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ORIGINAL ARTICLE

Women With Gout: Efficacy and Safety of Urate-Lowering With Febuxostat and Allopurinol

SAIMA CHOHAN,[1] MICHAEL A. BECKER,[1] PATRICIA A. MacDONALD,[2] SOLOMON CHEFO,[2] AND ROBERT L. JACKSON[2]

Objective. **To compare the characteristics of female versus male gout patients and assess urate-lowering efficacy and safety of febuxostat or allopurinol treatment in women with gout.**

Methods. **This was a retrospective analysis of 4,101 hyperuricemic (serum urate [sUA] level ≥8.0 mg/dl) gout subjects enrolled in 3 phase III comparative trials and randomized to receive placebo, febuxostat (40 mg, 80 mg, 120 mg, or 240 mg daily), or allopurinol (100 mg, 200 mg, or 300 mg daily, based on renal function). Baseline demographics and characteristics were summarized and compared between female and male subjects. Urate-lowering efficacy, which was defined as the proportion of subjects with sUA levels <6.0 mg/dl at final visit, was assessed for all subjects and, among women, according to baseline renal function.**

Results. **Female gout subjects (n = 226) were older with significantly higher rates of obesity and metabolic and cardiovascular comorbidities than their male counterparts. The percentage of female subjects with sUA levels <6.0 mg/dl at final visit was 0% in the placebo group, 54.3%, 85.1%, 81.0%, and 100.0% in the febuxostat 40 mg, 80 mg, 120 mg, and 240 mg groups, respectively, and 45.9% in the allopurinol group. Similar patterns of urate-lowering efficacy rates were observed when stratified by renal function. Among all the female subjects, febuxostat 80 mg was significantly more efficacious than allopurinol ($P < 0.001$). Rates of adverse events (AEs) were low. The most frequently reported AEs were upper respiratory tract infections, musculoskeletal/connective tissue disorders, and diarrhea.**

Conclusion. **These data suggest that febuxostat 80 mg may be more efficacious than commonly prescribed doses of allopurinol in female gout subjects with high rates of comorbidities.**

INTRODUCTION

Both the incidence and prevalence of gout have increased over the past few decades, with especially dramatic increases observed in the elderly population in both men and women (1–3). Increasing recognition of gout among women parallels increases in obesity in women, type 2 diabetes mellitus, chronic kidney disease, hypertension, and diuretic use (4), each of which is a morbidity independently associated with hyperuricemia and gout (5).

Febuxostat is a selective, nonpurine analog xanthine oxidase inhibitor (6) approved for the treatment of the hyperuricemia of patients with gout (7). Data from 3 randomized controlled trials (RCTs) comparing treatment of gout patients with febuxostat and allopurinol (8–10) or placebo (9) have demonstrated the superior urate-lowering efficacy of febuxostat at 80 mg daily compared with commonly prescribed doses of allopurinol (≤300 mg daily) (11) or with placebo. Few published reports specifically address the efficacy and safety of urate-lowering therapy in women with gout. For this reason, we carried out post hoc analyses of data from these trials with the aims of comparing the baseline characteristics of female versus male gout patients and assessing the relative urate-lowering efficacy and safety data of febuxostat and allopurinol treatment in women with gout.

PATIENTS AND METHODS

Patient selection and design. Patients of either sex, ages 18–85 years, with a diagnosis of gout according to the

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[1]Saima Chohan, MD, Michael A. Becker, MD: University of Chicago Pritzker School of Medicine, Chicago, Illinois; [2]Patricia A. MacDonald, RN, NP, Solomon Chefo, PhD, Robert L. Jackson, MD, MBA: Takeda Global Research & Development Center, Inc., Deerfield, Illinois.

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Address correspondence to Saima Chohan, MD, 5841 South Maryland Avenue MC 0930, University of Chicago Medical Center, Chicago, IL 60637. E-mail: schohan@medicine.bsd.uchicago.edu.

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Significance & Innovations

- This study confirms that female gout subjects are older and have significantly higher rates of cardiovascular, metabolic, and renal comorbidities than their male counterparts.
- Treatment of hyperuricemia in female gout subjects, even those with mild or moderate renal failure, may be more effectively managed with febuxostat 80 mg daily than with commonly prescribed doses of allopurinol or with febuxostat 40 mg daily.

American College of Rheumatology preliminary criteria (12), and a baseline serum urate (sUA) level of ≥8.0 mg/dl were eligible for enrollment in the 3 trials. In the Febuxostat Versus Allopurinol Controlled Trial (FACT) (8), subjects with a serum creatinine (sCr) level ≤1.5 mg/dl or an estimated creatinine clearance rate (eCLcr) ≥50 ml/minute determined by the Cockroft-Gault formula (13) were included, while in the Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat (APEX) trial (9), subjects with sCr levels ≤2.0 mg/dl were included. Subjects with normal renal function (eCLcr ≥90 ml/minute) or mild or moderate renal impairment (eCLcr of 60 to <90 ml/minute or 30 to <60 ml/minute, respectively), as determined by the Cockroft-Gault formula corrected for ideal body weight (13,14), were included in a phase III, randomized, multicenter, double-blind, allopurinol-controlled study assessing the efficacy and safety of oral febuxostat in gout patients (CONFIRMS) (10). Exclusion criteria included secondary hyperuricemia, hypersensitivity to allopurinol, naproxen, or colchicine, or severe renal impairment. As a consequence of differences in assessing renal function during patient selection among the 3 trials, 10 women initially categorized as having moderate renal impairment by sCr level at enrollment were reclassified as severely impaired (eCLcr 15 to <30 ml/minute) when eClcr was corrected for ideal body weight. Salient features of the study designs for the FACT, APEX, and CONFIRMS trials have been described in detail elsewhere (8–10) and are shown in Table 1.

Data analyses. An analysis of variance model was used to determine the statistical significance of differences in the baseline mean age, body mass index (BMI), and sUA level between women and men. Fisher's exact test was used for all other baseline variables. Urate-lowering efficacy was assessed by the proportion of women in each treatment group achieving an sUA level <6.0 mg/dl at the final study visit. Efficacy was further stratified by baseline renal function. Data from all subjects receiving allopurinol, regardless of dose, were pooled for the urate-lowering efficacy analyses. Fisher's exact test was used for the pairwise comparison between treatment groups. Adverse events (AEs) and serious AEs (SAEs) are reported for all febuxostat doses combined and all allopurinol doses combined.

RESULTS

Of the 4,101 subjects enrolled in the 3 trials, 226 (5.5%) were women. Eleven female subjects received placebo, 139

Table 1. Study designs of the FACT, APEX, and CONFIRMS studies*

Study	Female subjects, %	Study drugs (daily doses) and randomization	Washout†	Study duration	Prophylaxis	Primary efficacy variable
FACT (n = 760)	4	Febuxostat, 80 mg Febuxostat, 120 mg Allopurinol, 300 mg 1:1:1	2 weeks	52 weeks after randomization	Colchicine 0.6 mg daily or naproxen 250 mg twice daily for first 8 weeks of study	Proportion of subjects in each treatment group with last 3 monthly sUA levels <6.0 mg/dl
APEX (n = 1,072)	6	Febuxostat, 80 mg Febuxostat, 120 mg Febuxostat, 240 mg Allopurinol, 300/100 mg‡ Placebo 2:2:1:2:1	2 weeks	28 weeks after randomization	Colchicine 0.6 mg daily or naproxen 250 mg twice daily for first 8 weeks of study	Proportion of subjects in each treatment group with last 3 monthly sUA levels <6.0 mg/dl
CONFIRMS (n = 2,269)	6	Febuxostat, 40 mg Febuxostat, 80 mg Allopurinol, 300/200 mg§ 1:1:1	30 days	24 weeks after randomization	Colchicine 0.6 mg daily or naproxen 250 mg twice daily for study duration	Proportion of subjects in each treatment group with sUA level <6.0 mg/dl at final visit

* FACT = Febuxostat Versus Allopurinol Controlled Trial; APEX = Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat; CONFIRMS = a phase III, randomized, multicenter, double-blind, allopurinol-controlled study assessing the efficacy and safety of oral febuxostat in subjects with gout; sUA = serum urate.
† Washout period only for subjects who were receiving urate-lowering therapy at enrollment.
‡ In APEX, patients who were randomized to receive allopurinol and had a serum creatinine level >1.5 mg/dl received a dose of 100 mg once a day.
§ In CONFIRMS, patients who were randomized to receive allopurinol and had an estimated creatinine clearance of 30 to <60 ml/minute (moderate renal impairment) received a dose of 200 mg once a day.

Table 2. Baseline demographics, gout history characteristics, and medical histories of all subjects in the phase III trials, by sex*

	Female subjects (n = 226)	Male subjects (n = 3,875)	*P*
Race			< 0.001
Asian	7 (3.1)	132 (3.4)	
African American/black	42 (18.6)	368 (9.5)	
White	169 (74.8)	3,116 (80.4)	
American Indian/Native Alaskan	1 (0.4)	21 (0.5)	
Pacific Islander	1 (0.4)	31 (0.8)	
Other	6 (2.7)	205 (5.3)	
Missing	0	2 (0.1)	
Age, mean ± SD years	61.9 ± 11.29	51.8 ± 11.73	< 0.001
BMI, mean ± SD kg/m^2	35.8 ± 8.08	32.6 ± 6.05	< 0.001
Alcohol use	85 (37.6)	2,675 (69.0)	< 0.001
Serum creatinine level			0.646
≤1.5 mg/dl	215 (95.1)	3,711 (95.8)	
>1.5 mg/dl	11 (4.9)	164 (4.2)	
Estimated creatinine clearance†			< 0.001
<30 ml/minute	10 (4.4)	4 (0.1)	
30 to <60 ml/minute	135 (59.7)	501 (12.9)	
60 to <90 ml/minute	68 (30.1)	1,685 (43.5)	
≥90 ml/minute	13 (5.8)	1,685 (43.5)	
Baseline sUA, mean ± SD mg/dl	9.7 ± 1.27	9.7 ± 1.22	0.982
Presence of tophi	43 (19.0)	817 (21.1)	0.460
Years since last gout flare			0.957
>10	2 (0.9)	32 (0.8)	
6–10	3 (1.3)	62 (1.6)	
1–5	26 (11.5)	484 (12.5)	
<1	195 (86.3)	3,269 (85.1)	
Missing	0	1 (<0.01)	
Years with gout, mean ± SD	7.9 ± 9.03	11.7 ± 9.23	< 0.001
Medical history			
Diabetes mellitus	58 (25.7)	397 (10.2)	< 0.001
Hyperlipidemia	105 (46.5)	1,441 (37.2)	0.005
Hypertension	184 (81.4)	1,846 (47.6)	< 0.001
Obesity (BMI ≥30 kg/m^2)	166 (73.5)	2,410 (62.2)	< 0.001

* Values are the number (percentage) unless indicated otherwise. BMI = body mass index; sUA = serum urate.
† Estimated creatinine clearance calculated by the Cockcroft-Gault formula corrected for ideal body weight.

received febuxostat (any dose), and 76 received allopurinol (any dose). Sixty (26.5%) female subjects discontinued prematurely. The most common reasons for study withdrawal were AEs (25 of 226, 11.1%), personal reasons (10 of 226, 4.4%), and lost to followup (7 of 226, 3.1%).

Table 2 compares, by sex, the baseline demographic, gout disease history, and comorbid characteristics of all subjects participating in the 3 RCTs. Compared with men enrolled in these studies, women were older (mean age 62 versus 52 years), heavier (mean BMI 36 kg/m^2 versus 33 kg/m^2), and less likely to consume alcohol (37.6% versus 69.0%). Despite the difference in mean age by sex, mean gout duration was greater in male than female subjects (12 years versus 8 years). Comorbidities were common in subjects of both sexes, but were more frequently represented among women than men, i.e., hypertension (81.4% versus 47.6%), diabetes mellitus (25.7% versus 10.2%), hyperlipidemia (46.5% versus 37.2%), obesity (BMI ≥30 kg/m^2; 73.5% versus 62.2%), and renal impairment (94.2% versus 56.5%).

Four female subjects who received a study drug (1 each in the febuxostat 80 mg and 240 mg groups, and 2 in the allopurinol group) had baseline sUA levels <8.0 mg/dl and were not included in the efficacy analyses. Therefore, the total number of female subjects included in the urate-lowering efficacy analyses was 222. The proportion of female subjects achieving an sUA level <6.0 mg/dl at final visit was greater in each febuxostat treatment group than in the allopurinol treatment group (Figure 1). Urate-lowering efficacy with febuxostat 80 mg or 120 mg was significantly greater than with allopurinol ($P < 0.001$ and $P = 0.006$, respectively). All demographic and baseline characteristics, with the exception of age, were similar between febuxostat 80 mg and allopurinol. The difference in mean age between women in the febuxostat and allopurinol treatment groups was statistically significant ($P = 0.013$).

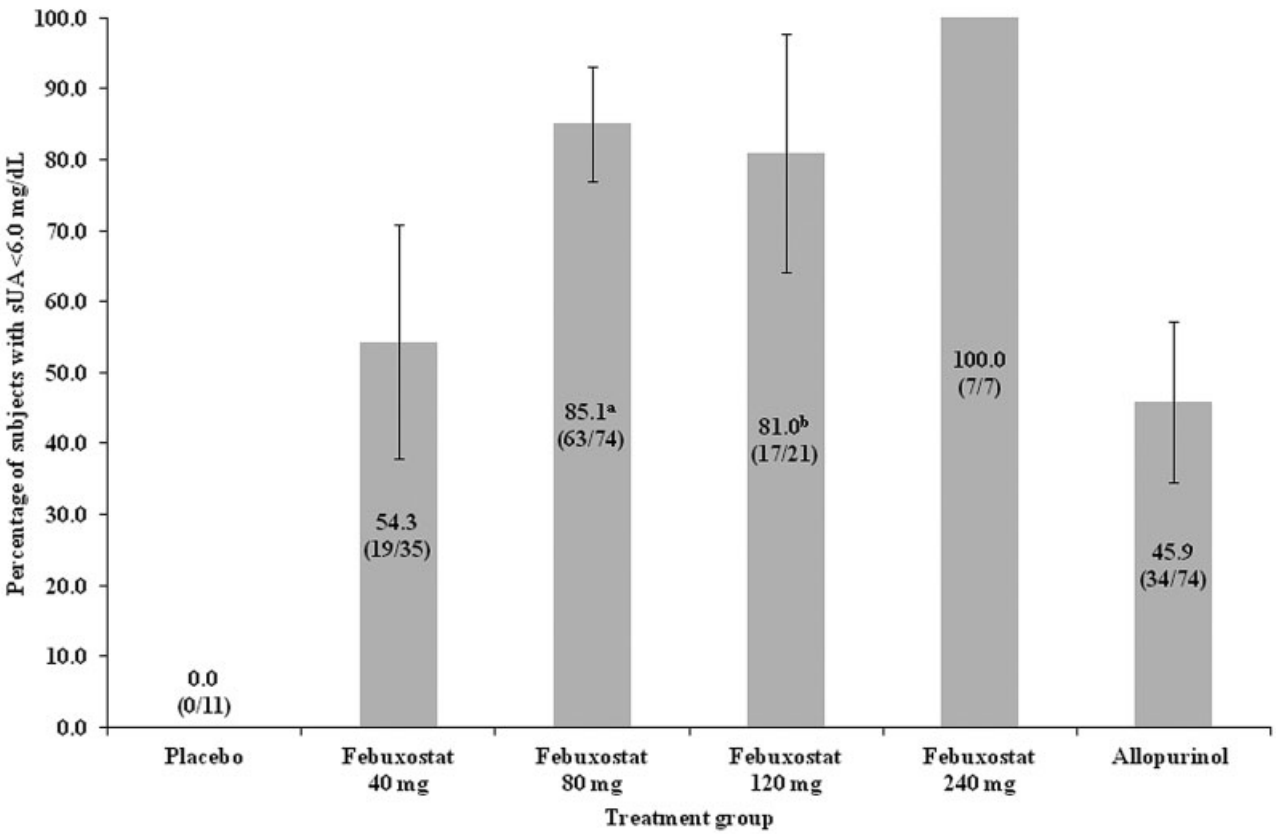

Figure 1. The proportion of female subjects achieving serum urate (sUA) levels <6.0 mg/dl at final visit. Fisher's exact test was used for comparison between febuxostat 80 mg versus allopurinol and febuxostat 120 mg versus allopurinol. Error bars represent 95% confidence intervals. [a] = for comparison with allopurinol, $P < 0.001$; [b] = for comparison with allopurinol, $P = 0.006$.

A sensitivity analysis adjusting for age was performed using logistic regression and the result after adjusting for age still supported the superiority of febuxostat 80 mg to allopurinol. Due to the small number of subjects in the febuxostat 240 mg group, no statistical test was performed to compare the efficacy rate with allopurinol. Within the allopurinol group, 2 women received 100 mg daily, 32 received 200 mg daily, and the remaining 40 women received 300 mg daily. Efficacy rates among the 3 different doses of allopurinol were 0%, 38%, and 55%, respectively. Achievement of sUA level <6.0 mg/dl at final visit stratified by baseline renal function is shown in Table 3. Small numbers of subjects in the resulting study groups preclude statistical confirmation, but febuxostat 80 mg, 120 mg, and 240 mg daily appear to have greater urate-lowering efficacy than allopurinol at the doses tested in female subjects with mild or moderate renal impairment. A similar trend appears to hold for febuxostat 40 mg daily in female subjects with mild renal impairment, but not in subjects with moderate/severe renal impairment.

All AEs reported among women are listed in Table 4. The most frequently reported AEs among female subjects were upper respiratory tract infections (15.5%), musculoskeletal/connective tissue disorders (11.1%), and diarrhea (10.6%). Abnormal or elevated liver function analyses were reported for 0, 4, and 5 female subjects in the placebo, fe-

Table 3. Achievement of sUA level <6.0 mg/dl in female subjects at final visit, by baseline renal function*

Baseline renal function (eCLcr)	Placebo	Febuxostat 40 mg	Febuxostat 80 mg	Febuxostat 120 mg	Febuxostat 240 mg	Allopurinol†
Normal (≥90 ml/minute)	0/1 (0)	1/2 (50.0)	7/7 (100.0)	1/1 (100.0)	–	1/2 (50.0)
Mild impairment (≥60 to <90 ml/minute)	0/5 (0)	8/10 (80.0)	21/25 (84.0)	4/5 (80.0)	3/3 (100.0)	9/18 (50.0)
Moderate or severe impairment (<60 ml/minute)‡	0/5 (0)	10/23 (43.5)	35/42 (83.3)	12/15 (80.0)	4/4 (100.0)	24/54 (44.4)

* Values are the number/total number (percentage). sUA = serum urate; eCLcr = estimated creatinine clearance rate.
† Two subjects with eCLcr <60 ml/minute received allopurinol 100 mg and 32 received allopurinol 200 mg, while the remaining subjects, regardless of eCLcr, received allopurinol 300 mg.
‡ Due to differences in assessment of renal function during patient selection in the 3 trials, 10 subjects initially categorized as having moderate renal impairment were reclassified as severely impaired when eCLcr was determined by ideal body weight.

Table 4. Most frequently reported AEs among female subjects*

	Placebo (n = 11)	All febuxostat doses (n = 139)	Allopurinol (n = 76)
Total subjects with ≥1 AE	8 (72.7)	100 (71.9)	56 (73.7)
Most frequently reported AEs†			
Upper respiratory tract infections	1 (9.1)	24 (17.3)	10 (13.2)
Musculoskeletal and connective tissue signs and symptoms	2 (18.2)	18 (12.9)	5 (6.6)
Diarrhea	1 (9.1)	18 (12.9)	5 (6.6)
Lower respiratory tract and lung infections	0	3 (2.2)	6 (7.9)
Urinary tract infections	1 (9.1)	11 (7.9)	7 (9.2)
Headaches	0	10 (7.2)	4 (5.3)
Joint-related signs and symptoms	0	13 (9.4)	1 (1.3)
Nausea and vomiting	1 (9.1)	9 (6.5)	5 (6.6)
Gastrointestinal and abdominal pains	0	8 (5.8)	2 (2.6)
Neurologic signs and symptoms	1 (9.1)	6 (4.3)	3 (3.9)
Osteoarthropathies	0	4 (2.9)	5 (6.6)
Edema	0	9 (6.5)	5 (6.6)
Liver function analyses	0	4 (2.9)	5 (6.6)

* Values are the number (percentage). Adverse events (AEs) classified by Medical Dictionary Regulatory Activities High Level Term.
† Most frequent AEs occurred in ≥5 subjects in either placebo, all febuxostat doses combined, or allopurinol groups.

buxostat, and allopurinol groups, respectively. The majority of AEs were transient and resolved during treatment.

At least 1 SAE was reported by 0%, 6.5%, and 9.2% of female subjects in the placebo, febuxostat, and allopurinol groups, respectively. The most common SAEs were cardiac disorders, i.e., febuxostat (2.2%) and allopurinol (3.9%). Reported cardiac SAEs, each reported by 1 subject, were cardiovascular disorder, hypertensive heart disease, coronary artery arteriosclerosis, congestive heart failure, bradycardia, and supraventricular tachycardia. Cardiac SAEs did not appear to be dose or time related. There were no abnormal or elevated liver function tests or rashes that were considered SAEs. One female subject in the febuxostat 80 mg group died; she was a morbidly obese (BMI 47 kg/m^2) participant in the CONFIRMS trial and died of hypertensive cardiovascular disease.

DISCUSSION

These are the first prospective RCT–generated data specifically focused on urate-lowering efficacy and safety in women with gout. Pooled data from the 3 phase III febuxostat/allopurinol comparative trials suggest that urate lowering by febuxostat at a dosage of 80 mg daily was significantly greater than that of allopurinol (300/200/100 mg) in female gout subjects, including those with mild or moderate renal impairment. This is reflective of the known efficacy of febuxostat in the broader gout population (8–10). Additional prospective randomized trials with greater numbers of female gout subjects will be needed to confirm these results.

The rates of AEs in the female subpopulation of these studies were comparable to those reported in the overall febuxostat/allopurinol RCTs (8–10). Therefore, despite the considerably higher rates of cardiovascular, metabolic, and renal comorbidities among women with gout, urate-lowering therapy with febuxostat and allopurinol appears generally safe.

In the febuxostat combined phase III studies, the cohort of female gout patients were a decade older than the enrolled men and were more often obese, with significantly higher rates of hypertension, renal impairment, hyperlipidemia, and diabetes mellitus. While the women participating in this analysis were selected by virtue of fulfilling inclusion criteria of the respective trials, it seems likely that they are generally representative of women with gout in that they have similar baseline demographic, disease (gout), and comorbidity characteristics as those described in other studies of women with gout (15–17).

The major limitations of this study are its post hoc nature and the small number of female subjects. The doses of allopurinol used in these trials are the most commonly prescribed doses in American clinical practice (11,18) and therefore representative of real-world patterns. Efforts should be made to increase enrollment of women with gout in clinical trials in order to further examine optimal management strategies for this cohort with high rates of comorbidities.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Chohan had full access to all of the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.

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