A Real-World Study of Switching From Allopurinol to Febuxostat in a Health Plan Database

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Objective: The objective of this study was to assess the real-world comparative effectiveness of continuing on allopurinol versus switching to febuxostat.

Methods: In a retrospective claims data study of enrollees in health plans affiliated with Optum, we evaluated patients from February 1, 2009, to May 31, 2012, with a gout diagnosis, a pharmacy claim for allopurinol or febuxostat, and at least 1 serum uric acid (SUA) result available during the follow-up period. Univariate and multivariable-adjusted analyses (controlling for patient demographics and clinical factors) assessed the likelihood of SUA lowering and achievement of target SUA of less than 6.0 mg/dL or less than 5.0 mg/dL in allopurinol continuers versus febuxostat switchers.

Results: The final study population included 748 subjects who switched to febuxostat from allopurinol and 4795 continuing users of allopurinol. The most common doses of allopurinol were 300 mg/d or less in 95% of allopurinol continuers and 93% of febuxostat switchers (prior to switching); the most common dose of febuxostat was 40 mg/d, in 77% of febuxostat switchers (after switching). Compared with allopurinol continuers, febuxostat switchers had greater (1) mean preindex SUA, 8.0 mg/dL versus 6.6 mg/dL ($P < 0.001$); (2) likelihood of postindex SUA of less than 6.0 mg/dL, 62.2% versus 58.7% ($P = 0.072$); (3) likelihood of postindex SUA of less than 5.0 mg/dL, 38.9% versus 29.6% ($P < 0.001$); and (4) decrease in SUA, 1.8 (SD, 2.2) mg/dL versus 0.4 (SD, 1.7) mg/dL ($P < 0.001$). In multivariable-adjusted analyses, compared with allopurinol continuers, febuxostat switchers had significantly higher likelihood of achieving SUA of less than 6.0 mg/dL (40% higher) and SUA of less than 5.0 mg/dL (83% higher).

Conclusions: In this "real-world" setting, many patients with gout not surprisingly were not treated with maximum permitted doses of allopurinol. Patients switched to febuxostat were more likely to achieve target SUA levels than those who continued on generally stable doses of allopurinol.

Key Words: comparative effectiveness, gout, medication switching, serum urate, urate-lowering therapy

G out is the most common inflammatory arthritis condition in men older than 40 years and is increasingly prevalent among postmenopausal women.[1] In addition, the prevalence of gout more than doubled between the 1960s and the 1990s.[1] The National Health and Nutrition Examination Survey data showed that 8.3 million Americans have gout (3.9%) and 43.3 million (21.0%) have hyperuricemia, a major risk factor for gout.[2] Hyperuricemia, defined as a serum uric acid (SUA) level greater than 6.8 mg/dL, is a key feature of gout.

Successful treatment of gout requires effective reduction of SUA with urate-lowering therapy (ULT). The most common pharmacologic approach to ULT is the use of xanthine oxidase inhibitors (XOIs), which reduce uric acid production. Allopurinol has been the principal XOI available for several decades, and febuxostat, a novel nonpurine analog XOI approved in the United States in 2009, has been shown to be noninferior in efficacy to allopurinol.[3] Compared with allopurinol, febuxostat may require fewer dose adjustments in patients with mild to moderate renal dysfunction.[4,5]

The European League Against Rheumatism[6,7] and the British Society for Rheumatology gout treatment guidelines[8] (which predate the US approval of febuxostat) recommend XOIs as the appropriate first-line treatment. The American College of Rheumatology guidelines recommend the use of allopurinol or febuxostat as the initial pharmacologic ULT.[9] Both the American College of Rheumatology and the European League Against Rheumatism recommend that SUA levels be maintained at less than 6.0 mg/dL.[6,9] Suboptimal treatment of gout and continued high SUA lead to recurrent attacks, tophaceous deposits, and joint damage.[10–12]

In practice, allopurinol has been the first-line treatment, and when it fails or is associated with adverse effects, febuxostat is the second ULT option considered by most providers.[13,14] To

our knowledge, studies comparing the effectiveness (SUA change and SUA goal attainment) of continuing allopurinol versus switching therapy to febuxostat in the real-world setting have not been done. This was the primary objective of our study. Secondary objectives were to describe patient characteristics associated with changes in SUA and target SUA achievement in patients who switch from allopurinol to febuxostat.

METHODS

This retrospective claims data study used medical and pharmacy claims, enrollment information, and laboratory results for commercial and Medicare Advantage (with part D) enrollees in health plans affiliated with Optum (a diversified health management company) to assess the effectiveness of treatment with allopurinol versus febuxostat. This study was conducted using deidentified data from the Optum Research Database (ORD) accessed using methods compliant with the provisions of the

Health Insurance Portability and Accountability Act of 1996. Because this study did not involve the collection, use, or transmittal of individually identifiable data, institutional review board review or approval was not required.

Data Source

The ORD contains encounter data from all health care sites (inpatient, hospital, outpatient, emergency room, physician's office, surgery center, etc) for all types of provided services, including specialty, preventive, and office-based care. Claims for pharmacy services in the ORD included drug name, dosage form, drug strength, fill date, days of supply, financial information, and deidentified patient and prescriber codes. In addition, a proportion of outpatient laboratory test results are available to be linked to health care utilization and pharmacy claims data. During the identification period used for this project, the database included more than 56 million commercial
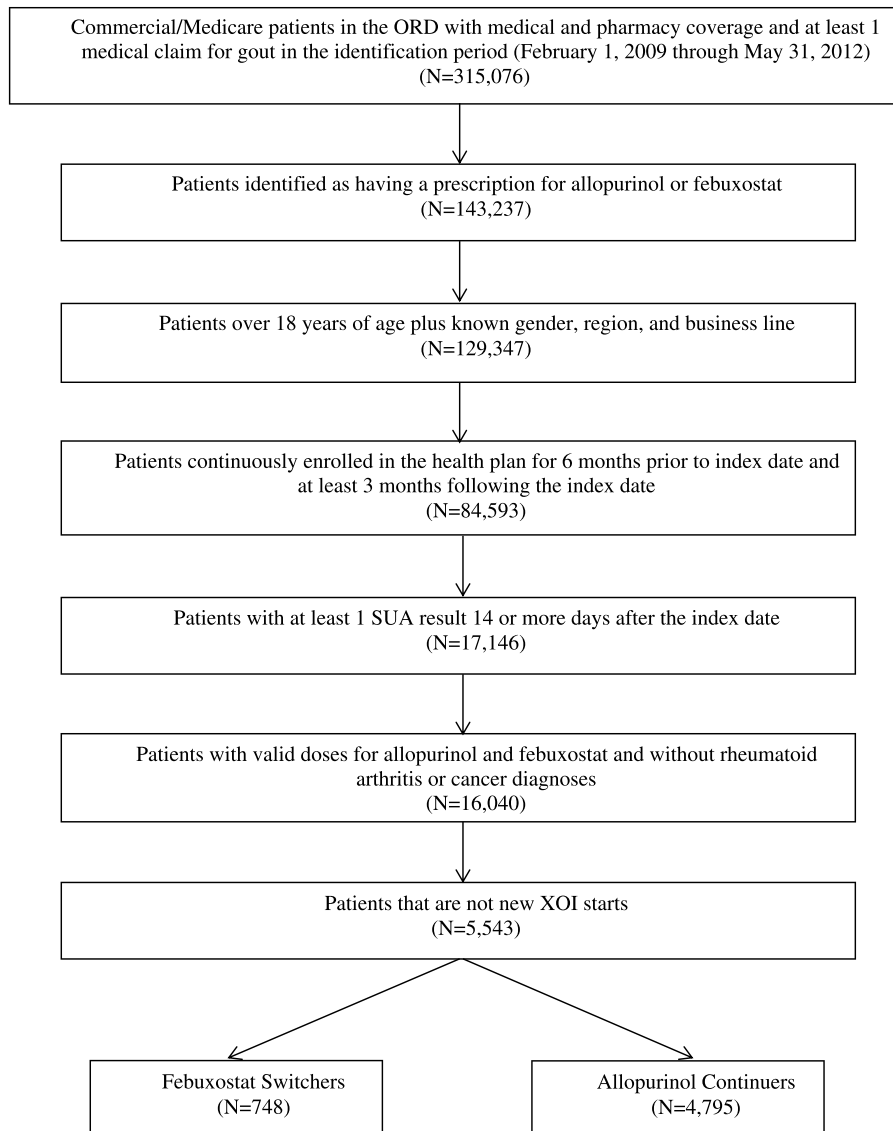
FIGURE 1. Cohort assignment.

SUA = serum uric acid; XOI = xanthine oxidase inhibitor

and Medicare enrollees with both medical and pharmacy insurance coverage. The ORD database has been used for multiple gout studies previously.[15–17]

Study Population

To be eligible for study inclusion, enrollees met the following criteria during the identification period, February 1, 2009, to May 31, 2012: (1) had at least 1 medical claim with the *International Classification of Diseases, Ninth Revision, Common Modification* diagnosis code for gout (274.xx); (2) had a least 1 pharmacy claim for allopurinol or febuxostat; (3) were continuously enrolled for at least 6 months prior to the index date and at least 3 months following the index date; and (4) had at least 1 SUA laboratory test (CPT codes 84550, 84560) result available at 14 days or more after the index date. This corresponds to the earliest post-ULT SUA test commonly used by clinicians to indicate ULT effectiveness, allowing for sufficient time for therapy to take effect. The date of first prescription fill, within the study period, for febuxostat or allopurinol was defined as the subject's index date. If a subject had prescription fills for both medications, the first fill for febuxostat was defined as the index date, and the subject was identified as a "febuxostat switcher" (from allopurinol to febuxostat). Subjects were excluded if they were younger than 18 years as of the year of the index date, had evidence of cancer by *International Classification of Diseases, Ninth Revision, Common Modification* codes during the study period, or received an index dose of XOI outside the recommended dosage range (<100 mg/d or >1500 mg/d for allopurinol and any dose not equaling 40 or 80 mg/d for febuxostat, doses approved for use by the US Food and Drug Administration [FDA]). Baseline data were obtained during the 6-month period prior to the index date. Subjects were followed up until September 30, 2012, until the subject was no longer enrolled in the health plan or death, whichever came first.

Study Cohorts

The study sample includes all available subjects in the database who met the study inclusion and exclusion criteria during the defined time period. Subjects (all of whom had prescriptions for allopurinol filled prior to the index date) were assigned to 1 of 2 study cohorts based on their index medication fill (febuxostat vs allopurinol): (1) continued allopurinol (allopurinol continuers) or (2) switched from allopurinol to febuxostat (febuxostat switchers).

Study Outcome Measures

Outcomes were assessed during a variable follow-up period of a minimum of 3 months through a maximum of 3½ years following the index date. The main outcome measure was change from preindex to postindex mean SUA level. The SUA test values were captured during the preindex (average and final values) and postindex periods. Effectiveness of allopurinol or febuxostat was assessed by their ability to lower SUA, which was examined as (1) change in SUA from baseline period to first available SUA in the follow-up period, (2) percentage of subjects achieving an SUA goal of less than 6.0 and less than 5.0 mg/dL, and (3) mean postindex SUA level. When subjects had more than 1 postindex SUA level, the earliest value that attained the goal was selected.

Statistical Analysis

The primary objective was to compare change in SUA, proportion of subjects achieving SUA target, and mean postindex SUA. Subject demographics (age, sex, and region) and baseline clinical characteristics (utilization and comorbid conditions

assessed by Quan-Charlson comorbidity score[18]) were compared using χ^2 or t test as appropriate. Comparisons of categorical outcomes of interest (postindex SUA goal <6.0 and <5.0 mg/dL) were conducted using a McNemar test (bivariate) and logistic regression (multivariable adjusted). Continuous measures (preindex and postindex prescription SUA and creatinine, time to SUA) were examined using a paired Student t test. Multivariable-adjusted analysis was conducted for binary indicators of achieving the target SUA of less than 6.0 mg/dL and less than 5.0 mg/dL using logistic regression controlling for demographics, comorbid conditions, baseline gout flare rates, and anti-inflammatory prophylaxis. Among febuxostat switchers, multivariable-adjusted logistic regression analyses were used to determine whether certain patient characteristics (age groups, sex, presence of renal failure) were associated with a greater degree of success in lowering or achieving the target SUA levels with febuxostat treatment. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata version 12 (StataCorp., College Station, TX, USA). The 2-tailed level of significance was set at the 0.05 level.

RESULTS

Study Cohort Selection and Baseline Characteristics

Figure 1 outlines the patient attrition and assembly of the cohorts. The final population meeting inclusion/exclusion criteria was 5543. Of these, 748 switched to febuxostat from allopurinol, and 4795 were continuing users of allopurinol. The average age of febuxostat switchers and allopurinol continuers was 56.7 and 55.2 years, respectively (Table 1; $P = 0.003$). The majority of subjects in both groups were male (83.2% of febuxostat switchers, 91.5% of allopurinol continuers; $P < 0.001$), were commercially insured (77.7% vs 93.7%; $P < 0.001$) and lived in the South (74.3% vs 68.2%; $P < 0.001$) in part because of the distribution of the affiliated health plan's enrollment. In allopurinol continuers, the most common dose was 300 mg/d (64%) followed

TABLE 1. Baseline Characteristics for Febuxostat Switchers and Allopurinol Continuers

	Febuxostat Switchers (n = 748)	Allopurinol Continuers (n = 4795)	P
Age, mean (SD), y	56.7 (12.7)	55.23 (10.4)	0.003
Age, n (%)			
18–44 y	138 (18.5)	760 (15.9)	0.073
45–64 y	396 (52.9)	3216 (67.1)	<0.001
65–74 y	145 (19.4)	634 (13.2)	<0.001
≥75 y	69 (9.2)	185 (3.9)	<0.001
Sex, n (%)			
Male	622 (83.2)	4385 (91.5)	<0.001
Insurance type, n (%)			
Commercial	581 (77.7)	4493 (93.7)	<0.001
Medicare Advantage	167 (22.3)	302 (6.3)	<0.001
Geographic region, n (%)			
Northeast	35 (5.1)	397 (8.3)	0.002
Midwest	60 (8.0)	426 (8.9)	0.438
South	556 (74.3)	3270 (68.2)	<0.001
West	94 (12.6)	702 (14.6)	0.133

TABLE 2. Unadjusted Pre- and Post-Index SUA Values in Febuxostat Switchers and Allopurinol Continuers

|	Febuxostat Switchers		Allopurinol Continuers		
	n	Mean (SD)	n	Mean (SD)	P
Preindex					
SUA[a]	445	7.96 (1.91)	1278	6.58 (1.80)	<0.001
Postindex					
SUA[b]	748	6.22 (1.95)	4795	6.21 (1.56)	0.902
Decrease in SUA[c]	445	−1.76 (2.16)	1278	−0.36 (1.67)	<0.001

[a]Average of all preindex SUA measurements.

[b]Average of all postindex SUA measurements.

[c]Among those with at least 1 baseline measurement and 1 follow-up measurement, decrease was defined as the difference between the mean preindex SUA measurement and the mean postindex SUA.

by less than 300 mg/d (31%) and rarely more than 300 mg/d (5%). Similarly, the most common allopurinol doses were 300 mg/d or less in 93% in febuxostat switchers, prior to switching from allopurinol to febuxostat. Febuxostat switchers mostly received 40 mg/d (77%) and less commonly received febuxostat dose of 80 mg/d (23%). Dose increase occurred in 21% of febuxostat switchers versus 15% allopurinol continuers.

SUA Outcomes: Febuxostat Switchers Compared With Allopurinol Continuers

Compared with allopurinol continuers, febuxostat switchers had statistically significantly higher mean preindex SUA (8.0 vs 6.6 mg/dL, $P < 0.001$; Table 2). Febuxostat switchers had a greater decrease in SUA (1.8 [SD, 2.2] mg/d decrease) following the initiation of febuxostat, compared with allopurinol continuers (0.4 (SD, 1.7) mg/dL decrease; $P < 0.001$). In the postindex period, 62.2% of febuxostat switchers versus 58.7% of allopurinol continuers achieved an SUA of less than 6.0 mg/dL ($P = 0.072$; Fig. 2). Respective proportions were 38.9% versus 29.6% for achieving SUA of less than 5.0 mg/dL ($P < 0.001$; Fig. 2).
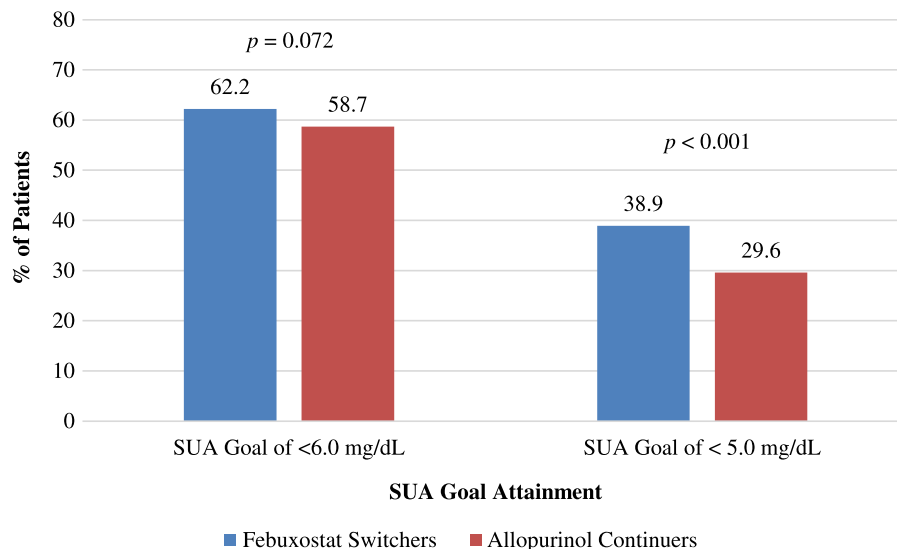
In multivariable-adjusted logistic regression models, patients who switched from allopurinol to febuxostat had a 40% higher likelihood of achieving SUA goal of less than 6.0 mg/dL and an 82% higher likelihood of attaining goal of less than 5.0 mg/dL (Table 3). The adjusted probability of goal attainment of less than 6.0 mg/dL was 65.6% among febuxostat switchers compared with 58.1% for allopurinol continuers (41.9% vs 23.9% adjusted probability of goal attainment <5.0 mg/dL).

SUA Outcomes Among Febuxostat Switchers

Febuxostat effectiveness was assessed among febuxostat switchers only by sex, age, presence of renal failure, and Quan-Charlson index (Supplementary Table S1, available at http://links.lww.com/RHU/A56). Females were more likely than males to achieve SUA of less than 5.0 mg/dL ($P = 0.045$) and achieved it an average of more than 3 months sooner than did men ($P = 0.003$; Supplementary Table S1). Among febuxostat switchers, compared with younger subjects, older subjects were significantly more likely to achieve SUA of less than 5.0 mg/dL ($P < 0.001$) or 6.0 mg/dL ($P = 0.006$) and achieved both goals sooner ($P < 0.001$ for both). For example, subjects 75 years or older achieved SUA of less than 5.0 mg/dL an average of approximately 8 months earlier than did subjects younger than 50 years. These older subjects achieved SUA of less than 6.0 mg/dL an average of approximately 6 months earlier than did subjects younger than 50 years. Subjects with renal failure had a greater percent SUA reduction (28.5% vs 18.4%, $P = 0.034$) and absolute SUA reduction (2.9 vs 1.7 mg/dL, $P = 0.013$) from pre- to post-SUA. No significant differences in SUA outcomes were noted by Quan-Charlson comorbidity index (Supplementary Table S1). Multivariable-adjusted analyses after controlling for patient characteristics showed that age had a borderline statistically significant trend for SUA goals of less than 6.0 and less than 5.0 mg/dL. A higher preindex SUA was associated with statistically significantly lower likelihood of achieving the target SUA (Table 4).

DISCUSSION

Our study population is comparable to the US population. Sixteen percent of enrollees reside in the Western census region,

SUA = serum uric acid

FIGURE 2. Percentages of patients achieving SUA goal.

TABLE 3. Multivariable-Adjusted Logistic Regression Analysis of SUA Goal Attainment Less Than 6 mg/dL and Less Than 5 mg/dL in Febuxostat Switchers Versus Allopurinol Continuers

Independent Variables	Dependent Variable SUA Goal Attainment <6 mg/dL				Dependent Variable SUA Goal Attainment <5 mg/dL			
	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*
Febuxostat switchers (vs allopurinol continuers)	1.403	1.166	1.687	<0.001	1.825	1.510	2.205	<0.001
Age[a]				<0.001				<0.001
18–44 y	0.637	0.544	0.745	<0.001	0.669	0.556	0.805	<0.001
65–74 y	1.364	1.130	1.646	0.001	1.300	1.079	1.565	0.006
≥75 y	1.330	0.939	1.884	0.108	1.605	1.143	2.254	0.006
Male[b]	0.829	0.676	1.018	0.073	0.675	0.552	0.826	<0.001
Baseline uricosuric/incidental uricosuric medication use	1.005	0.871	1.160	0.942	1.049	0.903	1.219	0.529
Baseline comorbidities								
Coronary artery disease	1.116	0.909	1.369	0.295	1.176	0.957	1.445	0.124
Heart failure	0.699	0.501	0.975	0.035	0.743	0.521	1.059	0.100
Hypertension	1.046	0.917	1.194	0.502	0.988	0.857	1.139	0.867
Hyperlipidemia	1.112	0.979	1.265	0.103	1.119	0.975	1.285	0.110
Kidney failure	1.086	0.679	1.738	0.730	1.121	0.690	1.822	0.644
Obesity	0.948	0.755	1.190	0.643	1.086	0.853	1.382	0.505
Baseline gout flare	0.938	0.831	1.058	0.297	0.869	0.763	0.990	0.034
Baseline per member per month health care costs (in $1000)	1.007	0.982	1.033	0.585	1.021	0.996	1.047	0.108
SUA quartiles[c]				<0.001				<0.001
q2 (6.21–7.90)	0.251	0.175	0.360	<0.001	0.226	0.169	0.302	<0.001
q3 (7.91–9.40)	0.129	0.090	0.184	<0.001	0.151	0.111	0.206	<0.001
q4 (9.41+)	0.094	0.065	0.136	<0.001	0.122	0.088	0.169	<0.001
Missing	0.207	0.150	0.286	<0.001	0.287	0.227	0.363	<0.001
SCr quartiles[d]				0.002				0.006
q2 (1.03–1.24)	0.980	0.762	1.262	0.878	0.960	0.748	1.232	0.748
q3 (1.25–1.53)	0.824	0.645	1.053	0.121	0.792	0.617	1.016	0.067
q4 (≥1.54)	0.724	0.557	0.940	0.016	0.810	0.620	1.060	0.125
Missing	0.694	0.560	0.861	<0.001	0.694	0.559	0.862	<0.001

Additional variables included in the model were insurance type, baseline comorbidities (angina, diabetes, dialysis, kidney stones, myocardial infarction, overweight, osteoarthritis, peripheral artery disease, stroke). Uricosuric medications were defined as probenecid and colchicine. Incidental uricosuric medications were defined as losartan, amlodipine, fenofibrate, niacin, or gemfibrozil.

[a]Reference group: 45 to 64 years of age.

[b]Reference group: females.

[c]Reference group: q1 (2.00–6.20).

[d]Reference group: q1 (0.58–1.02).

CI indicates confidence interval; q, quartiles; SCr, serum creatinine.

compared with 24% for the US population overall; 36% of members reside in the Southern regions, 20% in the Midwest, and 27% in the Northeastern region (compared with 37%, 21%, and 18% in the US population overall).[19] In addition, the commercial and Medicare Advantage Health plan enrollees in the ORD health plans used in this study are similar to US insured and Medicare populations, respectively.[20] The ORD has been used in numerous research studies in patients with gout evaluating gout treatment patterns, costs, and the occurrence of flares.[15–17] In this retrospective study that included patients similar to the general US population, we made several important observations that merit further discussion.

We found that patients who switched from allopurinol to febuxostat achieved the target SUA of less than 6.0 mg/dL and less than 5.0 mg/dL more often than did the allopurinol continuers, despite having a higher preindex SUA, 8.0 versus 6.6 mg/dL, respectively. This observation persisted in multivariable-adjusted analyses after accounting for demographics, comorbidity, annual costs, preindex SUA, and serum creatinine, among other factors. Patients who switched from allopurinol to febuxostat had a 1.40 and 1.83 times higher likelihood of achieving SUA goal of less than 6.0 mg/dL and less than 5.0 mg/dL, respectively. Febuxostat switchers appeared to have more severe disease (higher SUA at baseline, more gout flares), higher medical comorbidity, and higher disease burden (health care resource utilization and cost) at baseline. The proportion of patients receiving allopurinol of 300 mg/d or less was similar in allopurinol continuers versus febuxostat switchers, 95% versus 93%. These results are supported by a large population-based cohort study that found patients initiated on febuxostat had more comorbidities and greater

TABLE 4. Multivariable-Adjusted Association of Clinical, Laboratory, and Health Coverage Variables With SUA Goal Attainment in Febuxostat Switchers

Independent Variables	Dependent Variable SUA Goal Attainment <6 mg/dL				Dependent Variable SUA Goal Attainment <5 mg/dL			
	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*
Age[a]				0.063				0.003
18–44 y	0.583	0.381	0.892	0.013	0.418	0.258	0.678	<0.001
65–74 y	0.770	0.463	1.280	0.314	0.859	0.517	1.427	0.557
≥75 y	1.123	0.532	2.368	0.761	1.303	0.639	2.653	0.467
Male[b]	0.830	0.513	1.343	0.448	0.986	0.623	1.559	0.952
Baseline uricosucoric/incidental medication use	0.874	0.595	1.285	0.494	1.001	0.682	1.471	0.994
Baseline comorbidities								
Coronary artery disease	0.676	0.400	1.142	0.143	0.875	0.519	1.475	0.616
Heart failure	0.644	0.317	1.306	0.223	0.653	0.314	1.359	0.254
Hypertension	1.201	0.810	1.781	0.363	1.198	0.801	1.793	0.379
Hyperlipidemia	1.322	0.936	1.867	0.113	1.325	0.933	1.883	0.116
Kidney failure	1.867	0.800	4.354	0.149	1.258	0.546	2.899	0.589
Obesity	0.713	0.406	1.253	0.240	1.231	0.698	2.168	0.473
Baseline gout flare	0.691	0.446	1.072	0.099	0.845	0.548	1.305	0.448
Baseline per member per month health care costs (in $1000)	0.997	0.957	1.040	0.897	1.023	0.982	1.065	0.279
SUA quartiles[c]				<0.001				<0.001
q2 (6.21–7.90)	0.429	0.224	0.823	0.011	0.527	0.298	0.932	0.028
q3 (7.91–9.40)	0.211	0.114	0.389	<0.001	0.260	0.148	0.457	<0.001
q4 (≥9.41)	0.249	0.128	0.485	<0.001	0.284	0.152	0.529	<0.001
Missing	0.358	0.192	0.669	0.001	0.436	0.251	0.758	0.003
SCr quartiles[d]				0.416				0.063
q2 (1.03–1.24)	0.834	0.465	1.493	0.541	0.785	0.455	1.354	0.384
q3 (1.25–1.53)	0.708	0.390	1.286	0.257	0.579	0.325	1.032	0.064
q4 (≥1.54)	0.558	0.291	1.073	0.080	0.465	0.242	0.892	0.021
Missing	0.631	0.353	1.127	0.120	0.480	0.273	0.842	0.010

Additional variables included in the model were insurance type, baseline comorbidities (angina, diabetes, dialysis, kidney stones, myocardial infarction, overweight, osteoarthritis, peripheral artery disease, stroke). Uricosuric medications were defined as probenecid and colchicine. Incidental uricosuric medications were defined as losartan, amlodipine, fenofibrate, niacin, or gemfibrozil.

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CI indicates confidence interval; q, quartiles; SCr, serum creatinine.

use of health care resources and gout-related drugs such as opioids, steroids, and anti-inflammatory drugs than did the allopurinol users.[14] This potentially implies that a higher severity of gout is associated with initiation or change in the treatment to febuxostat. Another interpretation of these data is that in patients with gout with significant comorbidity burden, who fail to lower the SUA appropriately (or achieve SUA goal) with allopurinol, febuxostat may be an effective alternative. An important consideration is that despite the FDA approved dose of allopurinol up to 800 mg/d, only 5% of allopurinol continuers had a daily allopurinol dose of greater than 300 mg/d, and allopurinol dose was titrated up only in 15% cases during the study period. This contrasts with 23% of febuxostat switchers receiving the highest FDA-approved febuxostat dose of 80 mg/d and the overall up-titration in 21% of cases. It is common knowledge that less than 50% of patients treated with allopurinol with doses 300 mg/d or lower achieve a target serum urate of less than 6 mg/dL.[11,21]

Multivariable-adjusted analyses showed that in febuxostat switchers increased age had borderline association with the higher likelihood of achieving SUA goals of less than 6.0 and less than 5.0 mg/dL. A higher preindex SUA was associated with a lower likelihood of achieving the target SUA during follow-up. None of the other investigated factors were associated with successfully reaching SUA target. Lower adherence to ULT and a higher body mass index in younger patients with gout may be the reasons for the older febuxostat switchers to be more likely to reach the target SUA than the younger patients. This phenomenon has been demonstrated recently in other studies as well[22,23] and suggests that the treatment of gout needs to be aggressive, especially in younger patients because they have less optimal outcomes with XOI treatment for urate lowering than do older patients.

Our study findings must be interpreted considering several limitations. Claims data are collected for the purpose of payment/reimbursement (not research), and therefore, it can have limitations

in terms of accuracy. The degree to which claims data can accurately capture medical history at the level of an individual is subject to errors in coding in the record and to codes included as a "rule-out" criterion rather than indicating the presence of actual disease. Pharmacy claims do not fully reflect actual patient dosing or compliance/adherence with a medication regimen. Socioeconomic factors and physician practice (subtherapeutic doses of allopurinol, poor adherence with quality care) could play a role in treated patients not achieving the target SUA goal. These data were not captured, a limitation of our study. This study does not control for adherence with ULT medications or the use of other medications such as diuretics, both of which can impact serum urate outcome; if they differed between the 2 groups, they might partially explain the differences in outcomes. However, the switch from allopurinol to febuxostat is usually done because of lack of efficacy or adverse effects associated with allopurinol and not based on use versus nonuse of diuretics. Both medications are administered once daily and have similarly low risk of adverse events, and therefore we do not anticipate major differences in adherence based on these factors. A study limitation is that adherence was not measured in our study. Therefore, if differences in adherence exist, they might partially explain febuxostat versus allopurinol difference. A numerically slightly higher dose titration for febuxostat switchers versus allopurinol continuers (21% vs 15%) might have partially contributed to outcome differences. However, these comparative effectiveness results from this "real world" are still valid, because we are comparing effectiveness, which incorporates factors such as adherence, dose titration, and so on. However, the reader must interpret these findings being from an effectiveness study, not an efficacy study. The results of this analysis are primarily applicable to the interpretation of trends or patterns of XOI use in patients with gout who are similarly insured in the US population and may not be generalizable to other patient populations such as the noninsured or Medicaid-insured patients.

In conclusion, this study shows that in allopurinol-to-febuxostat switchers, almost two-thirds achieve SUA of less than 6.0 mg/dL, and a third achieve SUA of less than 5.0 mg/dL. These proportions were slightly higher than those achieved in patients who continued allopurinol. In addition, febuxostat switchers achieved the target SUA faster than did the allopurinol continuers. Further studies are needed to evaluate if this leads to any significant differences in quality of life or functional ability or gout flare frequency, outcomes directly relevant to patients, and if these findings are sustained over time. We also identified the factors associated with effectiveness of febuxostat in achieving the target SUA goal, in patients with gout who switched to febuxostat. These findings should help to identify high-risk gout patient populations who are likely to benefit the most with aggressive ULT with a frequent monitoring of their disease and SUA.

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