criteria for primary gout were enrolled in a 28-day, multicenter, Phase 2, randomized, blinded, placebo-controlled trial if they met all inclusion and none of the exclusion criteria. Patients, male or female, had to be 18 to 85 years of age with sUA ≥ 8.0 mg/dl at baseline. Exclusion criteria included serum creatinine (sCr) > 1.5 mg/dl or estimated creatinine clearance (eClcr; calculated by Cockcroft-Gault method[23]) < 50 ml/min; concurrent use of other ULT or medications containing aspirin (> 325 mg) or other salicylates; a history of xanthinuria, active liver disease, or hepatic dysfunction; or a history of alcohol abuse or intake of ≥ 14 alcoholic drinks per week.

After a 2-week washout for those subjects already receiving ULT, subjects were randomized 1:1:1:1 to receive febuxostat 40, 80, or 120 mg daily or placebo. For all subjects, colchicine 0.6 mg twice daily was provided for flare prophylaxis during the washout period and the first 2 weeks of the double-blind treatment. During weekly visits, including at enrollment (baseline visit), sUA was measured using an enzymatic method, and adverse events (AE) were recorded. At baseline and final visit at Day 28, 24-hour urine collection was carried out for measurement of urinary uric acid (uUA) and Clcr—uUA was measured by a standard uricase-dependent color assay on a Hitachi 911 analyzer. Subjects were classified as either underexcretors (uUA ≤ 800 mg/24 h) or overproducers (uUA > 800 mg/24 h) at baseline.

The primary efficacy endpoint was the proportion of subjects with sUA < 6.0 mg/dl at Day 28. Secondary efficacy endpoints included percentage reductions in sUA and uUA from baseline to Day 28. Baseline demographics, gout and comorbid characteristics, and efficacy endpoints are stratified here by baseline uUA status (underexcretor vs overproducer). AE rates are reported by treatment group.

RESULTS

Of the 153 subjects enrolled, 118 (77%) were underexcretors and 32 (21%) were overproducers. This analysis of the primary efficacy endpoint excluded 15 subjects due to missing baseline sUA or uUA. Baseline demographics and gout and comorbid disease characteristics, except for the percentage of subjects with tophi, were similar across treatment groups, regardless of baseline uUA (Table 1). Baseline sUA did not differ in the 2 groups.

Treatment with any dose of febuxostat led to the majority of subjects achieving sUA < 6.0 mg/dl at Day 28 in both overproducers and underexcretors (Figure 1). There was a trend for febuxostat 40 mg to be more efficacious in overproducers, but the number of subjects in each baseline uUA category in each treatment group was too low to determine significance.

The percentage change in sUA from baseline to Day 28 was similar between overproducers and underexcretors among all treatment groups; however, the mean percentage change was numerically greater for underexcretors in each treatment group and the difference between overproducers and underexcretors was greatest in the febuxostat 40 mg group (Figure 2).

Mean percentage change in uUA and Clcr from baseline to Day 28 is provided in Table 2. Treatment with any dose of febuxostat led to significantly greater percentage reductions in uUA than that observed in the placebo group, for both underexcretors and overproducers ($p \leq 0.002$). There was no significant influence on Clcr ($p = 0.422$), regardless of treatment group or baseline uUA status.

The most frequently reported AE were diarrhea and pain, reported by 17 (11%) and 15 (10%) of all subjects (N = 153), respectively. Rates of AE were generally similar across treatment groups (Table 3).

DISCUSSION

This is the first study to assess the efficacy of febuxostat specifically in uric acid overproducers and underexcretors. In the United States, febuxostat is approved for use as ULT in gout patients at 40 mg and 80 mg daily doses[14]. Initial examination of Figure 1 suggests comparable efficacy of febuxostat in both overproducers and underexcretors at the 80 mg dose, and perhaps more so in overproducers at 40 mg, based on the proportion of subjects achieving final sUA < 6.0 mg/dl. Efficacy in overproducers and underexcretors appears similar at the 120 mg dose; this dose is not approved for use in the United States[14]. However, when efficacy is assessed by change in sUA from baseline, underexcretors appear to experience a numerically greater benefit at 40 or 80 mg than do overproducers (Figure 2). The numbers of subjects in each uUA category are small, limiting the interpretation of these data. Together, the data presented in the 2 figures suggest that febuxostat is comparably efficacious in both overproducers and underexcretors at 40 mg and 80 mg.

Increases in sUA due to overproduction can arise because of an underlying condition, inherited metabolic error, or excessive consumption of purine-rich animal protein, fructose, or alcohol[4]. The majority of patients with endogenous overproduction of urate are hyperuricemic because of salvaged purines that arise from increased cell turnover in proliferative and inflammatory disorders (e.g., hematologic cancer or psoriasis), from pharmacologic intervention resulting in increased urate production (e.g., chemotherapy), or from tissue hypoxia[4]. Only a small portion of urate overproducers (~ 10%) have well characterized inborn errors of metabolism, such as 5′-phosphoribosyl-1-pyrophosphate synthetase superactivity or hypoxanthine-guanine phosphoribosyl transferase deficiency[4]. For such patients with overproduction of uric acid, inhibition of XO-mediated uric acid production is an attractive therapeutic option.

However, most patients with gout and hyperuricemia are not overproducers but underexcretors. Perez-Ruiz, *et al*[24] examined the change in renal handling among 25 gout subjects considered overproducers (uUA > 700 mg/day) by comparing various measures of urate renal handling before and after ULT with allopurinol. Their results suggest that even among overproducers, renal urate excretion is lower than in normouricemic adults[24].

Roughly two-thirds of urate excretion occurs by the kidney, while the remainder is excreted by the gastrointestinal tract[25]. In normouricemic adults, the fractional excretion of urate by the kidney is < 10%[26]. Recent identification and characterization of urate transport proteins in the proximal tubule provide evidence for the complicated processes of urate reabsorption and excretion that ultimately determine the amount

Table 1. Baseline characteristics and demographics by treatment group and urinary uric acid status.

Variable	Underexcretors				Overproducers			
	Febuxostat				Febuxostat			
	40 mg, N = 29	80 mg, N = 29	120 mg, N = 30	Placebo, N = 30	40 mg, N = 8	80 mg, N = 9	120 mg, N = 7	Placebo, N = 8
Male, n (%)	25 (86)	27 (93)	25 (83)	24 (80)	8 (100)	9 (100)	7 (100)	8 (100)
Age, yrs, mean ± SD	54 ± 13.3	57 ± 11.7	56 ± 11.0	53 ± 11.5	46 ± 15.9	45 ± 11.4	56 ± 11.8	50 ± 17.0
Body mass index (kg/m^2), n	29	29	29	30	8	9	7	8
Mean ± SD	32 ± 4.7	33 ± 6.5	30 ± 5.0	32 ± 5.0	30 ± 3.7	35 ± 7.3	36 ± 8.0	31 ± 4.4
Tophi present, n (%)	5 (17)	7 (24)	10 (33)	9 (30)	1 (13)	1 (11)	0	0
Nephrolithiasis present, n (%)	2 (7)	4 (14)	1 (3)	3 (10)	0	3 (33)	0	0
Serum urate (mg/dl), n	27	27	28	28	7	8	6	7
Mean ± SD	9.3 ± 0.95	10.0 ± 1.31	9.5 ± 1.09	9.9 ± 1.42	8.9 ± 0.88	9.8 ± 1.49	10.1 ± 1.13	9.7 ± 0.94
Urine uric acid (mg/day), n	26	27	28	27	7	8	6	7
Mean ± SD	494 ± 162.5	523 ± 155.1	473 ± 180.3	507 ± 139.0	982 ± 178.0	1065 ± 336.9	1006 ± 206.5	934 ± 135.5
Creatinine clearance (ml/min), n	29	28	29	29	8	9	6	8
Mean ± SD	70 ± 15.4	72 ± 18.6	64 ± 18.1	69 ± 21.5	99 ± 31.3	112 ± 37.7	108 ± 39.4	97 ± 8.8
Comorbidities, n (%)								
Cardiovascular disease	6 (21)	6 (21)	6 (20)	9 (30)	1 (13)	0	3 (43)	2 (25)
Congestive heart failure	0	4 (14)	0	0	0	0	0	1 (13)
Diabetes	5 (17)	7 (24)	3 (10)	2 (7)	1 (13)	1 (11)	1 (14)	0
Hypercholesterolemia	4 (14)	6 (21)	5 (17)	2 (7)	2 (25)	1 (11)	2 (29)	1 (13)
Hyperlipidemia	12 (41)	15 (52)	13 (43)	13 (43)	4 (50)	3 (33)	5 (71)	4 (50)
Hypertension	13 (45)	16 (55)	16 (53)	17 (57)	2 (25)	2 (22)	3 (43)	3 (38)
Obesity	4 (14)	12 (41)	6 (20)	8 (27)	1 (13)	4 (44)	4 (57)	2 (25)

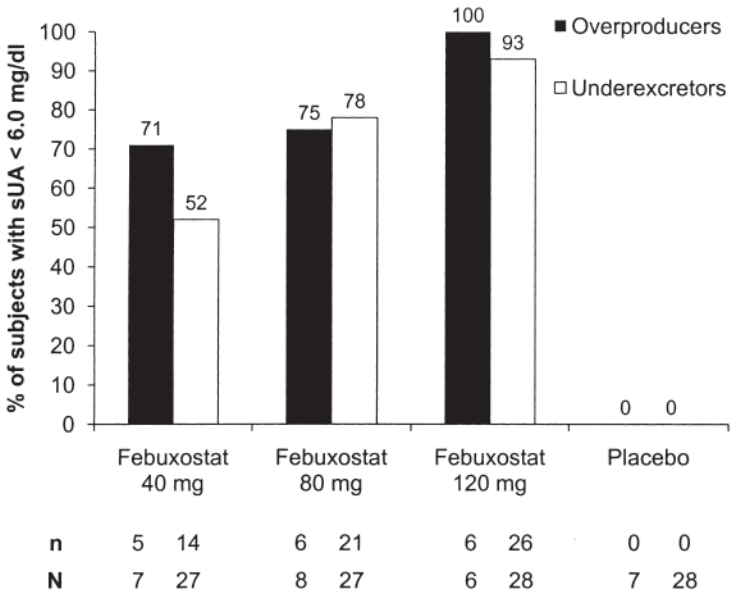

Figure 1. Treatment with any dose of febuxostat led to the majority of subjects achieving sUA < 6.0 mg/dl at Day 28 in both overproducers and underexcretors.

of urate excreted by the kidneys[27]. Deficient renal urate excretion could occur because of decreased glomerular filtration, increased urate reabsorption in the proximal tubule, or decreased tubular urate secretion. Although all these mechanisms may contribute to decreased renal clearance of urate, decreased tubular secretion may be the most prominent and widely prevalent disorder accounting for most cases of gout and hyperuricemia. Despite the frequency of this abnormality in renal handling of urate, inhibition of XO activity is considered the treatment of choice regardless of a patient's underlying mechanism of hyperuricemia[8]. As the goal of gout therapy is to lower sUA and thereby promote crystal dissolution and prevent crystal formation, success is not determined by whether pathophysiologic mechanisms specific to a patient are attacked. Current guidelines regarding gout management therefore do not recommend distinguishing underexcretors

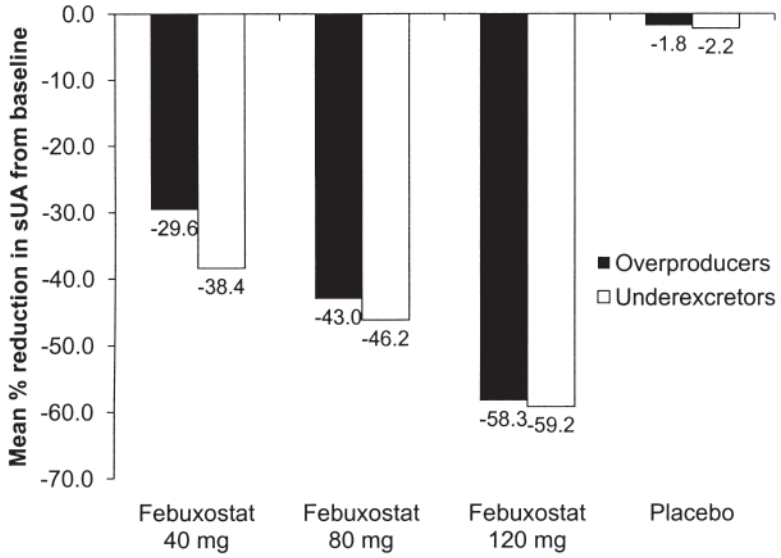

Figure 2. The percentage change in sUA from baseline to Day 28 was similar between overproducers and underexcretors among all treatment groups; the mean percentage change was numerically greater for underexcretors in each treatment group and the difference between overproducers and underexcretors was greatest in the febuxostat 40 mg group.

Table 2. Mean percentage reduction in urinary uric acid and creatinine clearance from baseline.

	Febuxostat 40 mg		Febuxostat 80 mg		Febuxostat 120 mg		Placebo	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Urinary uric acid, mg/day								
Underexcretors	26	–39 ± 30.5	27	–43 ± 28.9	28	–42 ± 29.4	27	12 ± 36.6
Overproducers	7	–61 ± 11.5	8	–60 ± 12.5	6	–62 ± 30.8	7	–16 ± 32.6
Creatinine clearance, ml/min								
Underexcretors	28	2 ± 18.9	25	1 ± 13.4	23	9 ± 19.0	25	6 ± 16.7
Overproducers	8	–11 ± 18.3	9	–18 ± 52.1	5	–9 ± 19.6	7	–10 ± 29.7

from overproducers. Whether there is any difference in the relative efficacy of febuxostat and allopurinol in overproducers or underexcretors is not established by our study.

Comparisons of the uricosuric agents probenecid and sulfinpyrazone are scanty and inadequate, but the European League Against Rheumatism guidelines rate them as "probably inferior to allopurinol in lowering sUA"[8]. Both are less effective in the presence of chronic kidney disease and unlike XO inhibitors, relatively contraindicated in a patient with low urine pH or a history of nephrolithiasis.

Although allopurinol demonstrates equal efficacy in both types of hyperuricemia in gout patients[12], it is recommended that allopurinol dosing be adjusted in gout patients with renal impairment[8,28]. Although the direction of the causal relationships is a topic of current investigation, a reduction in glomerular filtration rate is often one contributor to underexcretion of uric acid. At both approved doses (40 mg and 80 mg), febuxostat is equally or more efficacious than allopurinol among gout subjects with mild (Stage 2, eClcr 60–89 ml/min) or moderate (Stage 3, eCLcr 30–59 ml/min) renal impairment[18]. Dose adjustment of febuxostat for patients with mild or moderate renal impairment is not needed[14]. The efficacy and safety of febuxostat in gout subjects with severe (eCLcr < 30 ml/min) renal impairment has not yet been evaluated.

These initial results demonstrate that treatment with febuxostat does not require measurement of baseline uUA excretion, as the proportions of subjects who are either overproducers or underexcretors achieving sUA < 6.0 mg/dl after 4 weeks of treatment are comparable to those reported in the longer Phase 3 trials[16,17,18]. Additional analyses of febuxostat efficacy in larger numbers of overproducers and underexcretors are needed to verify the results reported here. In those responsive to ULT, longterm use has been shown to improve the clinical outcomes of gout by reducing acute flares and reducing tophi[29,30]. Thus, treatment with febuxostat provides an effective, well tolerated therapeutic option for the longterm management of gout, regardless of a patient's uUA.

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Table 3. Most frequent adverse events (reported by ≥ 2 subjects in any treatment group).

	Febuxostat			
	40 mg, N = 37	80 mg, N = 40	120 mg, N = 38	Placebo, N = 38
Total subjects with ≥ 1 adverse event, n (%)	20 (54)	23 (58)	19 (50)	19 (50)
Adverse event*, n (%)				
Diarrhea	1 (3)	8 (20)	4 (11)	4 (11)
Pain	6 (16)	3 (8)	2 (5)	4 (11)
Back pain	3 (8)	2 (5)	3 (8)	1 (3)
Headache	3 (8)	2 (5)	2 (5)	1 (3)
Abdominal pain	1 (3)	1 (3)	2 (5)	3 (8)
Myalgia	1 (3)	1 (3)	2 (5)	2 (5)
Liver function tests abnormal	2 (5)	1 (3)	1 (3)	1 (3)
Arthralgia	2 (5)	1 (3)	2 (5)	0 (0)
Flu syndrome	1 (3)	0 (0)	1 (3)	2 (5)
Rash	0 (0)	1 (3)	3 (8)	0 (0)
Infection	1 (3)	0 (00	1 (3)	2 (5)
Pharyngitis	0 (0)	1 (3)	0 (0)	2 (5)
Dyspepsia	1 (3)	2 (5)	0 (0)	0 (0)
Accidental injury	0 (0)	2 (5)	1 (3)	0 (0)
Increased appetite	2 (5)	0 (0)	0 (0)	0 (0)

* Adverse events reported with Coding Symbols for a Thesaurus of Adverse Reaction Terms.

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