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Urate lowering therapies in the treatment of gout: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: In patients with gout, serum uric acid (sUA) concentrations should be lowered at least below the target of 6 mg/dL (even below 5 mg/dL in patients with severe gout). To achieve this goal, urate lowering medications (ULMs) should be considered. Currently-used ULMs include xanthine-oxidase inhibitors such as allopurinol, febuxostat, as well as available uricosuric agents. However, evidence comparing these agents remains scant.

We have conducted a systematic review and meta-analysis to retrieve evidence on the clinical trials on the above-mentioned drugs in the treatment of gout.

MATERIALS AND METHODS: The following efficacy outcomes were considered in the meta-analysis: (1) % of patients meeting the therapeutic target for sUA level (<6 mg/dl) and (2) percentage reduction in sUA concentration at the end of the study compared with baseline values. An explorative analysis on safety was also conducted.

RESULTS: In total, 16 papers concerned febuxostat, 15 allopurinol, 4 benzbromarone and none involved probenecid.

Overall, 70.7% of patients reached the target of sUA with febuxostat therapy; the reduction in sUA was 45.3%. Corresponding figures with allopurinol were 44.4% and 33.8%, respectively. The number of patients on benzbromarone (N=129) was too low to retrieve definitive findings. The advantage for febuxostat over allopurinol was evident also in patients with renal dysfunction. Safety analysis favored febuxostat over allopurinol (OR 0.85; 95% CI: 0.75-0.97).

CONCLUSIONS: On the basis of the reported data, febuxostat can play a major role in the treatment of hyperuricaemia and gout. Febuxostat is a suitable pharmacological option for first line treatment of gout, given its established efficacy and safety, documented in a high number of clinical studies and in daily practice.

Key Words:
Gout, Urate lowering therapy, Febuxostat, Allopurinol, Benzbromarone.

Introduction

Gout represents the most frequent inflammatory joint disease in the general population[1], and it largely contributes to healthcare burden[2]. Monosodium urate deposition due to longstanding hyperuricemia leading to urate crystal formation in tissues represents the pathophysiological mechanism of gout[3]. Recent evidence suggests that the mean serum urate (sUA) levels in the general population are increasing worldwide, due to a number of factors such as the "epidemic" of overweight and obesity in developed countries, as well as the shifts in diet with overconsumption of foods rich in purines, alcohol, fructose-sweetened soft drinks[4-6], in addition to the use of diuretic drugs to treat comorbid conditions. Of note, patients with gout often present comorbid conditions in addition to obesity, such as cardiovascular diseases, arterial hypertension, diabetes mellitus, and chronic kidney disease (CKD)[7]. There is evidence suggesting that increased sUA may be a risk factor also of these conditions[8-10]. The management of hyperuricemia thus represents the key strategy in the treatment of gout and, potentially, of associated diseases.

A number of guidelines are available to improve gout management and reduce hyperuricemia[11-14]. In particular, sUA should be generally lowered below the target of 6 mg/dL, and even further below 5 mg/dL in patients with severe gout[11,12]. To achieve this goal, urate lowering therapies (ULTs) should be considered and discussed with patients prescribed as soon as diagnosis of gout is established. Currently-used ULTs include xanthine-oxidase inhibitors such as allopurinol, febuxostat, and topiroxostat (labelled only in Japan), as well as uricosuric agents, such as benzbromarone and probenecid. However, evidence directly comparing these two classes of drugs remains scant.

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We have conducted a systematic review and meta-analysis to retrieve evidence on the clinical trials on the most widely-used of the above-mentioned drugs in the treatment of gout.

Materials and Methods

Literature searches were conducted on PubMed with the following keywords: hyperuricemia, gout, febuxostat, allopurinol, benzbromarone, and probenecid as labelled ULMs at the moment of the search. It included papers published through March 2015 with no lower date limit on the search results. The studies included in the analysis were both interventional and non-interventional studies of prospective and retrospective nature; we also considered studies with naturalistic design.

The criteria for including studies in the present review were as follows: baseline hyperuricemic (sUA ≥ 7.0 mg/dl) adults (aged ≥18 years), with gout, and at least one of the study outcomes assessed after treatment with one of the drugs commercialized at the time of analysis for the treatment of gout: allopurinol, benzbromarone, febuxostat or probenecid. Efficacy outcomes considered for this review were: (1) proportion of patients meeting the therapeutic target for sUA level, defined as < 6 mg/dl, and (2) percentage reduction in sUA concentration at the end of the study compared with baseline values. Papers on combination of two ULTs were not considered. An explorative analysis on safety was also conducted.

Statistical Analysis

Proportions of patients reaching target were obtained from each treatment arm or subgroup reported in the studies and a pooled estimate was calculated via a random-effects logistic regression, according to a Binomial-Normal model. Summary estimates of mean sUA reduction percentage were also obtained pooling the raw percentage reduction means by fitting an inverse-variance weighted, random-effects, linear model. These two analyses were conducted separately for each drug.

Reported treatment comparison effect-sizes between allopurinol and febuxostat, when available, were pooled in terms of odds-ratios, for patients-at-target rates, and mean differences, for sUA reduction percentage, respectively; the summary effect-size was obtained using a weighted random-effects linear model heterogeneity was assessed when appropriate with the Pearson χ^2 and evaluated with the I^2 statistics; I^2 >50% was taken as the criterion for the use of a random-effect model. All these analyses were performed on overall rates and overall weighted mean reductions, thus mixing reported outcomes for different dosage arms when necessary (9 out of 16 studies, n=9718, investigated recommended doses of febuxostat 80 or 120 mg/day as approved in Europe). Between-study variances were estimated with the Restricted Maximum Likelihood Estimator. Analyses were performed with the *metafor* package in the R Statistical Computing environment [see www.R-project.org/].

Retrieved Papers: an Overview

In total, 37 potentially relevant study publications were retrieved and the full-text was examined for compliance with eligibility criteria. Fourteen studies failed to meet the criteria (7 were duplicate reports of the same study, 6 did not report the outcomes of interest, 1 assessed only a combined treatment). Among the remaining 23 studies: 8 were related to febuxostat only; 8 included an allopurinol and a febuxostat treatment arm; 3 were related to allopurinol only; 4 included both an allopurinol and a benzbromarone treatment arm.

In total, 16 papers concerned febuxostat therapy, 15 allopurinol treatment, 4 benzbromarone therapy and none involved probenecid. An outline of the main characteristics and results collected from the identified studies on febuxostat and allopurinol is provided in Tables I and II.

Efficacy outcomes

Febuxostat

All the 16 studies including febuxostat treatment arms reported the proportion of patients reaching therapeutic target. Overall, the pooled analysis showed that, in the identified studies, 70.7% of patients reached the target of sUA with febuxostat therapy (Figure 1).

Eight studies reported the percentage reduction of sUA concentration with febuxostat, overall showing a 45.3% reduction at the end of the study with respect to baseline values (Figure 2).

Allopurinol

Fourteen studies reported the proportion of patients who reached the target level of sUA with allopurinol. Overall, the pooled percentage of

Table I. Summary of the main data collected from the interventional studies*.

Drug	Number of studies	Time span (years)	Total n. of patients	% patients at SUA target (6 mg/dl)	Average sUA reduction
Allopurinol (dose was ≤300 mg/day in 7/8 studies, with 1622 subjects)	8	2005-2014	1667	41.61%	33-36%
Febuxostat (dose was ≤ 120 mg/day, n=3635)	10	2005-2014	3635	65.03%	33.8-52%

*Data not referred to the whole body of studies, because not always available. Data on benzbromarone are not reported as only very few studies are available on this drug (n=129 patients treated with benzbromarone)

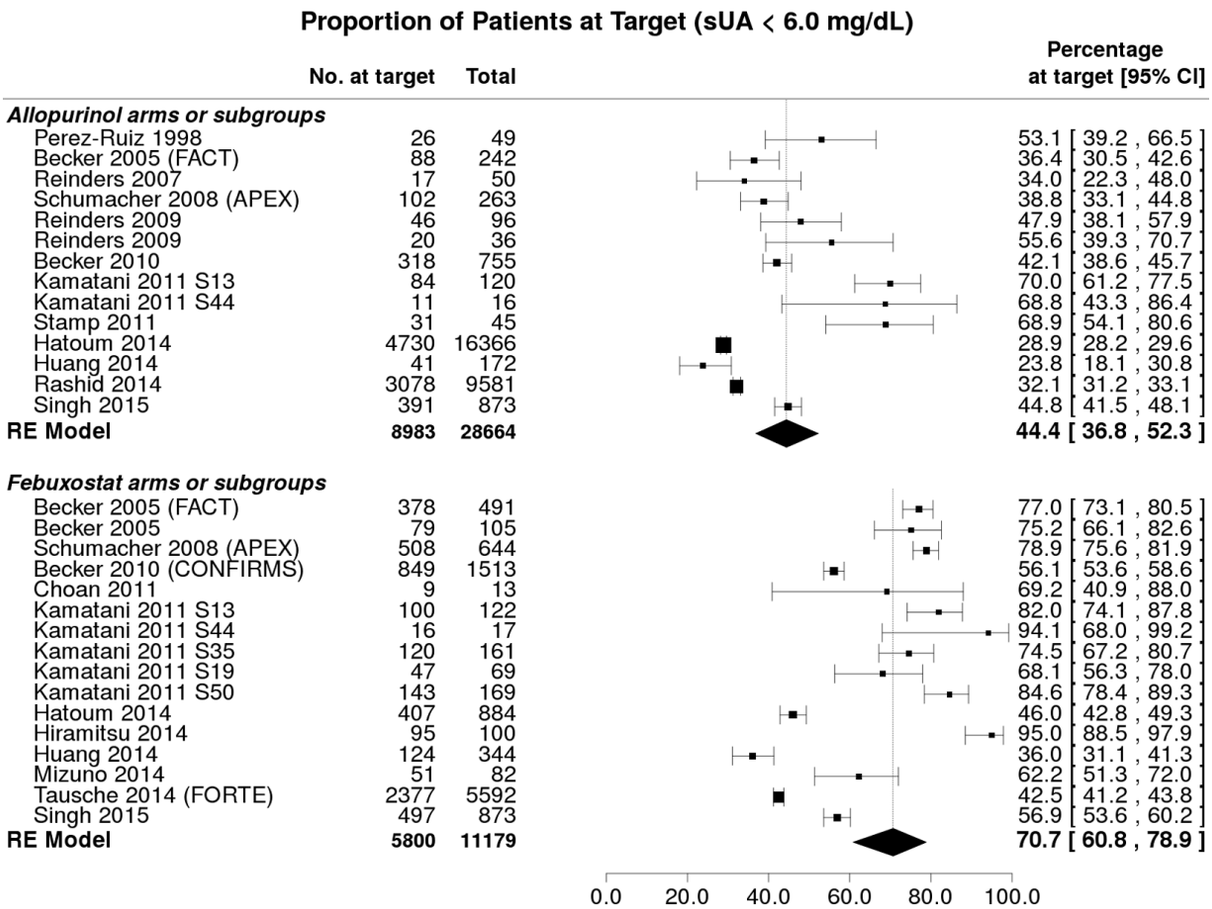

Figure 1. Pooled analysis of proportion of patients who achieved target values of sUA (≤ 6 mg/dl).

Table II. Summary of the main data collected from observational studies.

Drug	Number of studies	Time span (years)	Total n. of patients	% patients at SUA target	Average sUA reduction
Allopurinol (dose was ≤300 mg/day in >24900 patients)	3	2014-2015	26820	30.57	NA
Febuxostat (dose was ≤ 120 mg/day, n=7544)	6	2011-2015	7544	45.54	44.7 (1 study)

*Data not referred to the whole body of studies, because not always available. NA: Not available;

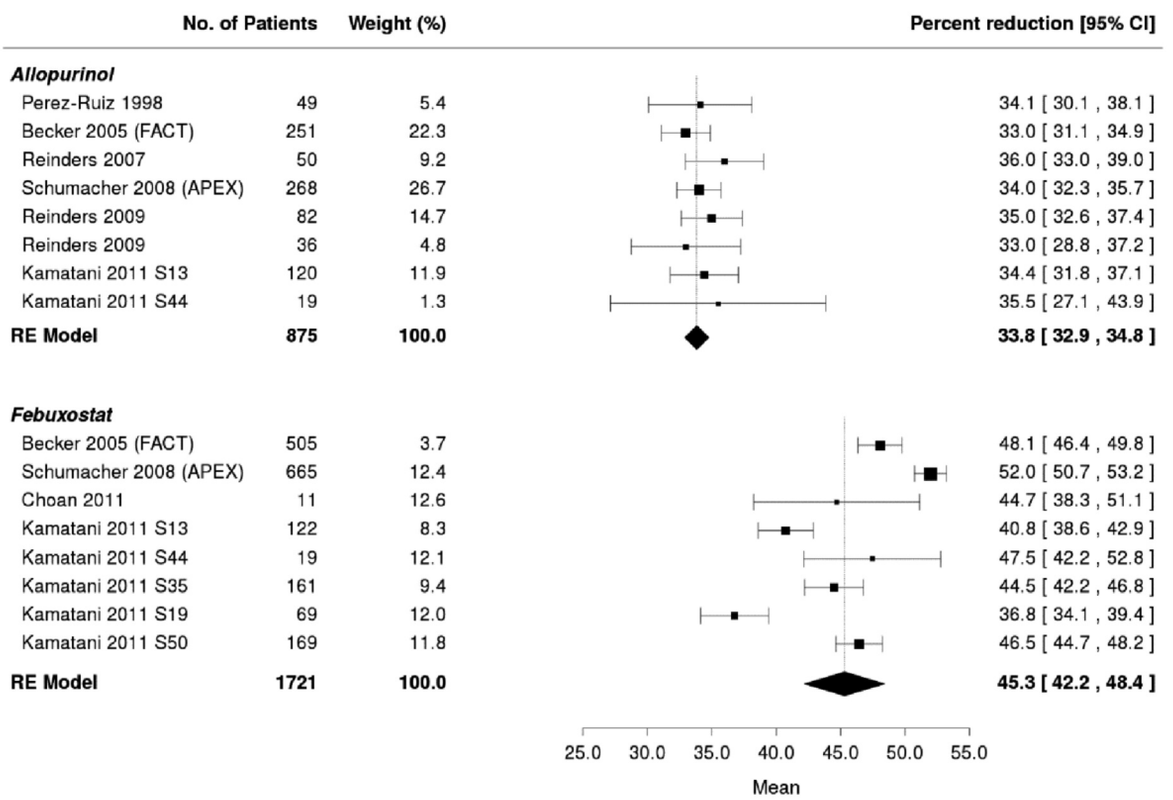

Figure 2. Pooled analysis of percentage reduction of SUA concentration compared with baseline values.

this parameter was 44.4% (Figure 1). The percentage reduction of sUA concentration, compared with baseline values was reported in 8 studies and it was equal to 33.8% (Figure 2).

Benzbromarone

Only four studies reported the proportion of patients at target of sUA and the reduction of sUA concentration with benzbromarone. Overall, the pooled analysis of data suggested that 81.8% (95% CI: 73.5-88.1) of patients could achieve the sUA target with this molecule, which is also associated with a 55.3% reduction (46.3-64.4) in uricaemia versus baseline values. However, the low number of studies reporting this parameter and the overall low number of patients enrolled in all studies (n= 310) may not allow to retrieve definitive conclusions on these two efficacy outcomes. In addition, only 129 patients were treated with benzbromarone.

Febuxostat Versus Allopurinol

All the 8 studies which included both a febuxostat and an allopurinol treatment arm were used to calculate a pooled summary effect of the difference between the two drugs in terms of percentage of patients at target, whereas only 4 reported comparisons of sUA reduction versus baseline values (Figure 3).

Overall, febuxostat resulted superior over allopurinol at the doses tested both in terms of probability to achieve the recommended target of sUA (odds ratio: 2.64, 95% confidence interval 1.74-4.01) and percentage reduction of uricaemia (mean difference: 13.08; 95% confidence interval 7.6-18.55) (Figure 3).

Efficacy CKD Patients

Two of the identified studies allowed a comparison of febuxostat and allopurinol in patients with CKD: the APEX trial[15] and the CONFIRMS trial[16]. Figure 4 reports the pooled analysis of the proportion of patients with renal dysfunction who achieved the target level of sUA, showing an advantage for febuxostat also in this setting (for this meta-analysis we were forced to use a fixed-effect model because we had available only two studies). Only one study on 36 patients, 17 of whom assigned to benzbromarone, explored the efficacy of benzbromarone in patients with renal dysfunction[17].

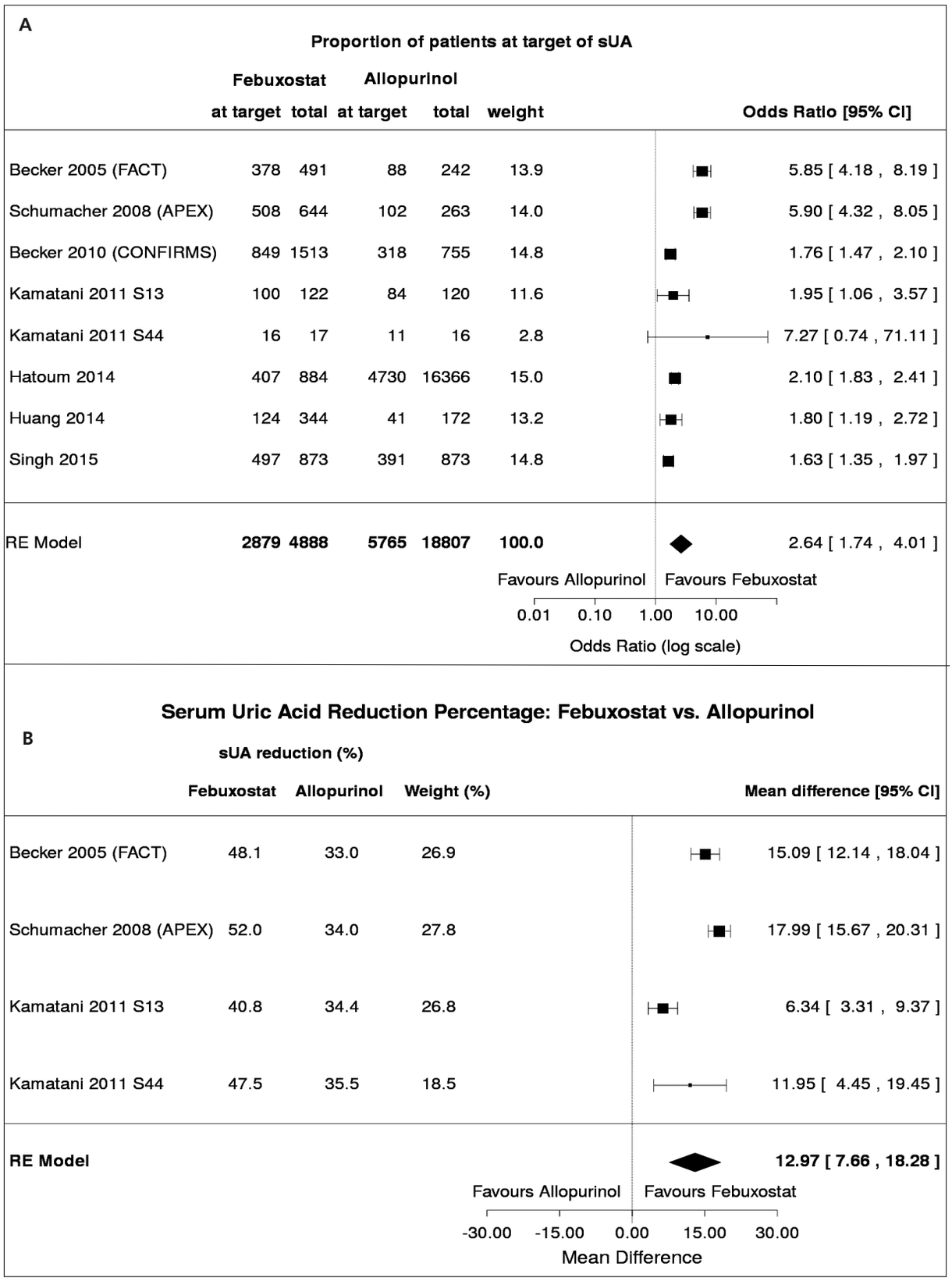

Figure 3. Comparison, in terms of odds ratio, between febuxostat and allopurinol in studies comparing the two drugs. ***A)*** proportion of patients who achieved target levels of sUA. ***B)*** percentage reduction of uricaemia.

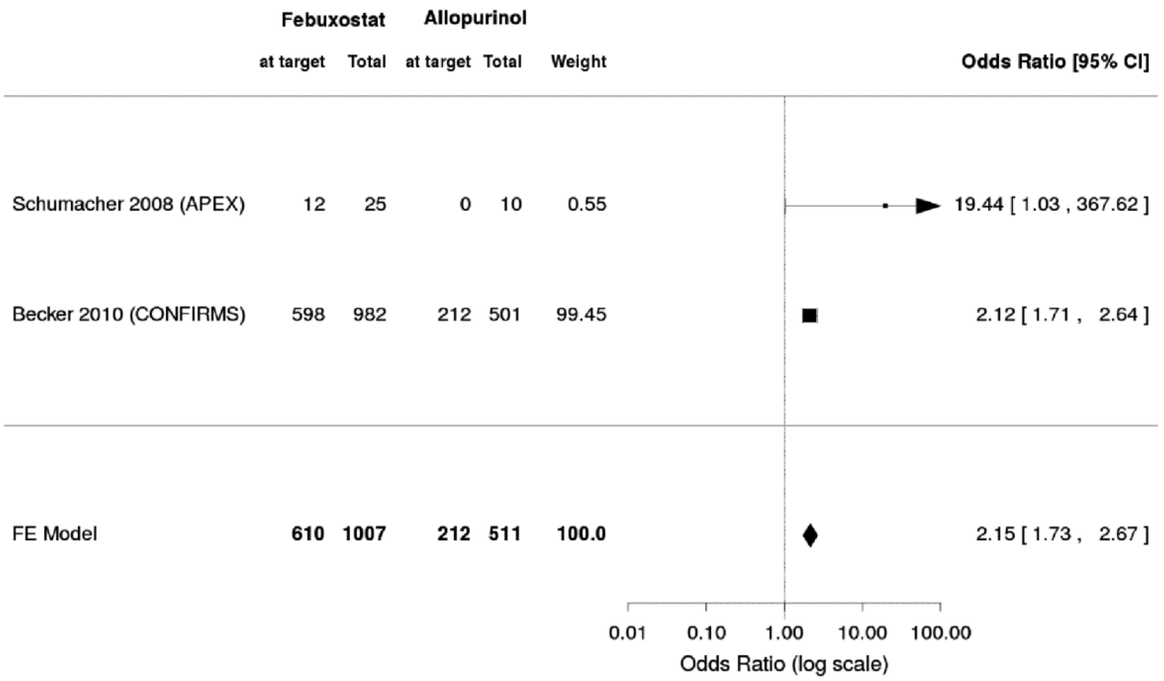

Figure 4. Pooled analysis of the proportion of patients with renal dysfunction who achieved the target level of sUA.

Safety

We also conducted an explorative analysis comparing the cumulative occurrence of adverse events of any grade with febuxostat and allopurinol (data on the safety of benzbromarone concerned a lower number of patients and were not considered for this sub-analysis).

Odds ratios were also obtained for the probability of any adverse event (febuxostat *vs*. allopurinol) from 6 of the 8 studies comparing the two drugs, and a pooled summary effect was produced. Overall, the odds ratio for the incidence of adverse events favored febuxostat over allopurinol (OR 0.85; 95% confidence interval: 0.75-0.97) (Figure 5).

Discussion

This systematic review explored the efficacy of ULTs in the treatment of gout. Overall, it appeared that only the two xanthine oxidase inhibitors, allopurinol and febuxostat had been extensively explored (scant data have been published on topiroxostat, a medication only labelled in Japan), whereas the uricosuric agent benzbromarone and probenecid had been investigated only in a limited number of studies, carried out on low numbers of subjects, and both are of restricted use due to safety (benzbromarone) and efficacy (probenecid) concerns[18,19].

It can be remarked that efficacy data of allopurinol are drawn only from clinical studies in comparison with febuxostat, although allopurinol had been marketed for decades before febuxostat development. This may be explained by the fact that clinical trials, as designed nowadays, were not performed at that time.

When comparing allopurinol and febuxostat in terms of proportion of patients at target and percentage reduction of sUA compared with baseline values, febuxostat at doses > 40 mg/day was superior to allopurinol 300 mg/day, in line with previous analysis[20]. Of note, while patients treated with febuxostat received different dosages mainly ranging from 10 to 80 mg/day (4 studies included febuxostat 120 mg/day); allopurinol was used at the maximum dosage of 300 mg/day in 98% of cases in interventional trials, reflecting the most commonly prescribed dose in clinical practice[21]. Indeed a retrospective analysis conducted on nearly 5 million patients with gout, revealed that allopurinol was prescribed at an average daily dose ≤300 mg in about 95% of the patients analyzed[21]. Noteworthy, the recently-published LASSO study[22] suggested that significant proportions of patients do not achieve target sUA levels when treated with such doses of allopurinol.

In addition, febuxostat was associated, although in an explorative-only analysis, with a lower incidence of adverse events compared with allopurinol. Evidence collected to date on this issue shows mixed results[20,23]. In terms of efficacy on sUA levels, the present findings are in line with previous systematic reviews that showed the superiority of febuxostat over allopurinol in achieving target levels of sUA[24-26]. In addition, the analysis of a large (>13,000) population of patients with gout treated with allopurinol in clinical practice showed that the proportion of subjects who reached the sUA target levels was low, and the adherence to this molecule remained poor[27]. These findings were also consistent, and even more evident, in patients with renal dysfunction, a common condition in gouty patients. Of note, a recent meta-analysis of 7 studies on chronic kidney disease patients has shown that pooled prevalence estimates of chronic kidney disease stage ≥3 in people with gout was 24%; at the same time, in this analysis gout was associated with chronic kidney disease (pooled adjusted odds ratio 2.41, 95% confidence interval 1.86 to 3.11)[28]. In gout patients with renal insufficiency, a number of molecules (febuxostat, rasburicase, benzbromarone) may be considered effective; on the other and, allopurinol seems less effective and may be contraindicated[29-32]. In the above-described meta-analysis, febuxostat appeared associated with a lower risk of adverse events compared with allopurinol, although this advantage was less evident than that reported for efficacy outcomes[28]. Moreover, a very recent retrospective study[33] which utilized 2009 to 2012 medical and pharmacy claims and laboratory data from a large US database, evaluated by a propensity analysis, analyzed 2015 patients taking febuxostat and 14,025 on allopurinol. A higher proportion of febuxostat users attained sUA goals of <6.0 mg/dl (56.9% *vs*. 44.8%; $p<0.001$) and <5.0 mg/dl (35.5% *vs*. 19.2%; $p<0.001$), respectively. Similar observations were made for overall propensity score-matched cohorts that included both treatment-naïve and current users (n=932 each). The Authors of this work concluded that febuxostat was more effective than allopurinol at the doses currently used in USA (40 mg/day for febuxostat in 83% users and 300 mg/day or lower for allopurinol in 97% users) in lowering sUA in gout patients. As a further confirmation of the superior efficacy of febuxostat, another recent "real-world" study[34] suggested that patients switched from allopurinol to febuxostat are more

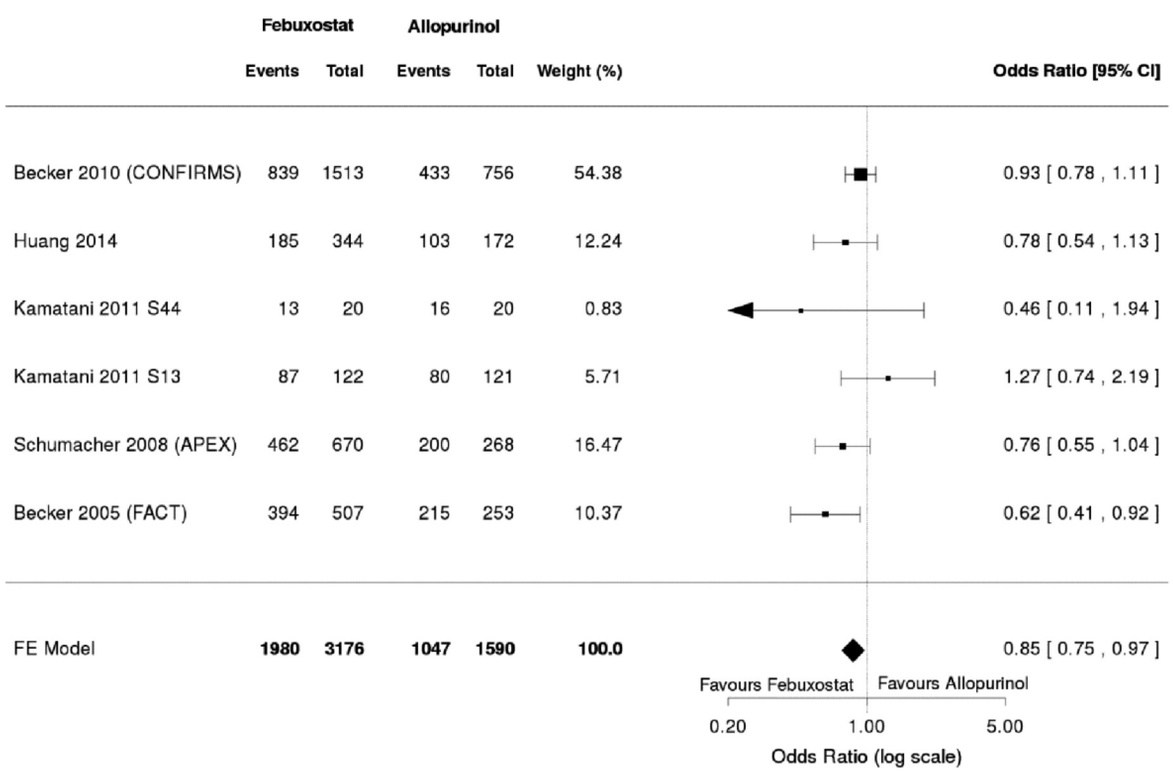

Figure 5. Pooled analysis of incidence of adverse events in studies comparing febuxostat and allopurinol.

likely to achieve target SUA levels than those who continue on allopurinol. Moreover, a pharmacoeconomic study[35] indicates that febuxostat may be a cost-effective alternative to allopurinol, especially for patients with more severe (stage 3-4) CKD.

The uricosuric agent benzbromarone was associated with some efficacy in gouty patients; however, the efficacy of this drug, according to the requirements of the present analysis, was explored only in four studies, with an overall low number of patients, and therefore caution should be exerted when evaluating this finding. Moreover, benzbromarone has been associated with cases of fulminant and sometimes fatal hepatotoxicity[36,37] and, therefore, it was withdrawn from the market in several countries.

Besides its remarkable impact on the treatment of gout, some additional evidence has suggested that febuxostat may exert some additional favorable effects in terms of prevention of cardio-renal diseases. Preliminary data suggest that the treatment with febuxostat might alleviate atrial fibrillation[38], reduce blood pressure, pulse wave velocity, and other cardiovascular indexes[39,40]. In a randomized study on 141 patients with hyperuricemia undergoing cardiac surgery[39], a 6-months treatment with febuxostat in comparison to allopurinol improved secondary endpoints related to CV and renal protection. The serum creatinine (1.14±0.30 *vs.* 1.26±0.39), urinary albumin (62.5±131.2 *vs.* 163.2±233.8), oxidized low-density lipoprotein (84.2±27.3 *vs.* 99.8±26.0), eicosapentaenoic acid/arachidonic acid ratio (0.46±0.35 *vs.* 0.36±0.18), and high-sensitivity C-reactive protein were significantly better in the febuxostat group than in allopurinol treated patients ($p<0.05$ for all comparisons). Similar results were obtained in patients with stage 3 chronic kidney disease[41], and the reno-protective effect of febuxostat has been also shown in long-term studies[42,43]. In a prospective study[40] carried out in 17 patients with chronic tophaceous gout, 1 year of treatment with febuxostat prevented the progression of arterial stiffening measured as carotid-femoral pulse wave velocity, while allopurinol was not effective. The additional benefit of febuxostat treatment beyond gout could represent an interesting perspective for the overall treatment of patients with hyperuricemia and the results of several ongoing trials comparing febuxostat and allopurinol are awaited (e.g., the FORWARD study, EUDRACT No.2014-005567-33; the CARES study, NCT01101035; and the FAST study, EUDRACT No: 2011-001883-23).

Conclusions

On the basis of reported data, febuxostat can play a major role in the treatment of hyperuricaemia and gout. Febuxostat is a suitable pharmacological option for first line treatment of gout, given its established efficacy and safety, documented in a high number of clinical studies and in daily practice.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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