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Achieving Serum Urate Goal: A Comparative Effectiveness Study Between Allopurinol and Febuxostat

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Abstract

Background: Febuxostat is recommended as 1 of 2 first-line urate-lowering therapies (ULT) for treating gout in the 2012 American College of Rheumatology Guidelines. Several efficacy trials have compared febuxostat with allopurinol treatment, but real-world comparative data are limited. **Methods:** We compared effectiveness of the 2 agents in reaching serum urate (sUA) level goal (< 6 mg/dL) within 6 months (main endpoint), factors impacting the likelihood of reaching goal, and outcomes in allopurinol patients who were switched to febuxostat therapy after failing to reach sUA level goal. Data from the General Electric Electronic Medical Record database on adult patients with newly diagnosed gout, who had started treatment with allopurinol or febuxostat in 2009 or thereafter were analyzed. Descriptive statistics, bivariate analyses, and logistic regressions were used. **Results:** Allopurinol (n = 17 199) and febuxostat (n = 1190) patients had a mean ± standard deviation (SD) age of 63.7 (± 13.37) years; most patients were men and white. Average daily medication doses (mg) in the first 6 months were 184.9 ± 96.7 and 48.4 ± 15.8 for allopurinol- and febuxostat-treated patients, respectively; 4.8% of allopurinol-treated patients switched to febuxostat, whereas 25.7% of febuxostat-treated patients switched to allopurinol. Febuxostat patients had lower estimated glomerular filtration rate levels, more diabetes mellitus, or tophi at baseline ($P < 0.05$) and 29.2% and 42.2% of patients in the allopurinol and febuxostat groups achieved goal sUA levels ($P < 0.0001$). Febuxostat was significantly more effective in patients reaching sUA goal (adjusted odds ratio, 1.73; 95% CI, 1.48–2.01). Older patients and women had greater likelihood of reaching sUA goal level; however, patients with higher Charlson Comorbidity Index scores, blacks, or those with estimated glomerular filtration rates between 15 to ≤ 60 mL/min had reduced likelihood of attaining goal ($P < 0.05$). Among allopurinol-treated patients who were switched to febuxostat after failing to reach goal, 244 (48.3%) reached goal on febuxostat (median = 62.5 days), with an average 39% sUA level reduction achieved within 6 months. Patients who did not reach goal had a 14.3% sUA level reduction. **Conclusions:** The real-life data support the effectiveness of febuxostat in managing patients with gout.

Keywords: urate-lowering therapy; febuxostat; allopurinol; comparative effectiveness

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Introduction

Gout is an arthritic condition characterized by increased levels of urate in the blood and a buildup of urate-containing crystals in the joints, often leading to severe patient pain and disability. A study based on the US National Health and Nutrition Examination Survey (NHANES) conducted in 2007–2008 found that 3.9% of the US population (or 8.3 million, including 6.1 million men and 2.2 million women) reported having been diagnosed with gout, with a 21.4% prevalence rate of hyperuricemia (defined as serum

urate [sUA] level of > 7.0 mg/dL in men and > 5.7 mg/dL in women).[1] Diet and lifestyle modifications are the first-line treatments for the majority of patients with gout,[2] although measures may not be sufficient to reduce sUA levels.[3]

Allopurinol and febuxostat represent the 2 first-line urate lowering therapy (ULT) agents for the management of patients with gout,[2] with the former remaining the most often prescribed medication to reduce sUA levels.[4] The recommended approach for determining the appropriate dose of allopurinol is to use a starting dose of 100 mg daily (50 mg/day in patients with ≥ stage 4 chronic kidney disease), with further 100-mg increments every 2 to 5 weeks until the target level of sUA is achieved.[2,5] Despite of its widespread use, long-term outcomes of allopurinol treatment in patients with advanced gout have not been well documented, and success with treatment remains modest. In a retrospective study, it was reported that little more than one-third of treated patients reached the therapeutic goal of sUA level < 6 mg/dL while on allopurinol.[6] In addition, low compliance with related quality-of-care indicators was reported, including monitoring for sUA levels post-allopurinol treatment and appropriate dosing in patients with renal insufficiency.[7]

Febuxostat is a novel nonpurine selective inhibitor of xanthine oxidase indicated for the chronic management of hyperuricemia in patients with gout.[8] In randomized controlled trials, the efficacy of febuxostat at 40 mg was reported comparable or superior to that of allopurinol 300 mg once daily, and 80 mg febuxostat was superior to allopurinol 300 mg.[9–11] In an open-label extension study, it was reported that > 80% of patients in the febuxostat group and 46% of patients in the allopurinol group achieved a goal sUA level < 6.0 mg/dL after 1 month of treatment,[12] with no significant difference between the treatment groups in the overall reported adverse event rates from any of the trials.[9–12] Febuxostat was also more effective than allopurinol in a subset of patients with impaired renal function, without the need for any dose adjustment in patients with mild-to-moderate renal impairment.[13]

Although several efficacy trials have compared febuxostat with allopurinol, real-world studies are needed to study the prescribing patterns of the 2 urate-lowering agents along with their related outcomes in patients with gout. The objectives of our retrospective cohort study were to: 1) identify the utilization patterns of ULT in ULT-naïve gout patients; 2) compare the effectiveness of febuxostat and allopurinol in reducing sUA levels—test the null hypothesis that there is no difference to be detected between allopurinol and febuxostat in achieving sUA goal level; 3) understand factors impacting the likelihood of reaching sUA goal; and 4) investigate outcomes of patients who switched to febuxostat after failing to reach sUA goal level on allopurinol therapy.

Materials and Methods

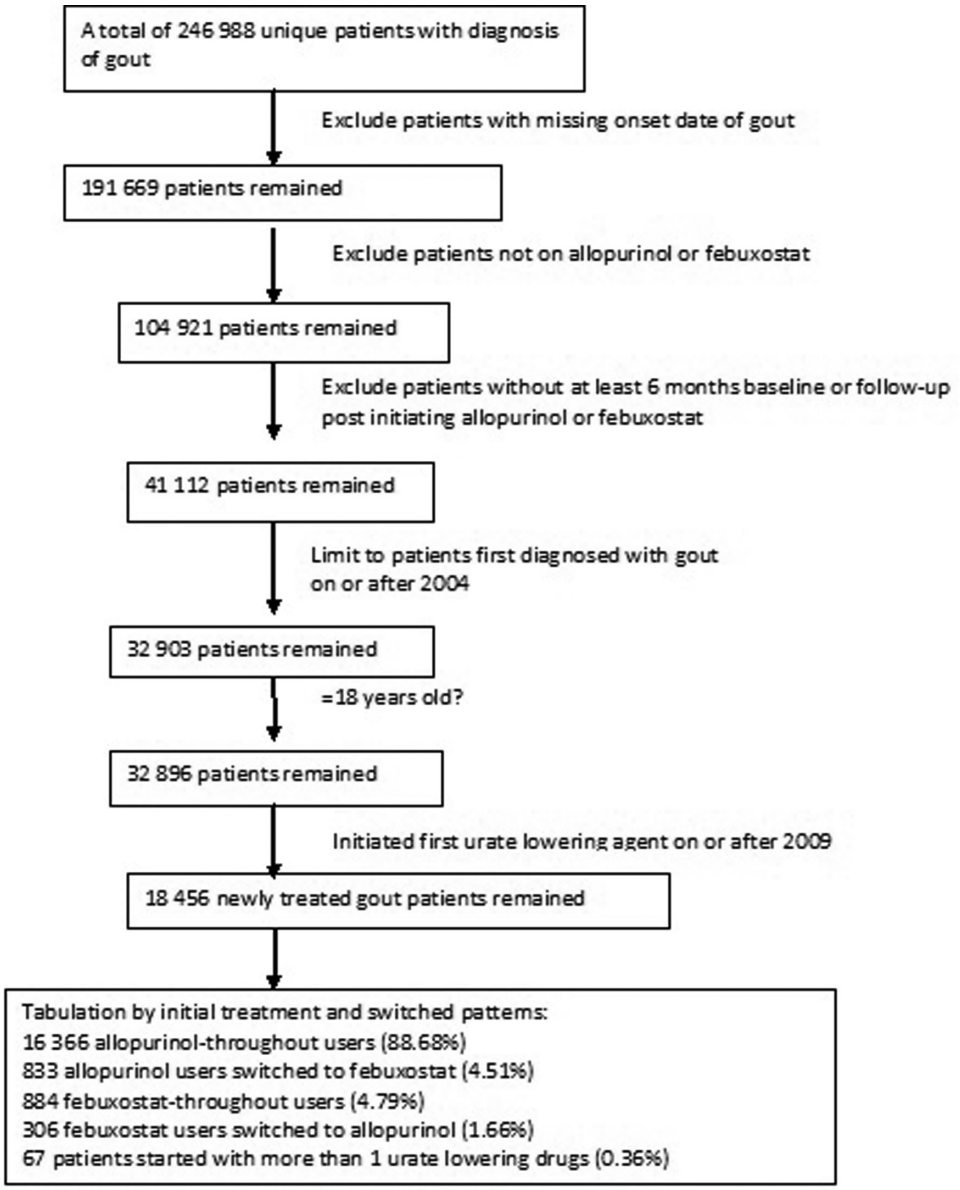
Data Source

General Electric Electronic Medical Record (GE EMR) database was used for our study. The GE EMR is a US ambulatory care-based EMR database, with health records collected on primary care patients. The database includes patient demographic information, vital signs, laboratory test results, and prescriptions. More than 1200 health care systems and 30 000 clinicians from mid-to-large size group practices in 49 US states have contributed to the database, which contains > 35 million patient records. The majority of the participating clinicians are primary care physicians, with 85% working as family physicians, or in internal medicine, obstetrics /gynecology, or pediatric specialties.[14]

Study Population

The study cohort included all adult patients (aged ≥ 18 years) who were newly diagnosed with gout (ICD-9, 274.xx) in the year 2005 or later and were newly treated with allopurinol or febuxostat on or after 2009 (the latter date chosen to coincide with market entry of febuxostat). Each patient's index date was defined as the date when allopurinol or febuxostat treatment was initiated. Eligible patients were those with continuous health plan enrollment for ≥ 6 months before and after the index date. Patients were assigned to the allopurinol or febuxostat group based on their first prescribed ULT, regardless of whether or not they eventually switched to the other. Collected baseline characteristics included patient age, gender, race, estimated glomerular filtration rate (eGFR), sUA, and body mass index (BMI). We used the following equation to compute eGFR: GFR (mL/min/1.73 m^2) = 175 × (serum creatinine level)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (1.212, if African American).[15] Patients were classified by their BMI values as underweight (BMI < 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), pre-obese (25.0–29.9 kg/m^2), or obese (≥ 30 kg/m^2). Comorbidities were quantified with the Charlson Comorbidity Index (CCI)[16,17] using ICD-9 codes captured within the 6-month baseline period. Time to initiating ULT after first diagnosis of gout was also investigated. Newly diagnosed patients with hypertension or diabetes after study index date were identified. Patients were followed until their last record in the database. Figure 1 depicts the patient selection results.

Figure 1. Patient selection process.



Primary Study Endpoint

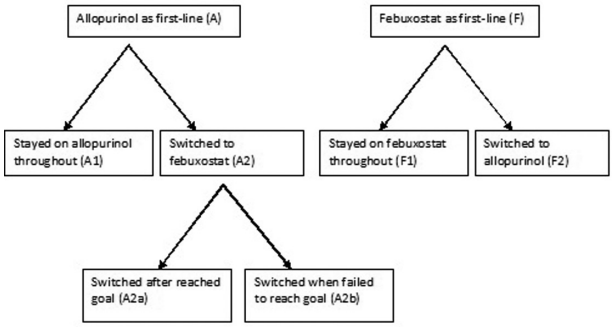
The primary study endpoint was met if a patient reached an sUA level $<$ 6 mg/dL within 6 months of his/her index date. Response rates at 2 years were also investigated. The impact of ULT on the likelihood of reaching goal was evaluated by comparing patients starting ULT with allopurinol versus febuxostat (Figure 2) as well as those who switched between allopurinol and febuxostat. Factors impacting the likelihood of reaching goal were examined by comparing patients who did or did not reach the goal within the allopurinol-treated group (study cohort A). A subgroup of patients who switched to febuxostat after failing to reach goal while on allopurinol was evaluated for outcomes after the switch.

Statistical Analyses

Descriptive statistics were produced for all study variables. Bivariate analyses were performed using X^2 tests for categorical variables, t tests for continuous variables with normal distribution, and non-parametric tests, such as Wilcoxon rank sum tests for continuous variables that did not meet normality assumption.

Logistic regressions were used to compare the likelihood of reaching sUA goal level for the allopurinol- and the febuxostat-treated groups, and to examine factors associated with the likelihood of reaching sUA goal level. Logistic regressions models accounting for several covariates such as age, sex, and CCI were performed. Additional logistic regressions

Figure 2. Study cohorts by ULT utilization patterns.



Abbreviation: ULT, urate-lowering therapy.

to investigate risk factors associated with failure to achieve sUA goal level were only possible in the allopurinol-treated patients because approximately 95% of patients initiated ULT with allopurinol. The overall level of statistical significance was set at $P < 0.05$.

Results

Treatment Patterns of ULT

A total of 18 456 patients met the inclusion criteria. There were 67 (0.4%) patients who were excluded from all analyses because they were started on both drugs on their index date. The study sample included 17 199 (93.2%) patients who were prescribed allopurinol initially and 1190 (6.4%) who were prescribed febuxostat initially. Mean (± SD) age was 63.7 ± 13.3 years; 69.4% of patients were men. Of patients with reported race (n = 10 768), 79.7% were white. Most patients (80.5%) were diagnosed with gout in 2009 or afterwards. At baseline, 71.3% were diagnosed with hypertension and 28.8% with diabetes mellitus (DM). Almost 1% had tophi diagnosis within 6 months prior to initiating ULT. Mean follow-up duration from the index date to last record was 541.5 ± 238 days (Table 1). For patients with baseline eGFR-related data, the proportions with eGFR < 15 mL/min, 15 to < 30 mL/min, 30 < 60 mL/min, 60 < 90 mL/min, or ≥ 90 mL/min were 0.6%, 8.1%, 44.3%, 38.0%, and 9.0%, respectively. Among the allopurinol group, 833 patients (4.8%) switched to febuxostat, whereas 306 of the 1190 febuxostat patients (25.7%) switched to allopurinol. The average dose in the first 6 months of treatment was 184.9 ± 96.7 mg/day (median, 100 mg/day) for allopurinol, and 48.4 ± 15.8 mg/day (median, 40 mg/day) for febuxostat.

Comparing Outcome by ULT

There were no significant differences between the allopurinol and febuxostat groups in age, CCI, sex, race, or rate of hypertension diagnosis. However, compared with patients in the febuxostat group, the allopurinol group had longer follow-up, and were slightly more obese or pre-obese (Table 1; $P < 0.05$). In contrast, patients in the febuxostat group was more likely to have low eGFR at baseline (8.0% vs 17.5% with eGFR < 30 mL/min for allopurinol and febuxostat groups, respectively), more patients had DM at baseline (33.3% vs 28.5%), and twice as many patients with tophi, also at baseline (1.7% vs 0.9%; $P < 0.05$ for all; Table 1).

Within the total study cohort, 10 871 (60.1%) patients had sUA level measurement performed before initiating ULT, including 10 119 patients in the allopurinol and 752 in the febuxostat groups. The proportions of patients who reached an sUA level of < 6 mg/dL within 6 months of initiating ULT were 29.2% and 42.2% in the allopurinol and febuxostat groups, respectively ($P < 0.0001$). At 2 years post initiation of ULT, 58.2% of the patients in the febuxostat group compared with 48.4% in the allopurinol group reached sUA goal level ($P < 0.0001$).

Logistic regressions were performed on the likelihood of reaching sUA goal within 6 months after initiating ULT, controlling for age, sex, CCI, race, year of gout diagnosis, and baseline tophi without (model 1) or with (model 2) the addition of sUA levels performed within the 6-month baseline before ULT (n = 7324 patients having the measure). Results of the 2 models were largely similar (Table 2). Older patients and women were more likely to reach sUA goal level, whereas patients with higher sUA at baseline were less likely to reach goal. In both models, patients treated with febuxostat were more likely to reach goal. The adjusted odds ratios (OR) were 1.73 (95% CI, 1.48–2.01) in model 1 and 1.86 (95% CI, 1.54–2.23) in model 2 ($P < 0.0001$).

Factors Associated With Reaching sUA Goal

Of 17 199 allopurinol-treated patients, 58.8% (10 119) had ≥ 1 sUA level after initiating allopurinol and were included in our analysis. Among the 10 119 patients, 2958 (29.2%) reached sUA goal level within 6 months of initiating treatment. Bivariate analyses performed on the latter group indicated that women, older patients, and those with lower sUA levels and BMI at baseline were more likely to reach goal ($P < 0.05$; Table 3). Neither race, year of diagnosis, low eGFR, or baseline tophi significantly impacted goal attainment. Logistic regressions with covariate adjustments showed that older patients and women were more likely to reach sUA goal, and that black patients and those with higher CCI and eGFRs of 15 to < 60 were less likely to reach goal ($P < 0.05$; Table 4, model 1). Patients with tophi at baseline were

Table 1. Baseline Characteristics of Study Cohort

Variable	Total N = 18 389	Allopurinol, First-line (n = 17 199)	Febuxostat, First-line (n = 1190)	*P* Value
Age, mean years (SD)	63.7 (13.3)	63.6 (13.3)	64.06 (13.1)	0.27
CCI, mean (SD)	0.4 (0.9)	0.4 (0.9)	0.4 (1.0)	0.25
Total follow-up duration, index date to last record, mean days (SD)	541.5 (237.9)	546.1 (239.5)	474.9 (201.9)	< 0.0001
Treatment lag, mean (SD) days[a]	186.3 (420.5)	181.5 (417.9)	255.5 (451.2)	< 0.0001
Gender, n (%)				
Women	5634 (30.6)	5244 (30.5)	390 (32.8)	0.10
Men	12 755 (69.4)	11 955 (69.5)	800 (67.2)	
Race/ethnicity, n (%)				0.18
Asian	194 (1.1)	181 (1.1)	13 (1.1)	
Black	1735 (9.4)	1636 (9.5)	99 (8.3)	
Hispanic	257 (1.4)	244 (1.4)	13 (1.1)	
Unknown	7621 (41.4)	7149 (41.6)	472 (39.7)	
White	8582 (46.7)	7989 (46.5)	593 (49.8)	
Gout diagnosis year, n (%)				
2005	339 (1.8)	314 (1.8)	25 (2.1)	< 0.0001
2006	518 (2.8)	471 (2.7)	47 (4.0)	
2007	920 (5.0)	854 (5.0)	66 (5.6)	
2008	1811 (9.9)	1690 (9.8)	121 (10.2)	
2009	5959 (32.4)	5663 (32.9)	296 (24.9)	
2010	6269 (34.1)	5833 (33.9)	436 (36.6)	
2011	2573 (14.0)	2374 (13.8)	199 (16.7)	
BMI group, n (%)[b]				
Underweight	48 (0.3)	41 (0.3)	7 (0.7)	0.01
Normal	1241 (8.5)	1146 (8.4)	95 (9.6)	
Pre-obese	3931 (26.9)	3699 (27.2)	232 (23.6)	
Obese	9384 (64.3)	8733 (64.1)	651 (66.1)	
Baseline eGFR, mL/min per 1.73 m^2, n (%)[c]				
< 15	77 (0.6)	66 (0.6)	11 (1.3)	< 0.0001
15 to < 30	993 (8.1)	854 (7.5)	139 (16.2)	
30 to < 60	5455 (44.3)	5053 (44.1)	402 (46.9)	
60 to < 90	4678 (38.0)	4437 (38.8)	241 (28.1)	
≥ 90	1103 (9.0)	1038 (9.1)	65 (7.6)	
Baseline sUA level group, n (%)[d]				
< 6 mg/dL	668 (6.4)	615 (6.3)	53 (7.2)	0.01
≥ 6 to < 7 mg/dL	824 (7.9)	770 (7.9)	54 (7.4)	
≥ 7 to < 8 mg/dL	1854 (17.7)	1732 (17.8)	122 (16.6)	
≥ 8 to < 9 mg/dL	2629 (25.1)	2477 (25.5)	152 (20.7)	
≥ 9 mg/dL	4487 (42.9)	4135 (42.5)	352 (48.0)	
Baseline tophi, n (%)	171 (0.9)	151 (0.9)	20 (1.7)	< 0.01
Ever diagnosed with hypertension, n (%)	13103 (71.3)	12252 (71.2)	851 (71.5)	0.84
Ever diagnosed with DM, n (%)	5300 (28.8)	4904 (28.5)	396 (33.3)	< 0.0005

[a]Time from first gout diagnosis to first prescription of ULT.
[b]3785 patients missing BMI information; WHO definition, underweight: BMI < 18.5; normal weight: 18.5–24.9; pre-obese: 25.0–29.9; obese: ≥ 30.
[c]6083 patients missing serum creatinine information required for computing eGFR.
[d]7927 patients missing the sUA information.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; eGFR, estimated glomerular filter rate; SD, standard deviation; sUA, serum uric acid; ULT, urea-lowering therapy; WHO, World Health Organization.

more likely to reach sUA goal level. When baseline sUA levels were accounted for, having higher CCI or tophi became non-significant (Table 4, model 2). Patients with higher sUA levels at baseline were also less likely to reach sUA goal level.

Outcome of Allopurinol Patients Who Switched to Febuxostat

Of the 17 199 allopurinol-treated patients, 833 (4.8%) switched to febuxostat, while 306 of the 1190 febuxostat patients (25.7%) switched to allopurinol. Proportions of

Table 2. Logistic Regression Comparing the Likelihood of Reaching sUA Goal Level Between Allopurinol- and Febuxostat-Treated Groups

Variable	Model 1: without baseline sUA, n = 10 871		Model 2: with baseline sUA, n = 7324	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	1.01(1.01; 1.02)	< 0.0001	1.01(1.01; 1.02)	< 0.0001
Female gender (male as reference)	1.45 (1.32; 1.58)	< 0.0001	1.43 (1.28; 1.59)	< 0.0001
CCI	0.93 (0.88; 0.98)	< 0.01	0.98 (0.91; 1.04)	0.45
Baseline sUA (< 7 mg/dL as reference group)				
≥ 7 to < 8 mg/dL	NA	NA	0.78 (0.65; 0.93)	< 0.01
≥ 8 to < 9 mg/dL	NA	NA	0.68 (0.57; 0.80)	< 0.0001
≥ 9 mg/dL	NA	NA	0.46 (0.39; 0.53)	< 0.0001
Race/ethnicity (white non-Hispanic as reference)				
Black	0.71 (0.60; 0.84)	< 0.0001	0.71 (0.58; 0.87)	< 0.001
Asian	0.66 (0.43; 1.01)	0.05	0.69 (0.42; 1.13)	0.14
Hispanic	1.08 (0.76; 1.54)	0.67	0.98 (0.63; 1.51)	0.91
Unknown Race	1.09 (1.00; 1.19)	0.05	1.08 (0.97; 1.20)	0.15
Febuxostat ULT (allopurinol as reference)	1.73 (1.48; 2.01)	< 0.0001	1.86 (1.54; 2.23)	< 0.0001
Gout diagnosis year (2005 as reference)				
2006	0.68 (0.47; 0.99)	0.04	0.70 (0.43; 1.12)	0.14
2007	0.83 (0.59; 1.16)	0.28	0.88 (0.57; 1.35)	0.55
2008	0.69 (0.51; 0.94)	0.02	0.74 (0.50; 1.10)	0.14
2009	0.82 (0.62; 1.10)	0.18	0.84 (0.58; 1.22)	0.37
2010 and after	1.03 (0.78; 1.37)	0.83	1.12 (0.78; 1.62)	0.54
Baseline tophi diagnosis	1.42 (0.98; 2.06)	0.07	1.36 (0.89; 2.09)	0.16

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; NA, not applicable; OR, odds ratio; sUA, serum uric acid; ULT, urea-lowering therapy.

patients who reached sUA goal level within 6 months were 28.9% for allopurinol throughout; 32.6% for febuxostat switched to allopurinol; 33.6% for allopurinol then switched to febuxostat; and 46.0% for febuxostat throughout groups (Figure 3).

Among the 833 allopurinol patients who switched to febuxostat and had ≥ 1 documented sUA value after treatment, 505 were switched after failing to reach the sUA goal level while on allopurinol, and the remaining 328 patients switched when sUA level were still under control. Within 6 months after switching, 186 patients (36.8% of 505 patients) reached sUA goal level. The percentage was significantly higher than for patients who were maintained on allopurinol throughout (28.9%), but significantly lower than for patients maintained on febuxostat throughout (46.0%; Figure 4).

When the 505 patients were followed to the end of EMR availability, 244 (48.3%) were found to reach sUA goal. There were no significant differences between those who reached or did not reach goal after switching in the distribution of sex, race, CCI, gout diagnosis year, BMI, baseline eGFR, sUA, or tophi diagnosis, except that patients who reached goal after switching were significantly older (Table 5). The median time for the 244 patients to reach goal was 62.5 days. For the 244 patients who reached goal, the average sUA level during the 6-month period after switching agents was 5.41 mg/dL, a 39% reduction from the mean value of 8.6 mg/dL at time of switch. The 261 patients who did not reach goal by the end of follow-up still had an average 14.3% sUA reduction in the 6 months after the switch.

Discussion

Results of our study using real-world practice data found proportions of patients achieving goal on febuxostat were significantly higher than those calculated for allopurinol-treated patients. In patients who were initiated with allopurinol but were unable to reach sUA goal level, almost half reached goal on febuxostat within a median time of 62.5 days, with a mean 39% reduction in sUA levels within 6 months. Evidence presented suggests that patients refractory to allopurinol could still benefit from febuxostat treatment.

Our findings showed that the effectiveness of febuxostat in real-world use (42.2% in 6 months and 58.2% in 2 years) is roughly comparable to its reported efficacy in randomized clinical trials. In a recent meta-analysis and systematic review of 10 randomized clinical trials, it was reported that a significantly greater proportion of patients on febuxostat achieved sUA goal level at the final visit compared with those on placebo or on allopurinol.[18] Moreover, the proportion of patients who achieved sUA goal at the final visit was significantly greater in the febuxostat-treated group (50.9% response rate, 40 mg/d) compared with the

Table 3. Bivariate Analyses: Allopurinol-Treated Patients Who Reached Compared With Patients Who Did Not Reach sUA Goal Levels Within 6 Months of Initiating Treatment

Variable	Did not reach sUA goal in 6 months (n = 7161)	Reached sUA goal in 6 months (n = 2958)	*P* Value
Age, mean years (SD)	63.3 (13.2)	66.1 (12.2)	< 0.0001
CCI, mean (SD)	0.3 (0.8)	0.3 (0.8)	0.16
Baseline sUA, mg/dL, mean (SD)	9.0 (1.9)	8.5 (1.8)	< 0.0001
Baseline BMI, mean (SD)	33.9 (7.5)	32.5 (7.3)	< 0.0001
Female gender, n (%)	2027 (28.3)	1148 (38.8)	< 0.0001
Gout diagnosis year, n (%)			< 0.0001
2005	147 (2.1)	68 (2.3)	
2006	226 (3.2)	69 (2.3)	
2007	387 (5.4)	135 (4.6)	
2008	788 (11.0)	244 (8.3)	
2009	2412 (33.7)	897 (30.3)	
2010 and 2011	3201 (44.7)	1545 (52.2)	
Race/Ethnicity, n (%)			< 0.0005
Asian	99 (1.4)	26 (0.9)	
Black	693 (9.7)	210 (7.1)	
Hispanic	103 (1.4)	44 (1.5)	
Unknown	2950 (41.2)	1296 (43.8)	
White	3316 (46.3)	1382 (46.7)	
BMI group, n (%)			< 0.0001
Underweight	16 (0.3)	6 (0.6)	
Normal	414 (7.1)	247 (10.1)	
Pre-obese	1514 (26.0)	773 (31.7)	
Obese	3885 (66.7)	1410 (57.9)	
Baseline eGFR, mL/min, n (%)			0.55
< 15	22 (0.4)	8 (0.4)	
15 to < 30	395 (7.6)	155 (6.8)	
30 to < 60	2385 (46.0)	1053 (46.1)	
60 to < 90	1976 (38.1)	901 (39.4)	
≥ 90	411 (7.9)	169 (7.4)	
Baseline sUA level group, n (%)			
< 6 mg/dL	197 (4.2)	140 (6.7)	< 0.0001
≥ 6 to < 7 mg/dL	279 (5.9)	210 (10.1)	
≥ 7 to < 8 mg/dL	764 (16.3)	428 (20.4)	
≥ 8 to < 9 mg/dL	1184 (25.2)	562 (26.8)	
≥ 9 mg/dL	2277 (48.4)	754 (36.0)	
Baseline tophi, n (%)	60 (0.8)	44 (1.5)	< 0.005

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; SD, standard deviation; sUA, serum uric acid.

allopurinol-treated group (45.6%, 100–300 mg/d). The response rate of febuxostat-treated patients in our systematic review increased to 71.4% and 82.0% when doses were increased to 80 and 120 mg/d, respectively.[18]

The adjusted ORs of 1.73 to 1.86 reported for febuxostat use in our study indicate that patients on febuxostat have a 42% to 48% higher likelihood of reaching sUA goal level than patients on allopurinol during a comparable treatment period. For patients who switched to febuxostat after failing to achieve sUA goal level with allopurinol use, the percentage of patients who reached the goal was 36.8% in 6 months. The success rate was significantly higher than the success rate achieved with allopurinol throughout, although not as high as that achieved in patients who were initiated and maintained on febuxostat throughout. It is noteworthy that, our calculated ORs for the likelihood of reaching sUA goal level in 6 months while on febuxostat are within the range reported by Ye et al for the 40-mg dose of febuxostat (OR 1.25) and the 80-mg febuxostat dose (OR 3.27).[18]

The reasons for the lower rate of achieving sUA goal level among the allopurinol-treated patients might be a function of the lower doses prescribed for the agent, ie, under-dosing. Due to the potentially severe but rare adverse effects of allopurinol, such as hypersensitivity syndrome, prescribers may have opted to under-dose allopurinol, which may have, in effect, reduced the effectiveness of the agent in reducing sUA level. Although

Table 4. Logistic Regression on Factors Associated With the Likelihood of Reaching sUA Goal Level Within Allopurinol Group

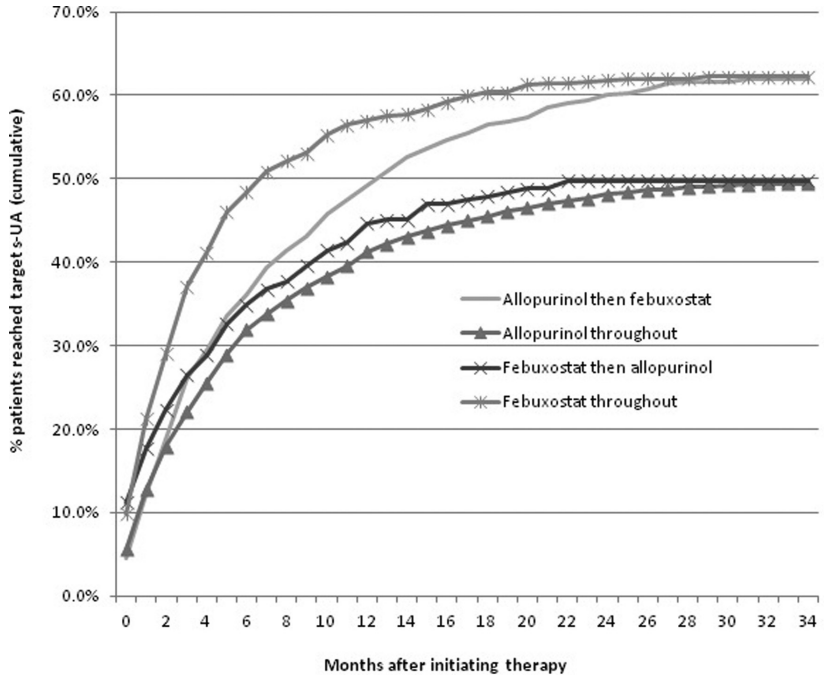
Parameter	Model 1: without baseline sUA, n = 10 119		Model 2: with baseline sUA, n = 6795	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	1.02 (1.01; 1.02)	< 0.0001	1.02 (1.01; 1.02)	< 0.0001
Female gender	1.53 (1.39; 1.68)	< 0.0001	1.49 (1.33; 1.68)	< 0.0001
CCI	0.94 (0.89; 0.99)	0.02	0.97 (0.91; 1.05)	0.46
Baseline sUA (< 7 mg/dL as reference group)				
≥ 7 to < 8	NA		0.79 (0.66; 0.95)	0.01
≥ 8 to < 9	NA		0.70 (0.58; 0.83)	< 0.0001
≥ 9	NA		0.48 (0.41; 0.57)	< 0.0001
Baseline eGFR group (≥ 90 as reference)				
60 to < 90	0.94 (0.77; 1.15)	0.54	0.99 (0.78; 1.24)	0.90
30 to < 60	0.70 (0.57; 0.87)	< 0.001	0.85 (0.67; 1.08)	0.18
15 to < 30	0.57 (0.43; 0.75)	< 0.0001	0.70 (0.50; 0.97)	0.03
< 15	0.68 (0.30; 1.59)	0.38	1.13 (0.36; 3.59)	0.83
eGFR missing	0.69 (0.56; 0.85)	< 0.0005	0.80 (0.62; 1.02)	0.07
Race/ethnicity (white non-Hispanic as reference)				
Black	0.70 (0.59; 0.82)	< 0.0001	0.70 (0.57; 0.86)	< 0.001
Asian	0.68 (0.43; 1.05)	0.08	0.73 (0.44; 1.21)	0.22
Hispanic	1.11 (0.77; 1.59)	0.59	0.94 (0.60; 1.47)	0.78
Unknown	1.1 (1.00; 1.21)	0.04	1.08 (0.97; 1.21)	0.17
Gout diagnosis year (2005 as reference)				
2006	0.69 (0.46; 1.02)	0.06	0.78 (0.47; 1.29)	0.33
2007	0.81 (0.57; 1.15)	0.24	0.89 (0.57; 1.40)	0.62
2008	0.70 (0.51; 0.97)	0.03	0.80 (0.52; 1.21)	0.28
2009	0.82 (0.61; 1.11)	0.21	0.88 (0.60; 1.30)	0.53
2010 and after	1.04 (0.78; 1.41)	0.78	1.18 (0.80; 1.74)	0.39
Baseline tophi	1.62 (1.09; 2.41)	0.02	1.49 (0.94; 2.35)	0.09

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; sUA, serum uric acid.

American College of Rheumatology guidelines have suggested that either febuxostat or allopurinol can be used as first-line ULT, we observed that febuxostat was reserved for the more severe patient cases. For example, the febuxostat-treated patient group had a higher proportion of patients with sUA ≥ 9 mg/dL than did the allopurinol-treated group. Moreover, treatment delay between first gout diagnosis and first ULT treatment was significantly longer for the febuxostat group than for the allopurinol group, by 2.5 months. Independent of treatment, we found that older age and being female increased the likelihood of reaching sUA goal, whereas higher CCI, black race, and an eGFR of 15 to < 60 reduced the likelihood. Patients with gout who are at higher risk for failing to reach sUA goal level merit additional clinician attention.

There were 306 (of 1190) febuxostat-treated patients who were switched to allopurinol and 833 (of 17 199) allopurinol-treated patients who were switched to febuxostat. The much higher switching rate for febuxostat could be a reflection of cost-savings measure or in instances where formulary coverage for the former was limited. Moreover, there was a much higher number of patients initiated on allopurinol in the earlier years of study data availability when febuxostat was newly approved. The exact reasons behind the switching decisions could be investigated in further studies that incorporate the patients' and payers' perspectives. Our results regarding the comparative superior effectiveness of febuxostat compared to allopurinol are relevant both clinically and economically. Reaching and maintaining sUA goal level are important for patients' outcomes. In a retrospective analysis of claims data, it was reported that the average annual number of patient gout flares increased by 11.9% ($P < 0.001$) with each unit-increase in sUA level above 6 mg/dL ($P < 0.001$).[19] Furthermore, among patients from the same study with very high sUA levels (> 9 mg/dL), the adjusted total and gout-related cost per gout episode were $2555 and $356 higher, respectively, than those of patients with normal sUA levels.[19] In addition to the direct-cost implications for gout, the condition has been shown to result in substantial indirect costs in the form of work absenteeism and reduced productivity. Employees with gout registered 4.6 days absent from work for all categories of health-related absence in excess of employees without gout. Employees with gout processed 3.5% fewer units per hour worked and 2.4% fewer units per year than employees without gout.[20] Future studies should examine the comparative impact of allopurinol and febuxostat treatment on economic and humanistic outcomes of patients with gout or hyperuricemia.

Figure 3. Proportion of patients who reached s-UA goal level by type of initial and subsequent ULTs.

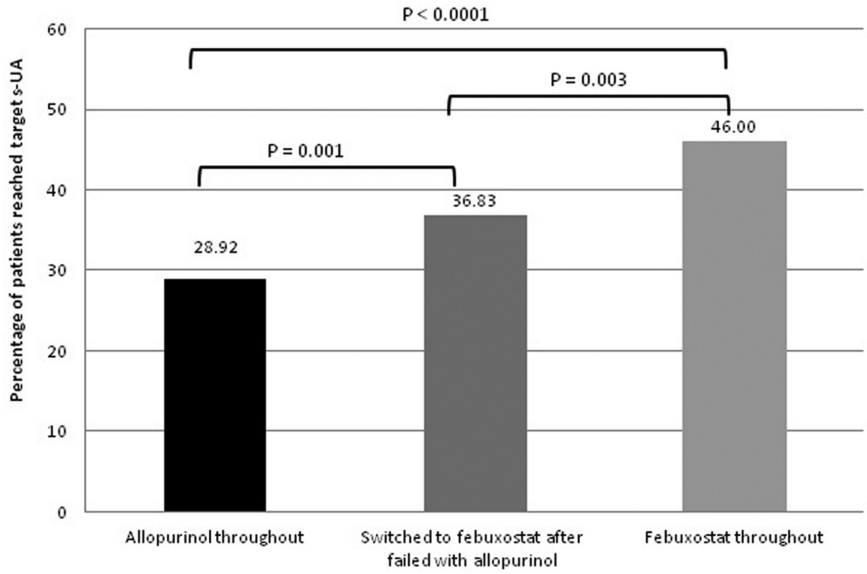


Abbreviations: s-UA, serum uric acid; ULT, urate-lowering therapy.

Limitations of the Study

Data used in our study were from electronic medical records for primary clinical practice clinics. Thus, the study most likely excluded treatment patterns and outcomes in specialty rheumatology clinics where more severe cases of gout are more often encountered. Missing data on eGFR and fasting blood glucose levels precluded the study of the impact of ULT on renal function and blood glucose. Although about one-third of patients did not have baseline sUA levels, comparisons between models with and without the variable showed similar results, indicating that the magnitude of missing data would not have materially altered the main findings. We reported on doses of the 2 agents based on what was noted in the EMR-based dataset, which unlike claims

Figure 4. Proportion of patients who reached s-UA goal level within 6 months of initiating or switching ULT.



Abbreviations: s-UA, serum uric acid; ULT, urate-lowering therapy.

Table 5. Bivariate Analyses Comparing Allopurinol-Treated Patients Who Reached or Did Not Reach sUA Goal Level After Switched to Febuxostat

Variable	Did not Reach Goal After Switch (n = 261)	Reached Goal After Switch (n = 244)	*P* Value
Age, mean (SD)	61.8 (14.2)	65.02 (12.6)	< 0.01
CCI, mean (SD)	0.5 (1.0)	0.38 (0.9)	0.38
Female gender, n (%)	79 (30.3)	91 (37.3)	0.10
Race/ethnicity, n (%)			0.21
Asian	4 (1.5)	4 (1.6)	
Black	29 (11.1)	19 (7.8)	
Hispanic	3 (1.2)	3 (1.2)	
Unknown	119 (45.6)	94 (38.5)	
White	106 (40.6)	124 (50.8)	
Gout diagnosis year, n (%)			0.84
2005	6 (2.3)	4 (1.6)	
2006	5 (1.9)	6 (2.5)	
2007	19 (7.3)	16 (6.6)	
2008	35 (13.4)	30 (12.3)	
2009	92 (35.3)	77 (31.6)	
2010 and 2011	104 (39.9)	111 (45.5)	
BMI group, n (%)			0.38
Underweight	0 (0)	1 (0.5)	
Normal	14 (6.4)	19 (9.2)	
Pre-obese	42 (19.2)	45 (21.8)	
Obese	163 (74.4)	141 (68.5)	
Baseline eGFR, mL/min, n (%)			0.36
< 15	0 (0.00)	3 (1.6)	
15 to < 30	23 (12.1)	30 (15.5)	
30 to < 60	105 (55.3)	102 (52.6)	
60 to < 90	49 (25.8)	44 (22.7)	
> 90	13 (6.8)	15 (7.7)	
Baseline serum UA level group, n (%)			0.34
< 6 mg/dL	2 (1.2)	4 (2.4)	
≥ 6 to < 7 mg/dL	8 (4.6)	12 (7.1)	
≥ 7 to < 8 mg/dL	19 (11.0)	22 (13.1)	
≥ 8 to < 9 mg/dL	39 (22.5)	46 (27.4)	
≥ 9 mg/dL	105 (60.7)	84 (50.0)	
Baseline tophi, n (%)	5 (1.9)	3 (1.2)	0.73

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; SD, standard deviation; sUA, serum uric acid; UA, uric acid.

datasets, does not have additional details on dosing regimens to probe adequacy of doses prescribed or doses consumed by the patients, or to perform a ULT dosing study and to assess the impact of dosing regimens on outcomes. Future studies are needed to account for compliance and dose adjustment, and to investigate whether the effectiveness of allopurinol in the real-world practice setting might have been adversely impacted by the lower than required and recommended dose of the agent needed to achieve the desired treatment goal.

Conclusion

Although febuxostat has been available in the United States since 2009, it appears to be used in only a small proportion of ULT-naïve patients as first-line treatment. Our study findings suggest that both allopurinol and febuxostat are being underutilized by physicians in the primary care setting. The significant differences between the allopurinol- and febuxostat-treated groups in eGFR, sUA level, and the prevalence of DM indicate that febuxostat was reserved for selected, more difficult to treat patients. It is plausible that the observed underdosing of allopurinol is behind the observed limited effectiveness of the agent in our study. Regardless, what we reported is that under current prescribing patterns for both allopurinol and febuxostat in real-world practice primary care settings, treatment with febuxostat was more effective than allopurinol. Future studies are needed to account for compliance and dose adjustment, and to investigate whether the effectiveness of allopurinol in the real-world practice setting might have been adversely impacted by the lower than required and recommended dose to achieve the desired

treatment goal. For patients who switched to febuxostat after failing allopurinol, nearly half reached sUA goal level; with a significant reduction in sUA level for those who did not reach goal within the time frame of the available data in our study.

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Conflict of Interest Statement

Hind T. Hatoum, PhD, is the president of Hind T. Hatoum and Company. Dinesh Khanna, MD, MSc, is a consultant for Takeda Pharmaceuticals, Inc. Swu-Jane Lin, PhD, is a consultant for Hind T. Hatoum and Company. Kasem S. Akhras, PharmD, was employed by Takeda Pharmaceuticals International, Inc, at the time of the study. Aki Shiozawa, MPH, MBA, is employed by Takeda Pharmaceuticals International, Inc. Puja Khanna, MD, MPH, is a consultant for Takeda Pharmaceuticals, Inc.

References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum*. 2011;63(10):3136–3141.
2. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012;64(10):1431–1446.
3. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol*. 2010;22(2):165–172.
4. Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin Pharmacokinet*. 2007;46(8):623–644.
5. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2006;65(10):1312–1324.
6. Pandya BJ, Riedel AA, Swindle JP, et al. Relationship between physician specialty and allopurinol prescribing patterns: a study of patients with gout in managed care settings. *Curr Med Res Opin*. 2011; 27(4):737–744.
7. Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. *Arthritis Rheum*. 2007;57(5):822–829.
8. Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals North America Inc; 2011.
9. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2):R63.
10. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450–2461.
11. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59(11):1540–1548.
12. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol*. 2009; 36(6):1273–1282.
13. Edwards NL. Febuxostat: a new treatment for hyperuricaemia in gout. *Rheumatology (Oxford)*. 2009;48(Suppl 2):ii15–ii19.
14. GE Healthcare. Clinical Data Services: New Product and Service Briefing. 2013; http://www.gehealthcare.com/usen/hit/cds/docs/CDS%20Brochure_v5pg.pdf. Accessed August 1, 2013.
15. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247–254.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
17. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130–1139.
18. Ye P, Yang S, Zhang W, et al. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. *Clin Ther*. 2013;35(2):180–189.
19. Wu EQ, Patel PA, Mody RR, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? *J Rheumatol*. 2009;36(5):1032–1040.
20. Kleinman NL, Brook RA, Patel PA, et al. The impact of gout on work absence and productivity. *Value Health*. 2007;10(4):231–237.