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REVIEW ARTICLE

Comparative effect of allopurinol and febuxostat on long-term renal outcomes in patients with hyperuricemia and chronic kidney disease: a systematic review

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Abstract

Patients with chronic kidney disease (CKD) are more likely to develop hyperuricemia and gout. Allopurinol and febuxostat are the most commonly used urate-lowering therapies with established safety and efficacy in CKD patients. The objective of the systematic review is to assess the long-term renal outcomes of allopurinol compared with febuxostat in patients with hyperuricemia and CKD or kidney transplantation. PubMed MEDLINE, Embase, Web of Science, Scopus, and Cochrane CENTRAL databases were searched from inception to December 2019 using the key terms "allopurinol," "febuxostat," "xanthine oxidase inhibitors," "gout suppressants," "hyperuricemia," "gout," "chronic renal insufficiency," and "kidney transplantation." Studies with follow-up duration ≥ 12 months were included. Risk of bias was assessed using the Cochrane Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool. Three retrospective observational studies with follow-up duration ranging from 1 to 5 years were reviewed. Febuxostat patients had a significantly higher estimated glomerular filtration rate, reduced risk for renal disease progression, and reduced serum uric acid levels compared with allopurinol patients. All studies had a serious risk of bias. Febuxostat may be more renoprotective than allopurinol in patients with both hyperuricemia and CKD based on evidence from small long-term retrospective studies with serious risk of bias. More methodologically rigorous studies are needed to determine the clinical applicability of these results.

Keywords Allopurinol · Chronic renal insufficiency · eGFR · Febuxostat · Gout · Hyperuricemia · Xanthine oxidase inhibitor

Introduction

Patients with chronic kidney disease (CKD) are more likely to develop hyperuricemia (uric acid ≥ 7 mg/dL) and gout compared with those with normal renal function [1]. More than 70% of uric acid is excreted by the kidneys and accumulation occurs with increasing renal impairment [2]. Development of hyperuricemia in CKD may worsen nephropathy through several mechanisms: intrarenal uric acid crystal deposition, systemic uric acid-induced endothelial dysfunction, activation of the renin-angiotensin system, and renal hypertension [3]. Additionally, a growing body of evidence suggests hyperuricemia is an independent risk factor for development of new-onset CKD [4–6], progressive CKD [7], and CKD-related mortality [8].

Preventing gout flares is a key patient-centered treatment goal and is generally achieved by targeting a serum uric acid level < 6 mg/dL [9–11]. However, achieving this goal in patients with CKD is challenging because recommended prophylaxis treatments—colchicine, NSAIDs, and uricosurics—are relatively contraindicated in patients with CKD and must be used with caution [12]. Urate-lowering therapy (ULT) with xanthine oxidase inhibitors is also indicated in patients with CKD. Previous retrospective and prospective studies have shown a potential renoprotective effect when serum uric acid levels are reduced with xanthine oxidase inhibitors in CKD patients [13–20].

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Xanthine oxidase inhibitors reduce serum uric acid levels by inhibiting uric acid synthesis. Allopurinol is commonly used as first-line ULT due to its low cost [10]. Dose adjustment is required in renal impairment since the major metabolite of allopurinol, oxypurinol, is primarily renally eliminated. Patients with renal impairment may also be at increased risk for developing life-threatening allopurinol hypersensitivity syndrome [21]. Achieving effective drug levels while minimizing risk for adverse drug reactions can be clinically difficult and often results in undertreatment of hyperuricemia in patients with renal impairment [22]. Febuxostat is a newer non-purine-selective xanthine oxidase inhibitor approved by the US Food and Drug Administration in 2009 [23]. It primarily undergoes hepatic metabolism and does not require dose adjustment in mild to moderate renal impairment [24]. Febuxostat was previously shown to be safe and effective in patients with moderate to severe CKD [25]. It is uncertain whether allopurinol or febuxostat provides better renal outcomes for the treatment of hyperuricemia in patients with established CKD.

Previous systematic reviews assessing the renal outcomes of xanthine oxidase inhibitors in hyperuricemia included patients without CKD [26] and compared febuxostat with allopurinol or placebo collectively [27]. Most studies in these reviews had follow-up durations of 6 months or less which may inadequately portray drug renal effects because CKD progresses over years. The objective of this systematic review is to assess the long-term renal outcomes of allopurinol compared with febuxostat in patients with hyperuricemia and CKD or kidney transplantation.

Materials and methods

Search strategy

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guideline [28]. The review was not registered in the International Prospective Register of Systematic Reviews (PROSPERO). A systematic search of PubMed MEDLINE, Embase, Web of Science Core Collection, Scopus, and Cochrane CENTRAL databases was performed to identify relevant published studies through December 16, 2019 using the keywords “allopurinol,” “febuxostat,” “xanthine oxidase inhibitors,” “gout suppressants,” “hyperuricemia,” “gout,” “chronic renal insufficiency,” and “kidney transplantation.” A search query was developed for PubMed MEDLINE (Online Resource 1) and adapted for other databases. No limits or filters were applied. Clinicaltrials.gov was also searched for recently completed clinical trials.

Study selection

Studies comparing allopurinol and febuxostat treatment on renal outcomes in patients with hyperuricemia and CKD were included if they met the following inclusion criteria: (1) primarily enrolled adult patients (age ≥ 18 years) with CKD or kidney transplantation; (2) mean or median follow-up duration of duration ≥ 12 months; (3) statistical comparison of allopurinol and febuxostat treatment groups for one or more specified renal outcomes (change in estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl), change in serum creatinine (Scr), change in albuminuria, incidence of kidney disease progression, or incidence of end stage renal disease (ESRD)) as a primary or secondary endpoint. Exclusion criteria were as follows: (1) studies investigating tumor lysis syndrome; (2) studies investigating dialysis-dependent patients; (3) case reports, case series, reviews, and abstracts; and (4) studies written in a language other than English. Two authors (AH and JB) independently screened for relevant studies. Discrepancies were resolved through discussion between the two authors.

Data extraction

Data was extracted by AH and verified by JB. The following data was extracted from included studies: first author, publication year, country, study design, sample size, follow-up duration, inclusion/exclusion criteria, allopurinol and febuxostat dosing, patient demographics, baseline eGFR, baseline serum uric acid, baseline gout, incidence of gout flares, and renal outcomes data.

Risk of bias assessment

Risk of bias for each study was assessed independently by each author (AH and JB) using the Cochrane Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool. ROBINS-I evaluates the risk of bias for a specified outcome based on signaling questions in the following 7 domains: baseline confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result [29]. Reported renal outcomes in each study were qualitatively assessed and determined to be at low, moderate, serious, or critical risk of bias for each domain and for the overall study. Discrepancies between authors were resolved through discussion.

Results

Study selection

A total of 3942 articles were initially identified from all database sources (Fig. 1). After removing duplicates, 1914 titles and abstracts were screened. Eleven studies were eligible for full-text review. A summary of the 3 studies included in the final review is provided in Table 1. These studies were small retrospective cohort studies conducted in Asian populations investigating the comparative effects of allopurinol and febuxostat on serum uric acid and eGFR. Definitions of CKD and hyperuricemia varied between studies. Follow-up durations for laboratory monitoring ranged from 1 to 5 years.

Risk of bias assessment

All 3 included studies had at least 1 domain at serious risk of bias and thus had a serious risk of bias overall for the change in eGFR outcome. Cox proportional hazards ratio for renal disease progression was also reported by Lee et al. and had a serious risk of bias. Risk of bias in these studies was primarily attributed to the common practice of prescribing febuxostat after allopurinol failure (i.e., bias due to baseline confounding) and inequivalent comparisons of patients continued on allopurinol with patients newly started on febuxostat in the study period (i.e., bias in selection of participants). Domain-level risk of bias assessment results are detailed in Online Resource 2.

Literature review

Tsuruta et al. conducted a retrospective cohort study including 84 patients with CKD stage 3b–5 on ULT (assumed hyperuricemia). Fifty-seven patients were switched from allopurinol to febuxostat at the beginning of the study period (febuxostat group) and 27 patients were continued on allopurinol. Baseline mean eGFR and serum uric acid were similar between the allopurinol and febuxostat groups. Baseline diuretic use was not reported. At the end of the 1-year follow-up period, eGFR in the febuxostat and allopurinol groups were both reduced from baseline, but the febuxostat group had a significantly higher mean eGFR compared with the allopurinol group. Febuxostat was independently associated with improved eGFR even in multiple regression analysis controlling for baseline age, gender, hemoglobin level, albumin level, eGFR, diabetes, renin-angiotensin-aldosterone blockers, and impact of switching from allopurinol to febuxostat ($p < 0.05$). Serum uric acid was significantly lower in the febuxostat group compared with the allopurinol group (5.7 vs. 6.6 mg/dL; $p < 0.01$) at 1-year of follow-up. Additionally, more patients in the febuxostat group achieved target serum uric acid levels (< 6 mg/dL) at 1 year (69% vs. 32%; $p < 0.01$). One case of transaminitis and 1 case of gout flare occurred in the febuxostat group during the follow-up period. No adverse drug reactions occurred in the allopurinol group [30].

Tsuji et al. conducted a retrospective cohort study including 86 CKD patients with hyperuricemia (uric acid levels > 7 mg/dL) and a follow-up duration of 2 years.

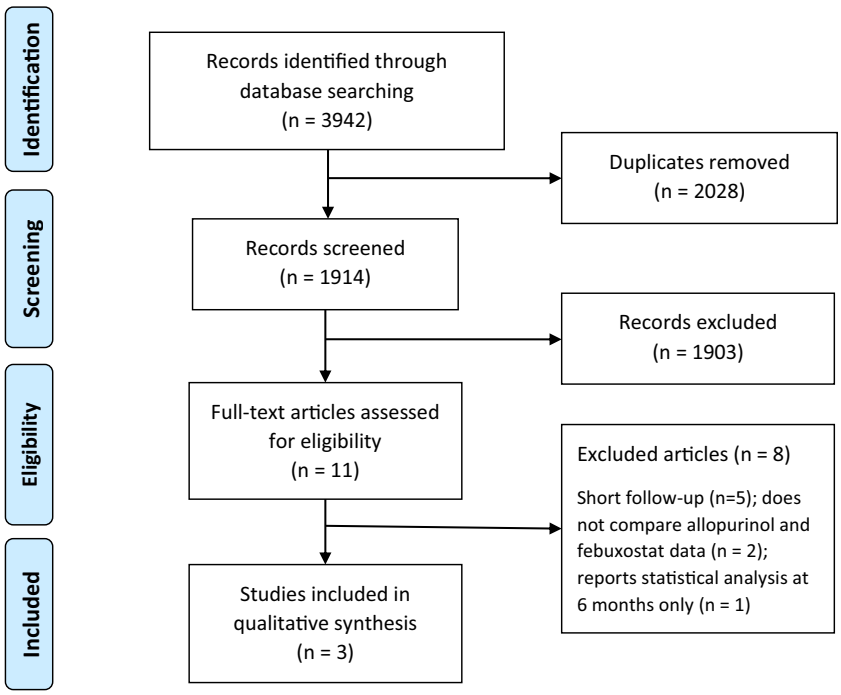

Fig. 1 Flow diagram of study selection process

Table 1 Summary of studies comparing allopurinol and febuxostat renal outcomes in patients with hyperuricemia and chronic kidney disease

First author (year; country) study design	Study period	Sample size	Population	Age (years)	Dosing (mg/day)	Baseline gout (%)	Baseline SUA (mg/dL)	Baseline eGFR (ml/min)	Renal outcomes	Gout flare incidence (*n*)	Risk of bias
Tsurata (2014; Japan) [30] Retrospective cohort	1 year	ALL, $n = 27$ FEB[a], $n = 57$	CKD 3b–5 (eGFR < 45 ml/min) on baseline ALL treatment	ALL, 72.9 ± 10.7 FEB, 67.4 ± 12.3	NR	NR	ALL, 6.2 ± 1.1 FEB, 6.1 ± 0.9	ALL, 26.2 ± 9.2 FEB, 27.2 ± 10.5	• FEB vs. ALL eGFR at 1 year, 25.7 vs. 19.9 ml/min, $p < 0.05$ • Febuxostat independently associated with improved eGFR in multiple regression analysis ($p < 0.05$)	ALL, 0 FEB, 1	Serious risk[e]
Tsuji (2018; Japan) [31] Retrospective cohort	2 years	ALL, $n = 30$ FEB, $n = 31$ SWI, $n = 25$	CKD (undefined) with hyperuricemia (SUA > 7.0 mg/dL)	ALL, 65.3 ± 11.1 FEB, 59.6 ± 16.1 SWI, 64.6 ± 14.9	ALL, 50–100 FEB, 10–20 SWI, 10–20	NR	ALL, 6.86 ± 0.87 FEB, 9.43 ± 1.63 SWI, 8.49 ± 1.32	ALL, 35.7 ± 13.8 FEB, 35.2 ± 12.8 SWI, 31.7 ± 11.9	• eGFR at 2 years, FEB 35.2, ALL 33.0, SWI 29.1 ml/min[b] • ≥ 30% decrease in eGFR over 2 years, FEB 6%, ALL 23%, SWI 24%[b]	ALL, 1 FEB, 3 SWI, 0	Serious risk[e]
Lee (2019; South Korea) [32] Retrospective cohort	5 years	ALL, $n = 40$ FEB[a], $n = 30$ CON, $n = 71$	CKD stage 3 (eGFR 30–59 ml/min) with hyperuricemia (SUA > 7.0 mg/dL)	ALL, 62.3 ± 14.6 FEB, 64.3 ± 13.1 CON, 62.0 ± 12.8	ALL, 164 ± 76.3 FEB, 54.6 ± 21.6	ALL, 45% FEB, 60% CON, 0%	ALL, 9.0 ± 1.5 FEB, 8.7 ± 1.6 CON, 8.3 ± 1.3	ALL, 41.9 ± 9.5 FEB, 45.4 ± 8.3 CON, 40.8 ± 8.5	• eGFR at last follow-up, FEB 45.8, ALL 35.5, CON 23.4 ml/min; $p < 0.001$ • Survival time from renal disease progression[c], FEB 87.7, ALL 77.6, CON 48.7 months; $p < 0.001$ • Reduction in risk to renal disease progression, FEB 74.3%, HR 0.257, CI 0.072–0.912; ALL increased risk, HR 1.112, CI 0.514–2.406[d]	NR	Serious risk[f]

ALL, allopurinol group; CI, confidence interval; CKD, chronic kidney disease; CON, control group; eGFR, estimated glomerular filtration rate; FEB, febuxostat group; HR, hazard ratio; NR, not reported; SUA, serum uric acid; SWI, allopurinol to febuxostat switch group

[a] Febuxostat group included all or some patients switched from allopurinol to febuxostat. Group nomenclature follows that used in the original study

[b] No *p* value reported

[c] eGFR decline > 30% baseline, eGFR < 15 ml/min, or initiation of dialysis

[d] Control group as reference

[e] Assessment for change in eGFR outcome

[f] Assessment for change in eGFR and risk of renal disease progression outcome

Most included patients had CKD stage 3b or 4. Patients were either continued on allopurinol ($n = 30$), switched from allopurinol to febuxostat ($n = 25$), or newly started on febuxostat ($n = 31$). Baseline eGFR was similar between groups. The febuxostat group had higher serum uric acid levels at baseline compared with the allopurinol and switch groups. Reported baseline diuretic use was similar across all 3 groups, ranging from 27% to 29%. Mean eGFR remained the same during the 2-year period in the febuxostat group, while mean eGFR in the allopurinol and switch groups declined from baseline. More patients in the allopurinol and switch groups experienced a greater than 30% decrease in baseline eGFR over 2 years compared with the febuxostat group. Mean serum uric acid levels were significantly reduced from baseline at 6 months and 2 years in the febuxostat (9.43 to 6.31 mg/dl, $p < 0.0001$) and switch groups (8.49 to 7.19 mg/dL, $p < 0.0001$), while serum uric acid levels increased in the allopurinol group (6.86 to 7.10 mg/dL). No severe adverse drug reactions were reported. However, 1 patient in the allopurinol group and 3 patients in the febuxostat group experienced a gout flare during the follow-up period [31].

Lastly, Lee et al. conducted a retrospective cohort study of 141 CKD stage 3 patients with hyperuricemia (uric acid levels > 7 mg/dL for males or > 5.7 mg/dL for females). Patients were categorized into either febuxostat ($n = 30$; 26/30 were previously on allopurinol), allopurinol ($n = 40$), or conventional CKD treatment (control; $n = 71$). EGFR was assessed at year 1, 2, 3, 4, and at last follow-up up to 5 years. Baseline mean eGFR and serum uric acid were similar between the febuxostat, allopurinol, and control groups. Patients with baseline gout were not included in the control group for ethical reasons. Baseline diuretic use was not reported. At the end of the study period, the febuxostat group had a significantly higher mean eGFR compared with the allopurinol and control groups. The survival time from renal disease progression (defined as eGFR decline > 30% baseline, eGFR < 15 ml/min, or initiation of dialysis) was also significantly longer in the febuxostat group compared with the allopurinol and control groups. In a Cox proportional hazards regression analysis controlling for potential confounders (baseline diabetes, proteinuria, eGFR, and serum uric acid level), the risk of renal disease progression in the febuxostat group was reduced compared with control, while allopurinol did not reduce renal disease progression risk compared with control (HR 1.112, CI 0.514–2.406). Febuxostat also more effectively reduced serum uric acid levels compared with the allopurinol and control groups (mean change − 4.8 vs. − 2.5 vs. − 0.49 mg/dL; $p < 0.001$). One patient developed a skin reaction in the allopurinol group. No adverse drug reactions were reported in the febuxostat group [32].

Discussion

Previous randomized controlled trials comparing allopurinol and febuxostat renal outcomes in CKD patients had follow-up durations of 6 months or less. In these short-term trials, febuxostat more effectively lowered serum uric acid levels compared with allopurinol, but eGFR was not significantly different between the febuxostat and allopurinol groups at the end of the follow-up duration [19, 33]. This systematic review aimed to assess the long-term renal outcomes of allopurinol compared with febuxostat in patients with hyperuricemia and CKD. Three retrospective studies with follow-up durations of 1–5 years were included. In all studies, febuxostat patients maintained a higher eGFR at the end of the study period compared with allopurinol and control groups. However, observed changes in eGFR between febuxostat and allopurinol groups were less than 5–10 ml/min in two studies and may represent clinically insignificant changes [30, 31]. Lee et al. included a control group, and serum uric acid and eGFR seemed to improve in a stepwise manner with more intensive ULT (control < allopurinol < febuxostat) [32]. Febuxostat most effectively reduced uric acid levels and preserved eGFR, suggesting high uric acid levels may play a significant role in renal disease pathology.

Of the 3 included studies, only Lee et al. performed survival analysis for renal disease progression (time to eGFR decline > 30% baseline, eGFR < 15 ml/min, or initiation of dialysis). Febuxostat was superior to the allopurinol and control groups in prolonging time to renal disease progression, reducing the risk to renal disease progression by 74.3% [32]. However, the confidence interval for this effect was wide and antihypertensive treatment was not a controlled confounder. Thus, the renoprotective effects of febuxostat may have been overestimated in this analysis.

The results of the included studies should be considered in the context of serious risk of bias. All were small retrospective cohort studies with higher baseline risk for bias compared with randomized controlled trials. In particular, febuxostat patients were commonly switched to febuxostat after failure on allopurinol and not ULT new-start patients. The clinical decision-making for switching patients was poorly described in the studies. In this way, patients more likely to improve on febuxostat may have been selected to the febuxostat group. Only Tsurata et al. attempted to account for the impact of switching ULT agents [30]. Failure to fully report diuretic use, other gout medications, baseline gout diagnosis, and incidence of gout flares in these studies could bias interpretation of serum uric acid lowering and treatment efficacy.

Risk of bias may have also led to underestimation of allopurinol effects on eGFR and serum uric acid. In the included studies, febuxostat patients were compared with patients continued on allopurinol therapy. The length of time patients were previously on allopurinol was not captured or described.

Inadequate allopurinol dose titration likely also contributed to underestimation of allopurinol effects; mean serum uric acid in the allopurinol group increased in Tsurata et al. and Tsuji et al. during the study period [30, 31]. In practice, only 15% of CKD patients on allopurinol have doses titrated to serum uric acid < 6 mg/dL [34]. In the present review, no studies reported on allopurinol dose titration. Tsurata et al. did not report any allopurinol or febuxostat dosing [30]. Allopurinol is likely more effective in CKD patients when titrated to serum uric acid < 6 mg/dL, rather than using creatinine clearance-based dosing [35].

Multiple factors should be considered when deciding between allopurinol and febuxostat for CKD patients with hyperuricemia. The American College of Rheumatology (ACR) 2012 and European League Against Rheumatism (EULAR) 2016 guidelines both recommend preventative urate-lowering therapy with xanthine oxidase inhibitors in CKD patients with gout [9, 10]. Due to the cost-effectiveness of allopurinol, EULAR recommends first maximizing allopurinol dosing based on creatinine clearance to target serum uric acid < 6 mg/dL before changing to febuxostat [10]. Febuxostat is also less preferred in CKD patients due to common cardiovascular comorbidities. In the CARES trial, patients on febuxostat had an increased risk of cardiovascular mortality compared with allopurinol patients [36]. In the presently reviewed studies, febuxostat patients had a significantly higher estimated glomerular filtration rate and reduced risk for renal disease progression compared with allopurinol patients. However, the clinical applicability of these results is low due to the serious risk of bias in these studies. Based on these considerations, allopurinol should be trialed before febuxostat in CKD patients with gout. The treatment of asymptomatic hyperuricemia in CKD patients remains controversial [37].

This systematic review had several limitations: (1) Included studies in this review were retrospective observational studies with serious risk for bias. (2) Published results may favor febuxostat due to publication bias. (3) The comparative effects of febuxostat and allopurinol in CKD patients with a history of kidney transplantation were not assessed. Additional research on the role of uric acid in kidney disease progression, the risks and benefits of treating asymptomatic hyperuricemia, and safety of dosing allopurinol above creatinine clearance-based recommendations is needed to improve hyperuricemia treatment in CKD patients [38–40].

Conclusion

Febuxostat may be more renoprotective than allopurinol in patients with both hyperuricemia and CKD based on evidence from small long-term retrospective studies with serious risk of bias. More methodologically rigorous studies are needed to determine the clinical applicability of these results.

Compliance with ethical standards

Disclosures None.

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