European Review for Medical and Pharmacological Sciences 2017; 21: 4186-4195

Potency on lowering serum uric acid in gout patients: a pooled analysis of registrative studies comparing febuxostat *vs.* allopurinol

M. CUTOLO[1], M.A. CIMMINO[1], F. PEREZ-RUIZ[2]

[1]Department of Internal Medicine, Research Laboratory and Academic Division of Clinical Rheumatology, University of Genova, Genoa, Italy
[2]Hospital Universitario Cruces and BioCruces Health Research Institute, Vizcaya, Spain

Abstract. – OBJECTIVE: Hyperuricemia leading to urate crystal formation in tissues represents the pathophysiological mechanism of gout. Guidelines recommend a therapeutic target of serum urate concentration (sUA) <6 mg/dL, or even lower (≤5 mg/dL) in patients with large deposits. We conducted an analysis with the aim to achieve additional insights into the urate-lowering efficacy of two xanthine oxidase inhibitors, allopurinol and febuxostat.

PATIENTS AND METHODS: This was a pooled analysis of phase III trials on allopurinol and febuxostat, including 4101 patients with gout and hyperuricemia. The efficacy outcomes were: mean reduction of sUA concentration from baseline; number of patients with target sUA levels (<6.0 mg/dL or ≤5 mgdL); time to reach target sUA levels.

RESULTS: Three registrative, phase III, randomized, multicenter, placebo-controlled/allopurinol-controlled trials assessing the efficacy of febuxostat, were included. The mean reduction of sUA concentration with any dose of febuxostat was higher (-2.92±2.87 mg/dL; -27%), with respect to placebo- (-0.62±1.84 mg/dL; -5%) and allopurinol-pooled groups (-2.41±2.20 mg/dL; -24%). Moreover, febuxostat showed a higher probability to achieve the recommended target sUA concentration than allopurinol [odds ratio: 2.43 (95% CI: 2.119-2.789) and 4.05 (95% CI: 3.41-4.82) for sUA levels <6 mg/dL and ≤5 mg/dL, respectively]. Patients on any-dose febuxostat reached target sUA faster than allopurinol-treated patients (86.04±71.47 *vs.* 98.76±70.88 days and 52.08±49.97 *vs.* 90.42±68.03 days for reaching sUA levels <6 mg/dL and ≤5 mg/dL, respectively; *p* <0.001 for both comparisons).

CONCLUSIONS: In patients with gout and hyperuricemia, febuxostat was significantly more effective and faster than allopurinol in obtaining the recommended target sUA levels, which were reached by a higher number of patients. Therefore, febuxostat was confirmed as an effective option for the treatment of hyperuricemia in gout.

Key Words
Allopurinol, Febuxostat, Gout.

Introduction

Uric acid is the ultimate catabolite of purine metabolism in humans and upper primates. It is a weak organic acid, that under physiologic conditions, exists mainly as a soluble monosodium urate (MSU)[1]. Therefore, hyperuricemia has been historically defined as serum urate concentration (sUA) equal or higher than 0.4 mmol/L corresponding to 6.8-7 mg/dL, above which MSU crystals start to form in body fluids[2]. An operative definition, based on the sUA target level of urate-lowering drugs, has been proposed by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines[3,4]. In particular, these guidelines generally recommended a therapeutic sUA below 0.36 mmol/L, corresponding to 6 mg/dL, or an even lower, below 0.3 mmol/L (corresponding to 5 mg/dL) in patients with uric acid deposits[3,4]. Hyperuricemia is nowadays considered to be more likely caused by inefficient renal or intestinal excretion rather than a result of overproduction from the hepatic purine degradation pathway[5,6].

Gout is the most common form of inflammatory arthritis and is caused by the nucleation of MSU crystals, which occurs predominantly in peripheral joints and subcutaneous tissues. If improperly treated, persistent hyperuricemia in gout can lead to frequent episodes of acute or chronic inflammation, and structural damage of joints[7]. Hyperuricemia and gout are also associated with cardiovascular and renal diseases, and other comorbid conditions[8-10]. Recent studies[11] suggest that developed countries have a higher burden of hyperuricemia and gout than developing countries, with increasing prevalence and incidence of the disease. Genetic predisposition as well as socioeconomic and lifestyle factors (alcohol, seafood, red meat, sugar-sweetened beverages) are associated to increased risk of hyperuricemia and gout[11].

Corresponding Author: Marco Amedeo Cimmino, MD; e-mail: cimmino@unige.it

Due to the rising burden and the adverse impact of hyperuricemia and gout, there is a critical need to assess effective control to target sUA. Among the main urate-lowering mechanisms, xanthine oxidase inhibitors (XOIs), uricosurics and uricases are considered as first-choice medications[12,13]. Febuxostat (Adenuric®, Menarini International, Florence, Italy) is a non-purine XOI approved in the last decade for the management of hyperuricemia in patients with gout that showed different pharmacokinetic and pharmacodynamic properties compared with allopurinol, a purine analog XOI[14-16].

In order to achieve additional insights into the urate-lowering efficacy of two different XOIs, allopurinol and febuxostat, we conducted an analysis from febuxostat registrative clinical trials.

Patients and Methods

This was a pooled analysis on registrative, phase III, double-blind, randomized, actively controlled, prospective trials comparing febuxostat and allopurinol for the treatment of hyperuricemia in patients with gout and hyperuricemia. The efficacy outcomes considered for this analysis were: gross reduction of sUA from the baseline value; number and percentage of patients reaching the target sUA levels (sUA <6 mg/dL or ≤5 mg mg/dL); time to reach the targets sUA (<6 mg/dL or ≤5 mg mg/dL). The daily dosage of the urate-lowering therapy applied in these studies were: 80 mg, 120 mg, 240 mg for febuxostat, 100 mg and 300 mg for allopurinol in the APEX (C02-009) study[17]; 80 mg and 120 mg for febuxostat, 300 mg for allopurinol in the FACT (C02-010) study[18]; and 40 mg and 80 mg for febuxostat, 200 mg and 300 mg for allopurinol in the CONFIRMS (F-GT06-153) study[19]. Dose reductions of allopurinol to the daily dosage of 100 mg or 200 mg were applied in patients with clinically significant chronic kidney disease (CKD)[20]. The determined time point to assess the efficacy outcomes was the end of each study: 28 weeks for APEX, 52 weeks for FACT and 26 weeks for CONFIRMS. sUA was measured in a blinded fashion at each study visit performed: at week 2 and 4, monthly thereafter for the FACT study; at week 2, 4, 6, 8, and monthly thereafter for the APEX study; at month 2, 4 and 6 for the CONFIRM study. The occurrence of adverse events (AEs), including serious AEs, was also investigated.

Statistical Analysis

The efficacy evaluation was based on an intention-to treat analysis (ITT population). The full analysis set (ITT Population) included all randomized patients who had taken at least one dose of study medication and had undergone at least one efficacy assessment for the primary efficacy outcome after baseline.

All efficacy outcome data derived from the studies included in the analysis were merged, taking into account the number of subjects. The data were reported individually per study and as weighted averages taking into account the number of subjects enrolled in each study. Cumulative occurrence of clinical outcome was evaluated by Kaplan-Meier analysis. Time (days) to reach the target serum urate levels was calculated based on the time from study enrollment to the visit date when the serum urate levels was <6.0 mg/dL for the first time. The survival curves by presence of target serum urate levels were compared using the log-rank test. We used proportional hazards regression models to assess the effect of baseline patient characteristics on time to reach the target serum urate levels. The Cox regression model was used to identify independent and significant predictors of time to reach the target serum urate levels <6.0 mg/dL.

Data were analyzed using ANOVA including baseline sUA values, gender and age as covariates and treatment as factor. ANOVA was validated by Tukey's HSD or independent samples *t*-test for normally distributed data. The same method used for the analysis of the end of treatment data was applied to the data obtained at the intermediate visits.

Frequency tables were provided at the relevant time-point for the rate of responders (sUA level ≤5 mg.0 mg/dL or sUA <6.0 mg/dL). Treatment responders were analyzed using a binary logistic regression model including treatment, gender, baseline values of sUA and age as covariate. The same descriptive statistics applied for the whole population, on changes from the baseline values in the sUA values, was also applied by stratifying in subgroup category. The impact of heterogeneity was summarized by the I2 statistics. Values of I2 close to 0% represent small heterogeneity, I2 >40% was the criterion for the use of a random-effect model. The analysis was performed in SAS (version 9.02). p <0.05 was considered statistically significant.

Results

Three phase III, randomized, multicenter, placebo-controlled/allopurinol-controlled studies assessing the efficacy of febuxostat were included in this an analysis (Table I).

Table I. Pooled Dataset: three randomized, phase III studies.

Study ID number	Study title	Treatment period	Treatment group (number of patients)								Number of patients/ study
			Placebo	Allopurinol 100 mg/ day	Allopurinol 200 mg/ day	Allopurinol 300 mg/ day	Febuxostat 40 mg/ day	Febuxostat 80 mg/ day	Febuxostat 120 mg/ day	Febuxostat 240 mg/ day	
C02-00917 multicenter,	A phase III, randomized, Allopurinol and placebo-controlled study assessing the safety and efficacy of oral Febuxostat in subjects with gout (APEX)	28 weeks	134	10	0	258	0	267	269	134	1072
C02-01018	A phase III, randomized, multicenter study comparing the safety and efficacy of oraltmx-67 versus Allopurinol in subjects with gout (FACT)	52 weeks	0	0	0	253	0	256	251	0	760
F-GT06-15319	A phase III, randomized, multicenter, double-blind, Allopurinol-controlled study assessing the efficacy and safety of oral Febuxostat in subjects with gout (CONFIRM)	6 months	0	0	145	611	757	756	0	0	2269
Pooled	—	—	134	10	145	1122	757	1279	520	134	4101

Table II. Demographic and baseline features (all treated patients, N=3967).

Parameter	Febuxostat (n=2690)	Allopurinol (n=1277)	*p*-value
Age (mean±SD)	52.3 ± 11.88	52.4 ± 12.03	0.764
Gender, n (%)			
Female	139 (5.2)	76 (6.0)	0.308
Male	2551 (94.8)	1201 (94.0)	
Race, n (%)			
Caucasian	2169 (80.6)	1029 (80.6)	0.969
Other	521 (19.4)	248 (19.4)	
sUA (mg/dL, mean ±SD)	8.8 ± 1.89	8.8 ± 1.86	0.738

SD: standard deviation

All studies included patients with gout, defined by the preliminary ACR criteria[21], and patients with hyperuricemia, defined as sUA≥8 mg/dL. The total number of patients analyzed for the efficacy outcomes was 4101. Of them, 3967 (96.7%) were treated with an active substance (2690 or 65.6% with febuxostat, 1277 or 31.1% with allopurinol). The population recruited had a high prevalence of men (3752 out of 3967, 94.6%) and its mean age was 52.4 years. No relevant differences between active agent-treated groups in demographics characteristics, life style, diet, and baseline sUA were observed (Table II).

Serum Urate Reduction from Baseline

The mean baseline sUA concentration in all analyzed patients (n=4101) was 8.86±2.17 mg/dL. The variations from baseline in sUA levels (ΔsUA) evaluated for each pooled treatment group at the end of each study (considering all treated patients with at least one post-baseline evaluation) are reported in Table III. Overall, the pooled analysis showed that the reduction of sUA concentration with febuxostat was higher (-2.92±2.87 mg/dL; -27%), in comparison with the placebo group (-0.62±1.84 mg/dL; -5%) and the allopurinol group (-2.41±2.20 mg/dL; -24%). There was a statistical heterogeneity among the included trials (I^2=86.97%; p <0.001) and a random effects model was used in this pooled analysis.

Percentage of Patients With Target sUA Levels (<6.0 mg/dL or ≤5 mg/dL)

Tables IV and V summarize for each treatment group the number of patients reaching the therapeutic target sUA <6 mg/dL and sUA ≤5 mg/dL, respectively. Among febuxostat-treated patients, 60.5% attained the sUA level <6.0 mg/dL compared with 38.7% of the allopurinol-treated patients and 3% of the placebo group (p <0.001; Figure 1). Interestingly, 41.5% of the febuxostat

Table III. Mean changes from baseline in serum urate levels (ΔsUA) following both treatments.

Treatment group	Number of patients (n=4047)	ΔsUA (mg/dL)	ΔsUA in pooled treatment group (%) and mg/dL
Placebo	134	-0.62±1.84 -0.62±1.84	(-5%) -0.62 ±1.84
Allopurinol 100 mg	10	-0.68±2.28	(-24%) -2.41±2.20
Allopurinol 200 mg	142	-2.63±1.96	
Allopurinol 300 mg	1108	-2.4±2.23	
Febuxostat 40 mg	745	-2.79±2.02	(-27%) -2.92±2.87
Febuxostat 80 mg	1254	-3.03±2.86	
Febuxostat 120 mg	520	-3.08±3.37	
Febuxostat 240 mg	134	-2.05±4.28	

Data are expressed as mean±standard deviation; Heterogeneity test: I^2=86.97%; p <0.001

Table IV. Number of patients with serum urate levels (sUA) <6 mg/dL. Chi Square test *p*-value < 0.001.

Treatment group	Number (and percentage) of patients with target sUA level		Number of patients (n=4047)
	<6 mg/dL	≥6 mg/dL	
Placebo	**4 (3%)**	**130 (97%)**	**134**
Allopurinol 200 mg	43 (28.3%)	109 (71.7%)	152
Allopurinol 300 mg	444 (40.1%)	664 (59.9%)	1108
Total Allopurinol	**487 (38.7%)**	**773 (61.3%)**	**1260**
Febuxostat 40 mg	325 (43.6%)	420 (56.4%)	745
Febuxostat 80 mg	814 (64.9%)	440 (35.1%)	1254
Febuxostat 120 mg	364 (70%)	156 (30%)	520
Febuxostat 240 mg	102 (76.1%)	32 (23.9%)	134
Total Febuxostat	**1605 (60.5%)**	**1048 (39.5%)**	**2653**

Table V. Number of patients with serum urate levels (sUA) ≤5 mg/dL. Chi Square test *p*-value < 0.001.

Treatment group	Number (and percentage) of patients with target sUA level		Number of patients (n=4047)
	≤5 mg/dL	>5 mg/dL	
Placebo	3 (2.2%)	131 (97.8%)	134
Allopurinol	188 (14.9%)	1072 (85.1%)	1260
Febuxostat	1102 (41.5%)	1551 (58.5%)	2653

patients reached the target sUA ≤5.0 mg/dL *vs.* 14.9% of the allopurinol group and 2.2% of the placebo group (p <0.001; Figure 1). In the efficacy outcome "number of patients with target sUA levels ≤5.0 mg/dL", there was statistical heterogeneity among the included trials (I^2 = 93.87%; p <0.001), and a random effects model was used in this pooled analysis.

In addition, the percentage of patients with a sUA <6 mg/dL was significantly (p <0.001) higher in the group treated with febuxostat than in those assuming placebo (odds ratio 47.0, 95% CI: 17.25-127.82) or allopurinol (odd ratio 2.5, 95% CI: 2.14-2.84). Also, in the allopurinol pooled group, the percentage of patients with a sUA <6 mg/dL was significantly higher than in the placebo group.

Overall, febuxostat showed a higher rate of target sUA achievement, compared to allopurinol (odds ratio: 2.43 [95% CI: 2.119-2.789] and 4.05 [95% CI: 3.41-4.82], respectively for sUA levels <6 mg/dL and ≤5 mg/dL).

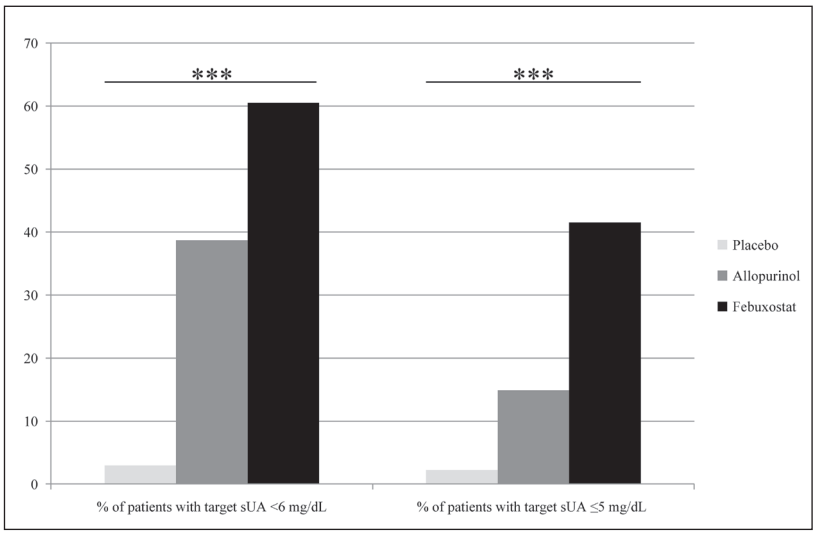

Figure 1. Proportion of patients reaching target sUA level in each pooled treatment group (≤5 mg/dL and <6.0 mg/dL). *** p≤0.001.

Table VI. Time to reach target serum urate levels <6 mg/dL in active compound-treated patients. Data are expressed as mean±standard deviation; ANOVA *p*-value <0.001.

Treatment group	Number of patients with target sUA level ≤5 mg/dL (n=2055)	Time to reach sUA ≤5 mg/dL (days)	Time to reach sUA ≤5 mg/dL (days) in pooled treatment group
Allopurinol 100 mg	—	—	90.42±68.03
Allopurinol 200 mg	18	117.39±45.63	
Allopurinol 300 mg	348	88.26±67.66	
Febuxostat 40 mg	215	94.26±45.98	52.08±49.97
Febuxostat 80 mg	887	61.14±49.65	
Febuxostat 120 mg	465	23.9±30.66	
Febuxostat 240 mg	122	14.81±4.53	

Table VII. Time to reach target serum urate levels ≤5 mg/dL in active compound-treated patients. Data are expressed as mean±standard deviation; ANOVA *p*-value <0.001.

Treatment group	Number of patients with target sUA level <6 mg/dL (n=2690)	Time to reach sUA≤6 mg/dL (days)	Time to reach sUA<6 mg/dL (days) in pooled treatment group
Allopurinol 100 mg	2	77.5±99.7	98.76±70.88
Allopurinol 200 mg	54	127.37±55.27	
Allopurinol 300 mg	664	96.5±71.53	
Febuxostat 40 mg	426	118.38±55.95	86.04±71.47
Febuxostat 80 mg	971	88.36±70.55	
Febuxostat 120 mg	458	52.33±69.18	
Febuxostat 240 mg	115	80.78±71.52	

Time to Reach the Target sUA (<6.0 mg/dL or ≤5 mg/dL)

In patients treated with active agents, the mean (± standard deviation) time to reach target sUA level <6 mg/dL was: 86.0±71.46 days in the febuxostat pooled group and 98.8±70.9 days in the allopurinol pooled group (Table VI). Of note, to reach target sUA level ≤5 mg/dL, febuxostat-treated patients took 52.1±50.0 days whereas allopurinol-treated patients took 90.4±68.0 days (Table VII). Febuxostat resulted significantly (p <0.001) more effective than allopurinol at shortening the time to achieve target sUA levels, both <6 mg/dL and ≤5 mg/dL (Figure 2). Only patients that reached the target sUA level (<6 mg/dL or ≤5 mg/dL) were considered in this analysis.

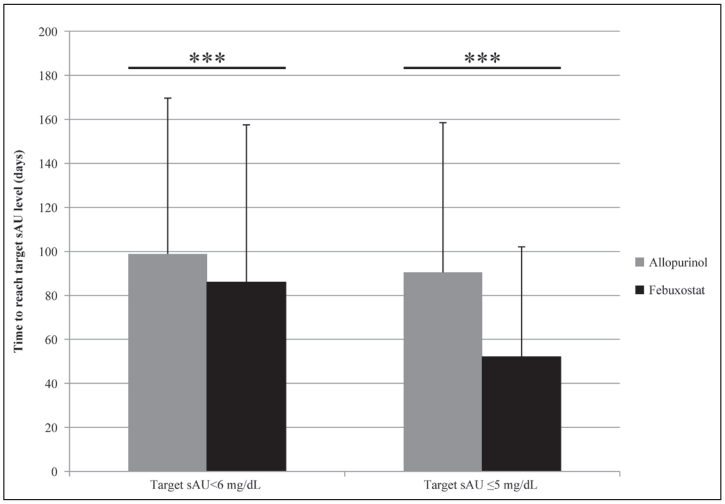

Figure 2. Time to achieve target serum urate (sUA) level in each pooled treatment group (≤5 mg/dL or <6.0 mg/dL). Error bars represent standard deviation. *** p≤0.001.

The Kaplan-Meier curves analysis for each treatment group, based on the estimating conditional probabilities that the sUA <6 mg/dL (Figure 3a) or sUA ≤5 mg/dL (Figure 3b) events occurred, were also performed.

Safety

Overall, 829 out of 4047 patients (20.5%) reported at least one AE. Analyzing each treatment group, 545/2653 (20.5%) febuxostat-treated patients, 253/1260 (20.1%) allopurinol-treated patients, and 31/134 (23.1%) placebo-treated patients reported at least one AE. The number of AEs of any grade in the study population was 1432, of which 45 were considered as definite AEs. Of the 957 AEs, which occurred in the febuxostat group, 31 were definite (3.2%); of the 432 in the allopurinol group, 14 were definite (3.2%); of the 43 in the placebo group, 0 were definite. Fifteen out of 1432 AEs (1%) were serious: 8 occurred in febuxostat-treated patients and 7 occurred in allopurinol-treated patients.

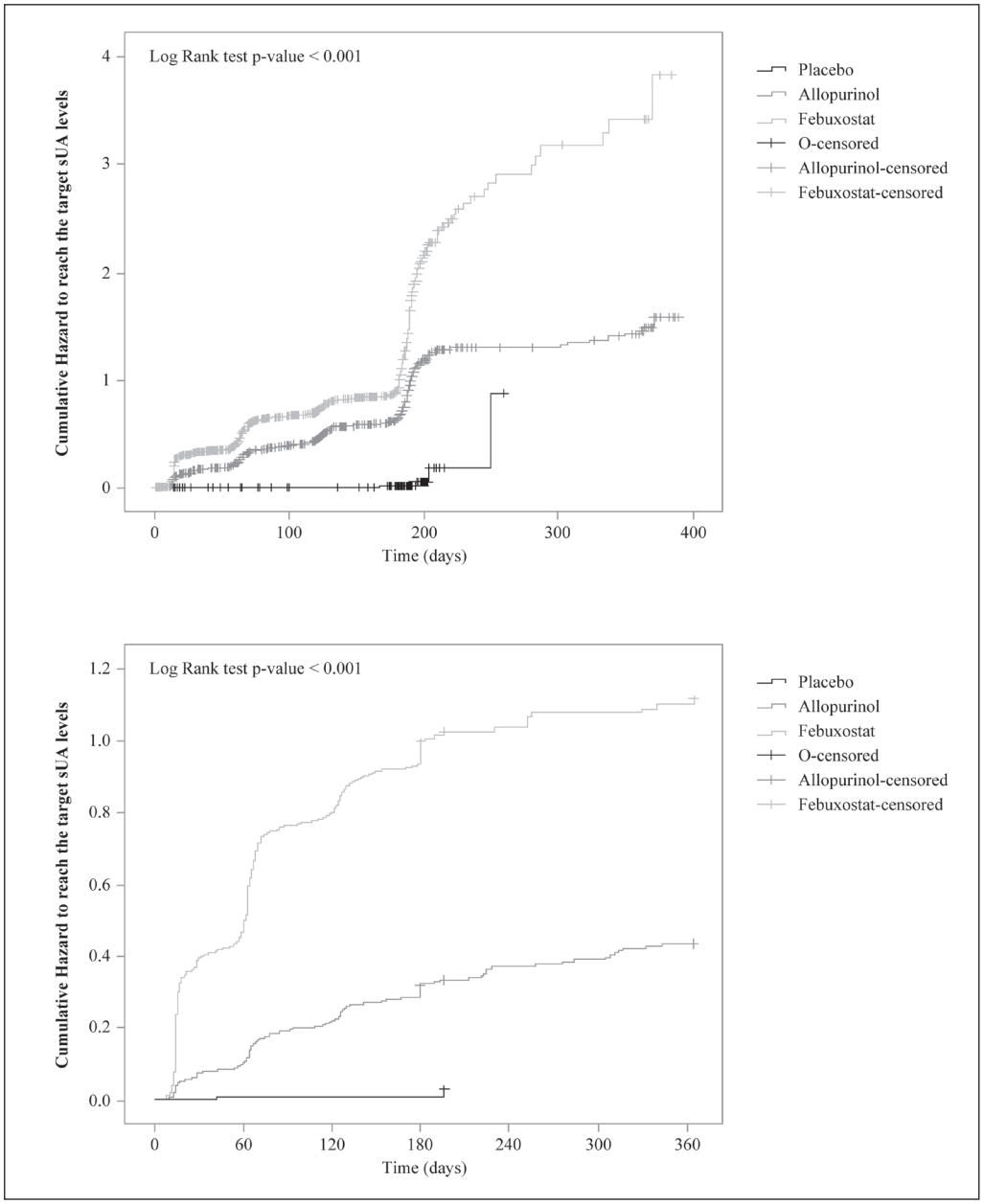

Figure 3. Kaplan-Meier analysis of the probability to reach the target sUA for each pooled treatment group. **A**, sUA <6 mg/dL; **B**, sUA ≤5 mg/dL.

Discussion

Overall, this analysis of pooled studies confirms that febuxostat achieved higher reduction of sUA concentration and higher rates of patients at target sUA levels (both <6 mg/dL and ≤5 mg/dL) compared with allopurinol and placebo, according to previous analyses[22-26]. In particular, Faruque et al[24] reported that patients receiving febuxostat were more likely to achieve a serum uric acid of <6 mg/dl than allopurinol recipients. Our analysis showed that this was true also for sUA concentrations <5 mg/dL. In addition, patients treated with febuxostat reached target sUA levels of <6 mg/dL and ≤5 mg/dL in 8-day less and 38-day less, respectively, than allopurinol-treated patients. For the last decades, the treatment of gout has mainly relied on allopurinol prescription, as the use of uricosuric medications is not commonly available or prescribed. Febuxostat was approved in 2008 in Europe and 2009 in the US, to treat hyperuricemia of gout when urate deposition has occurred, becoming a real alternative to allopurinol. Comparative studies on the efficacy and safety of these two drugs are still useful to provide information for the treatment of gout.

In the present investigation, the daily dosage of the urate-lowering therapy ranged from 40 mg to 120 mg (with only a small number with the unlabeled 240 mg dose) for febuxostat, and 300 mg for allopurinol (a small number of patients with CKD treated with lower doses). Consistently, in the pooled data from the identified trials, the most represented daily dose in the febuxostat-treated group was 80 mg (1279 out of 2690; 47%), and in the allopurinol-treated group was 300 mg (1122 out of 1277; 88%). The approved doses of febuxostat are 40 mg and 80 mg daily in the US market, and 80 mg to 120 mg daily in the European market[22]. The 240 mg/day dose did not show overall additional benefit to the approved dosages concerning rate of target sUA. Allopurinol is most commonly prescribed in clinical practice with dosage not exceeding 300 mg/day[27], although higher doses are worldwide approved[3,4].

Almost similar observations were made by Singh et al[25], in a recent retrospective study including data of 2015 patients treated with febuxostat and 14025 allopurinol-treated patients from a large US commercial and medicare advantage health plan. The authors reported that the time to achieve target sUA levels <6 mg/dL and ≤5 mg/dL in the febuxostat group was respectively 31 and 29 days shorter than in the group receiving allopurinol[25]. There is a clear and linear pharmacodynamic dose-dependent effect of febuxostat on sUA levels in the pooled analysis, as nicely shown from results obtained by using 40 mg/day, 80 mg/day and 120 mg/day doses. Shorter time to reach target sUA level <6 mg/dL was observed in the 120 mg/day febuxostat-treated group, in comparison with the 80 mg/day and 40 mg/day febuxostat-treated groups. Also, the urate-lowering effect of allopurinol was overall dose-dependent, with the greatest effect observed in patients assuming the highest dosage of 300 mg/day. Noteworthy, based on the potential risk of adverse events in patients with CKD[28], the guidelines suggest to reduce the initial doses of allopurninol and careful step-up increases in patients with renal insufficiency[29]. By contrary, the pharmacokinetics of febuxostat is not influenced by mild to moderate CKD[20]. Finally, gout is a common condition and new studies suggest continuous changes in the epidemiological characteristics, as well interesting further methods for counting monosodium urate crystals in the synovial fluid of patients with gout[30,31].

Conclusions

In spite of some differences in the design of the three studies selected for this pooled analysis, febuxostat resulted significantly more effective than allopurinol in reducing sUA levels from baseline and in achieving the target sUA both <6.0 mg/dL and the most stringent ≤5 mg/dL for severely affected patients.

Acknowledgements

We thank Dr. Giorgio Reggiardo (Mediservice srl) for the statistical analysis. Content Ed Net provided editorial assistance, with the helpful contribution of Luca Giacomelli, Ph.D. Editorial assistance was supported by Menarini International Operations Luxemburg S.A..

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Barr WG. Uric Acid. In: Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 165.

2) Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum 1972; 15: 189-192.
3) Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen TL, Janssens H, Lioté F, Mallen C, Nuki G, Perez-Ruiz F, Pimentao J, Punzi L, Pywell T, So A, Tausche AK, Uhlig T, Zavada J, Zhang W, Tubach F, Bardin T. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76: 29-42.
4) Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Lioté F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R; American College of Rheumatology 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012; 64: 1431-1446.
5) Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016; 388: 2039-2052.
6) Perez-Ruiz F, Calabozo M, Erauskin GG, Ruibal A, Herrero-Beites AM. Renal underexcretion of uric acid is present in patients with apparent high urinary uric acid output. Arthritis Rheum 2002; 47: 610-613.
7) Dalbeth N, Stamp L. Hyperuricemia and gout: time for a new staging system? Ann Rheum Dis 2014; 73: 1598-1600.
8) Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, Manolis AJ, Perez-Ruiz F, Mancia G. Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33: 1729-1741.
9) Mancia G, Grassi G, Borghi C. Hyperuricemia, urate deposition and the association with hypertension. Curr Med Res Opin 2015; 31: 15-19.
10) Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012; 125: 679-687.
11) Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015; 11: 649-662.
12) Sivera F, Andrés M, Carmona L, Kydd AS, Moi J, Seth R, Sriranganathan M, van Durme C, van Echteld I, Vinik O, Wechalekar MD, Aletaha D, Bombardier C, Buchbinder R, Edwards CJ, Landewé RB, Bijlsma JW, Branco JC, Burgos-Vargas R, Catrina AI, Elewaut D, Ferrari AJ, Kiely P, Leeb BF, Montecucco C, Müller-Ladner U, Ostergaard M, Zochling J, Falzon L, van der Heijde DM. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2014; 73: 328-335.
13) Kiltz U, Smolen J, Bardin T, Cohen Solal A, Dalbeth N, Doherty M, Engel B, Flader C, Kay J, Matsuoka M, Perez-Ruiz F, da Rocha Castelar-Pinheiro G, Saag K, So A, Vazquez Mellado J, Weisman M, Westhoff TH, Yamanaka H, Braun J. Treat-to-target (T2T) recommendations for gout. Ann Rheum Dis 2016; 76: 632-638.
14) Khosravan R, Kukulka MJ, Wu JT, Joseph-Ridge N, Vernillet L. The effect of age and gender on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. J Clin Pharmacol 2008; 48: 1014-1024.
15) Jansen TL, Richette P, Perez-Ruiz F, Tausche AK, Guerne PA, Punzi L, Leeb B, Barskova V, Uhlig T, Pimentão J, Zimmermann-Górska I, Pascual E, Bardin T, Doherty M. International position paper on febuxostat. Clin Rheumatol 2010; 29: 835-840.
16) Frampton JE. Febuxostat: a review of its use in the treatment of hyperuricemia in patients with gout. Drugs 2015; 75: 427-438.
17) Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher C, Joseph-Ridge N. 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: 1540-1548.
18) Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353: 2450-2461.
19) Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, Lademacher C. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther 2010; 12: R63.
20) Chinchilla SP, Urionaguena I, Perez-Ruiz F. Febuxostat for the chronic management of hyperuricemia in patients with gout. Expert Rev Clin Pharmacol 2016; 9: 665-673.
21) Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977; 20: 895-900.
22) Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. Cochrane Database Syst Rev 2012; 11: CD008653.
23) Ye P, Yang S, Zhang W, Lv Q, Cheng Q, Mei M, Luo T, Liu L, Chen S, Li Q. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. Clin Ther 2013; 35: 180-189.
24) Faruque LI, Ehteshami-Afshar A, Wiebe N, Tjosvold L, Homik J, Tonelli M. A systematic review and meta-analysis on the safety and efficacy of febuxostat versus allopurinol in chronic gout. Semin Arthritis Rheum 2013; 43: 367-375.
25) Singh JA, Akhras KS, Shiozawa A. Comparative effectiveness of urate lowering with febuxostat versus allopurinol in gout: analyses from large U.S. managed care cohort. Arthritis Res Ther 2015; 17: 120
26) Borghi C, Perez-Ruiz F. Urate lowering therapies in the treatment of gout: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2016; 20: 983-992.
27) Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, Nuki G. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 2008; 67: 960-966.

28) Lupton GP, Odom RB. The allopurinol hypersensitivity syndrome. J Am Acad Dermatol 1979; 1: 365-374.
29) Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984; 76: 47-56.
30) Zampogna G, Andracco R, Parodi M, Cutolo M, Cimmino MA. Has the clinical spectrum of gout changed over the last decades? Clin Exp Rheumatol 2012; 30: 414-416.
31) Montagna P, Brizzolara R, Ferrone C, Cutolo M, Paolino S, Cimmino MA. A method for counting monosodium urate crystals in synovial fluid. Reumatismo 2015; 67: 29-32.