Understanding Predictors of Reaching Serum Uric Acid Goal in Febuxostat Utilizers

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INTRODUCTION

- Clinical guidelines recommend allopurinol or febuxostat as first-line pharmacologic urate-lowering therapy for gout patients to achieve a serum uric acid (sUA) goal of <6 mg/dL.[1] Previous studies have established febuxostat's effectiveness[2,3,4] in achieving sUA goal, but further evidence is needed to determine the predictors of attaining sUA goal among febuxostat users.
- The objective of this study was to identify clinical characteristics of febuxostat utilizers in order to develop and validate a predictive model for achieving a goal of sUA <6 mg/dL.

METHODS

Study Design
- Retrospective database analysis

Data Source
- The study sample was selected from the Humana Research Database (Louisville, KY)

Inclusion Criteria
- Members in commercial and Medicare Advantage with Prescription Drug (MAPD) plans meeting all of the following inclusion criteria were eligible for the study:
  - Initiation of febuxostat therapy between February 1, 2009 and December 31, 2013. The first febuxostat prescription was considered the index date.
  - ≥1 medical claim with a gout diagnosis code (ICD9 code: 274.xx) in either the inpatient or outpatient setting during the 12-month pre-index period or within 30 days after the index date.
  - Continuous enrollment in a fully-insured commercial or MAPD plan for 12 months pre- and post-index.
  - Age between 18 and 89 on the index date.
  - Valid sUA test results (LOINC codes '3084-1', '21587-1', '16259-4') on or before the index date AND at least 120 days after the index date.
  - At least one valid serum creatinine test result (LOINC code '2160-0') during the 24 month observation period.

Exclusion Criteria
- Members with an allopurinol script during the post-index period.
- Members having a cancer diagnosis, without any other gout medications, at any time during the 24-month study period.
- Members with any of the following during the pre-index period: Stage 5 chronic kidney disease, evidence of an organ transplant, a diagnosis or therapy for HIV/AIDS, or use of pegloticase (within 2 months pre-index).

Group Definition
- Among eligible members, the first valid sUA test result ≥ 120 days and ≤ 365 days post-index was used to determine whether members attained a sUA goal <6 mg/dL. The study sample was then divided into two cohorts: those who achieved sUA goal and those who did not achieve goal.

Statistical Analyses
- Descriptive statistics were used to compare demographic and baseline clinical characteristics between the two cohorts:
  - T-tests and non-parametric tests were used to compare continuous measures. Chi-square tests were used for categorical measures. All variables where p<0.2, plus additional variables deemed important from a clinical viewpoint, were included in the initial models.

Predictive Modeling
- The study sample was divided using a 2:1 ratio into a training dataset for model development and a holdout dataset for model validation.
- Separate logistic and linear regression models were developed:
  - Both models employed multivariable stepwise regression with backward elimination. A p-value of <0.2 was required for retention in the model.
  - The dependent variable in both models was the sUA value associated with the first valid sUA test result at least 120 days after the index date.
  - The primary independent variable was adherence to febuxostat, calculated using the proportion of days covered (PDC) method. Sixteen additional input variables were included in the initial models.
  - For each variable retained in the final models, parameter estimates (PE), odds ratios (OR – logistic model), 95% confidence intervals (CIs), and p-values were reported.
  - The final models were validated using the holdout dataset. Model performance and fit statistics were reported for each. Receiver Operating Characteristic (ROC) curves were generated for the logistic model.
  - An additional test for robustness was employed by reducing the pre-index data capture period from 365 to 180 days.

- A total of 678 eligible members satisfied all inclusion and exclusion criteria and were identified for the study sample. Among these members, 356 met the sUA goal of <6 mg/dL and 322 had a sUA ≥6 mg/dL. Demographics and baseline clinical measures were assessed for these cohorts (Table 1).

Table 1. Patient Demographic and Baseline Clinical Characteristics

Measure	sUA level (< 6 mg/dL) Mean (SD) or N (%)	sUA level (≥ 6 mg/dL) Mean (SD) or N (%)	*P*-value	Overall study sample Mean (SD) or N (%)
N	356	322		678
Mean age (SD)	68.8 (11.0)	67.9 (11.4)	0.3037	68.3 (11.2)
% Male	226 (63.5%)	198 (61.5%)	0.6527	424 (62.5%)
% White	228 (64.0%)	183 (56.8%)	0.5922	411 (60.6%)
% Residing in South	287 (80.6%)	260 (80.7%)	0.9665	547 (80.7%)
Febuxostat adherence (PDC)	0.82 (0.21)	0.59 (0.30)	<0.0001	0.71 (0.28)
Days on febuxostat therapy	171 (71)	126 (77)	<0.0001	150 (78)
Index febuxostat dose (80 mg vs. 40 mg)	113 (31.7%)	75 (23.3%)	0.0141	188 (27.7%)
Patient out-of-pocket expenses per febuxostat script	$33 ($23)	$32 ($24)	0.4210	$33 ($24)
Pre-index use of:				
Allopurinol	217 (61.0%)	187 (58.1%)	0.4453	404 (59.6%)
Urate-lowering medications	N < 10	N < 10	0.8494	14 (2.1%)
Thiazide diuretics	36 (10.1%)	37 (11.5%)	0.5631	73 (10.8%)
Number of symptomatic gout medications	5.1 (5.0)	4.7 (4.7)	0.3310	4.9 (4.9)
Presence of:				
Coronary artery disease	123 (34.6%)	115 (35.7%)	0.7512	238 (35.1%)
Stroke	52 (14.6%)	48 (14.9%)	0.9124	100 (14.7%)
Hyperlipidemia	293 (82.3%)	264 (82.0%)	0.9146	557 (82.2%)
Peripheral vascular disease	44 (12.4%)	47 (14.6%)	0.3936	91 (13.4%)
Congestive heart failure	68 (19.1%)	77 (23.9%)	0.1270	145 (21.4%)
Chronic kidney disease	164 (46.1%)	149 (46.3%)	0.9572	313 (46.2%)
Hypertension	321 (90.2%)	300 (93.2%)	0.1599	621 (91.6%)
Type 2 diabetes	156 (43.8%)	162 (50.3%)	0.0908	318 (46.9%)
Gouty tophi	15 (4.2%)	11 (3.4%)	0.5893	26 (3.8%)
Number of gout flares	1.2 (1.2)	1.2 (1.3)	0.8154	1.2 (1.2)
Deyo-Charlson comorbidity index	2.3 (2.4)	2.4 (2.2)	0.7206	2.4 (2.3)
RxRisk-V comorbidity index	7.8 (3.2)	8.0 (3.1)	0.3596	7.9 (3.2)
Baseline sUA level	7.9 (2.3)	8.8 (2.3)	<0.0001	8.4 (2.4)

- Variables included in the initial models on the basis of p<0.2 were febuxostat adherence, days on febuxostat therapy, index febuxostat dose, congestive heart failure, hypertension, type 2 diabetes, and baseline sUA level.
- Ten additional variables were added to the initial models: age, gender, race; presence of coronary artery disease, stroke, hyperlipidemia, peripheral vascular disease, chronic kidney disease, and hypertension; use of allopurinol in the pre-index period, and the RxRisk-V score.
  - RxRisk-V was chosen over Deyo-Charlson because of its applicability to a 180-day baseline period

Logistic regression model
- Among the 17 input variables, three were retained in the final model (Table 2):
  - febuxostat PDC (OR = 1.03, 95% CI 1.02 – 1.04, p<0.01)
  - baseline sUA level (OR = 0.84, 95% CI 0.77 – 0.91, p<0.01)
  - pre-index allopurinol use (OR = 0.72, 95% CI 0.48 – 1.10, p=0.13)

Linear regression model
- Five of the 17 input variables were retained in the final model (Table 2):
  - febuxostat PDC (PE = -0.040, 95% CI -0.046 – -0.033, p<0.01)
  - baseline sUA level (PE = 0.184, 95% CI 0.111 – 0.257, p<0.01)
  - age (PE = -0.025, 95% CI -0.041 – -0.009, p<0.01)
  - presence of congestive heart failure (PE = 0.512, 95% CI 0.090 – 0.935, p=0.02), and
  - allopurinol use in the pre-index period (PE = 0.253, 95% CI -0.102 – 0.609, p=0.16)

RESULTS

Table 2. Parameter estimates for multivariate logistic and linear model of sUA

	Parameter	Logistic model: Parameter Estimate	Logistic model: Adjusted Odds Ratio (95% CI)	Logistic model: *P*-value	Linear model: Parameter Estimate	Linear model: 95% Confidence Limits	Linear model: *P*-value
Initial Model (n=453)	Age	0.021	1.02 (1.00, 1.05)	0.0853	-0.033	(-0.054, -0.013)	0.0013
	Presence of congestive heart failure	-0.498	0.61 (0.34, 1.09)	0.0922	0.377	(-0.110, 0.864)	0.1286
	Febuxostat adherence following the index date (PDC)	0.028	1.03 (1.02, 1.04)	<.0001	-0.045	(-0.054, -0.035)	<.0001
	Baseline sUA level	-0.170	0.84 (0.77, 0.92)	0.0002	0.183	(0.107, 0.259)	<.0001
	Allopurinol use in the pre-index period	-0.358	0.70 (0.45, 1.08)	0.1056	0.258	(-0.108, 0.624)	0.1665
Final Model (n=453)	Age	-	-	-	-0.025	(-0.041, -0.009)	0.0021
	Presence of congestive heart failure	-	-	-	0.512	(0.090, 0.935)	0.0175
	Febuxostat adherence following the index date (PDC)	0.029	1.03 (1.02, 1.04)	<.0001	-0.040	(-0.046, -0.033)	<.0001
	Baseline sUA level	-0.180	0.84 (0.77, 0.91)	<.0001	0.184	(0.111, 0.257)	<.0001
	Allopurinol use in the pre-index period	-0.326	0.72 (0.48, 1.10)	0.1256	0.253	(-0.102, 0.609)	0.1621
Final Model (180 days pre-index; n=418*)	Age	-	-	-	-0.027	(-0.043, -0.010)	0.0015
	Presence of congestive heart failure	-	-	-	0.496	(0.022, 0.970)	0.0401
	Febuxostat adherence following the index date (PDC)	0.030	1.03 (1.02, 1.04)	<.0001	-0.040	(-0.047, -0.033)	<.0001
	Baseline sUA level	-0.190	0.83 (0.75, 0.91)	<.0001	0.170	(0.093, 0.247)	<.0001
	Allopurinol use in the pre-index period	-0.542	0.58 (0.38, 0.90)	0.0150	0.353	(-0.017, 0.722)	0.0614

*Only 418 of the 453 members in the training sample had a baseline sUA test result in the 180-day pre-index period

- Parameter estimates for the robustness test (180-day pre-index period) were similar to the 365-day base model.
- Febuxostat PDC and baseline sUA level remained the strongest predictors (p<0.01 for both), while age (p<0.01), congestive heart failure (p=0.04), and pre-index allopurinol use (p=0.06) had similar predictive ability (Table 2).

Model Performance
- Performance and fit were assessed for the both the logistic and linear models. The logistic model developed on the training dataset had a c-statistic of 0.73 and a Hosmer-Lemeshow goodness-of-fit statistic of 2.92 (p=0.94). This model was then validated in the holdout sample (n=225), and achieved similar performance metrics (c-statistic = 0.78; goodness of fit = 3.82, p=0.87) (Table 3).
- The final linear model had an R-square of 0.31 and an F-statistic of 40.3 (p<0.01); when run on the validation sample, the model achieved similar performance, with an R-square of 0.32 and an F-statistic of 103.4 (p<0.01) (Table 3).
- For the logistic model, ROC curves were generated for both the training and validation datasets, with both indicating strong model performance (Figure 1).

Figure 1. ROC Curves for the logistic model: training and validation samples

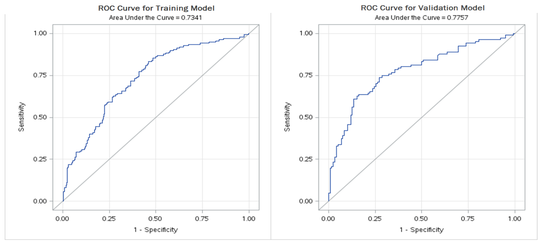

Table 3. Performance measures for predicting sUA goal attainment

	Training (n=453)	Validation (n=225)
Logistic model		
Goodness of fit statistic	2.92 (p=0.94)	3.82 (p=0.87)
C-statistic	0.725	0.776
Linear model		
R-square	0.3107	0.3168
F statistic	40.30 (p<0.01)	103.40 (p<0.01)

DISCUSSION

- Febuxostat adherence, baseline sUA level and prior allopurinol use were the main predictors of attaining sUA goal of <6 mg/dL, estimated by both logistic and linear regression models. Age and presence of CHF were found to be significant predictors in the linear model.
- These results are consistent with what has been reported in previous claims-based analyses:
  - Older patients were more likely to reach target sUA goal[2,5,6], and patients with a higher baseline sUA level were less likely to reach goal.[3]
- Febuxostat users in this study population had a higher number of comorbidities. A similar patient profile was seen in the Kim et al. study, where febuxostat users had comorbidities such as cardiovascular disease, heart failure, and chronic kidney disease.[3]
- This research suggests the importance of adherence on achieving sUA goal, even after accounting for other important characteristics that have been shown to influence sUA goal attainment. The effect of adherence over time, including dose adjustments in this population, needs to be examined in future studies.

LIMITATIONS

- Limitations common to studies using administrative claims data apply to this study. These include lack of certain information in the database (e.g., socioeconomic factors and health behavior information) and errors and omissions in claims coding. Generalizing the study findings to the US population should be approached with caution.
- Presence of multiple comorbidities in the study population indicates other factors that might have influenced treatment decisions. Exposure to febuxostat was determined by the presence of a prescription claim; this does not necessarily mean that the drug was taken.

CONCLUSIONS

- Among febuxostat users diagnosed with gout in a real world setting, adherence to febuxostat and baseline sUA level were the primary predictors of attaining sUA goal.
- These findings may help clinicians identify appropriate patients most likely to benefit from febuxostat treatment, and underscore the importance of medication adherence in this challenging patient population.

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