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A systematic review and meta-analysis on the safety and efficacy of febuxostat versus allopurinol in chronic gout

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ABSTRACT

Objective: To evaluate the safety and efficacy of febuxostat compared to allopurinol for the treatment of chronic gout.
Methods: We did a systematic review and meta-analysis of randomized and non-randomized controlled trials that compared oral febuxostat to oral allopurinol for treatment of chronic gout. Two reviewers independently selected studies, assessed study quality, and extracted data. Risk ratios (RR) were calculated with random effects and were reported with corresponding 95% confidence intervals (CI).
Results: From 1076 potentially relevant citations, 7 studies and 25 associated publications met inclusion criteria; 5 studies were ultimately included in the analysis. Febuxostat did not reduce the risk of gout flares compared with allopurinol (RR = 1.16, 95% CI = 1.03–1.30, I^2 = 44%). Overall, the risk of any adverse event was lower in febuxostat recipients compared to allopurinol (RR = 0.94, 95% CI = 0.90–0.99, I^2 = 13%). Patients receiving febuxostat were more likely to achieve a serum uric acid of < 6 mg/dl than allopurinol recipients (RR = 1.56, 95% CI = 1.22–2.00, I^2 = 92%). Subgroup analysis did not indicate any significant difference between high- and low-dose febuxostat on the risk of gout flares.
Conclusion: Although febuxostat was associated with higher likelihood of achieving a target serum uric acid level of < 6 mg/dl, there was significant heterogeneity in the pooled results. There was no evidence that febuxostat is superior to allopurinol for clinically relevant outcomes. Given its higher cost, febuxostat should not be routinely used for chronic gout.

Introduction

Gout is the most common inflammatory arthropathy in people aged > 40 years [1]. The increasing incidence and prevalence of gout [2–4] and the association between hyperuricemia and vascular sequelae have increased interest in hyperuricemia and its management [5]. Plasma uric acid concentration is considered an important determinant of developing gout [6], so long-term pharmacological interventions to lower serum uric acid levels are recommended in people with prior gout, chronic tophaceous gout, or uric acid stones [7].

There are limited options for treating and preventing gout: treatment of acute flares, prophylaxis to prevent future acute flares, and chronic urate-lowering therapy [8,9]. Allopurinol (available since 1965) is the most common urate-lowering agent prescribed by rheumatologists for the treatment of gout [7]. However, its use is limited by rash (2% of treated patients), allopurinol hypersensitivity, and potential for suboptimal response in certain subgroups [10,11]. In addition, the effective dosage of allopurinol among people with chronic kidney disease is controversial [12].

A novel drug (febuxostat) was approved by the European Medical Agency in 2008 and the US Food and Drug administration in 2009 [13]. Unlike allopurinol, febuxostat selectively inhibits xanthine oxidase without affecting other activities of purine metabolism and does not require dose adjustment for mild to moderate renal impairment [14–16].

To our knowledge, no published systematic review compares the clinical effects of febuxostat and allopurinol. Given the increasing use of febuxostat and the relatively large number of recent trials, this information appears relevant to clinicians and policy-makers. We did a systematic review and meta-analysis comparing the safety and efficacy of various doses

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of febuxostat compared to allopurinol for the treatment of hyperuricemia (> 480 μmol/l or 8 mg/dl) in patients with chronic gout.

Methods

We did this systematic review according to a structured protocol that was developed *a priori*.

Inclusion criteria: Patients, outcomes, and study design

Patients of all ages with chronic gout were included in the current review. The presence of gout was defined by the presence of monosodium urate crystal in synovial fluid from the affected joint or tophus, or meeting at least six of the twelve American College of Rheumatology (ACR) criteria on the basis of clinical, biochemical, and x-ray findings [17]. Since no standardized outcomes have been established for studies of chronic gout, we selected outcomes for our review based on findings of a consensus report [18–20].

The primary efficacy outcome was the proportion of gout flares [21]. Gout flares are usually defined as joint symptoms leading to urgent evaluation or office/emergency room visit with acute pain and at least one typical gout treatment within 7 days of the visit [22,23]. Studies that presented data on patient-reported gout flares were also included in the current review. The primary safety outcome was the proportion of any adverse event (cardiovascular events, elevated liver enzymes, withdrawal, or death).

We also considered the following secondary outcomes:

1. Proportion of patients meeting the therapeutic target for serum uric acid level, defined as < 6 mg/dl or < 360 μmol/l [24];
2. Patient global and physician global assessment of response by Visual Analog Scale or Likert Scale [25];
3. Resolution of tophi and velocity of tophus regression; velocity is measured in mm/month [26,27].

We included all randomized controlled trials (RCTs) that reported one or more of the primary or secondary outcomes and compared febuxostat with allopurinol for the treatment of chronic gout. In addition, non-randomized controlled clinical trials were included if they were of adequate methodological quality (meaning that treatment allocation and blinding were well described; baseline characteristics of participants and loss to follow-up were reported by treatment group; and methods for ascertaining outcomes were described). Trials that enrolled patients with either gout or asymptomatic hyperuricemia were included; but those studying only patients with asymptomatic hyperuricemia were excluded.

Febuxostat and allopurinol are administered orally for treatment of gout patients; allopurinol sodium is available in injectable preparation for treatment of hyperuricemia in patients receiving cancer chemotherapy for leukemia, lymphoma, and solid tumor malignancies [28]. Therefore, all oral doses of febuxostat and allopurinol were eligible for inclusion. Co-interventions such as NSAIDs or colchicine were allowed. The trials were not restricted by any minimum duration of follow-up or minimum sample size. Unpublished studies were included for this review.

Data sources and search strategy

Searching was done in February 2012 according to the Cochrane Handbook for Systematic Reviews of Interventions [29]. An expert research librarian (LT) helped to design the search strategy (Appendix A). The search was not limited by language, year of publication, or type of publication.

Study selection, quality assessment, and data extraction

Two reviewers (A.A. and L.F.) reviewed all identified records independently and in duplicate. We retrieved the full text of the study for review if either reviewer felt that a study should definitely be included or was uncertain about the inclusion of a study; studies that both reviewers agreed were irrelevant were not retrieved. Authors of unpublished studies identified from trial registries were contacted for additional information, as necessary. After retrieving the full text, the two reviewers independently screened the studies based on pre-specified inclusion criteria including study design, study population, interventions, and outcomes. Any disagreement was resolved by discussion between the two reviewers.

Two reviewers (A.A. and L.F.) separately reviewed the studies meeting the inclusion criteria and assessed the methodological quality using the Cochrane Risk of Bias tool [30]. This tool assessed the following six domains: randomization; allocation concealment; blinding of participants, caregivers, and outcome assessors; incomplete outcome data (dropout rates and reason for withdrawal); selective outcome reporting; and other potential threats such as differential discontinuation rates or failure to present baseline characteristics or flow diagram for intervention and control groups. The quality of studies was characterized as yes (low risk of bias), no (high risk of bias), and unclear (lack of information or uncertain). Disagreements were resolved by consensus of the reviewers.

One reviewer (L.F.) extracted data into a standardized form. Another reviewer (A.A.) verified the extracted data. We collected data on general study information including title, authors, publication source and year, country, funding agency; trial characteristics of the study such as study design and setting and inclusion/exclusion criteria; baseline characteristics of the study population by intervention groups as follows: age, sex, presence of comorbidity (renal impairment, obesity, hypertension, DM, or insulin resistance), previous and concurrent treatments, and sample size; intervention details such as treatment comparators, dose, frequency of administration, and duration of treatment/follow-up; and details of outcome measures as mentioned above and results. Means, standard deviations, counts, and rates were extracted for results. When these statistics were not available, other statistics were extracted and converted (algebraically) into these forms [31]. Data was extracted from figures when raw data was not provided. Data was entered into MS Excel 2007 and RevMan 5.1 software. Intention-to-treat results were preferentially selected over per-protocol results. Any disagreement in data extraction was resolved by consensus via discussion between the two reviewers.

Data analysis and synthesis

The results of each trial were plotted as point estimates with 95% confidence intervals in metagraphs. Dichotomous outcomes (e.g. occurrence of gout flares, improvement in serum uric acid level of < 6 mg/dl, and occurrence of adverse events) were presented as relative risks. We performed meta-analysis using random effect models; we pooled relative risks of the dichotomous outcomes. We quantified statistical heterogeneity using I^2 statistics. I^2 values of 25, 50, and 75 percent were considered low, moderate, and high degrees of heterogeneity, respectively [32].