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KIDNEY RESEARCH AND CLINICAL PRACTICE

Renoprotective effects of febuxostat compared with allopurinol in patients with hyperuricemia: A systematic review and meta-analysis

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Background: Hyperuricemia is reported to be related to rapid progression of renal function in patients with chronic kidney disease (CKD). Allopurinol, a uric acid lowering agent, protects renal progression. However, it is not widely used in patients with CKD because of its serious adverse event. Febuxostat can be alternatively used for patients who are intolerable to allopurinol. We aimed to determine renoprotective effect and urate-lowering effect between the two drugs.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials to assess the effects of febuxostat compared to allopurinol in patients with hyperuricemia. MEDLINE, Embase, and Cochrane Library databases were searched to identify research publications.

Results: Four relevant publications were selected from among 3,815 studies. No significant differences were found in the changes in serum creatinine from baseline between the febuxostat and allopurinol groups. Changes in estimated glomerular filtration rate (eGFR) were observed between the two groups at 1 month (mean difference 1.65 mL/min/1.73 m^2, 95% confidence interval [CI] 0.38, 2.91 mL/min/1.73 m^2; heterogeneity $\chi^2 = 1.25$, $I^2 = 0\%$, $P = 0.01$); however, the changes in eGFR were not significantly different at 3 months. A significant difference did exist in the changes in albuminuria levels from baseline between the febuxostat and allopurinol groups (mean difference −80.47 mg/gCr, 95% CI −149.29, −11.64 mg/gCr; heterogeneity $\chi^2 = 0.81$, $I^2 = 0\%$, $P = 0.02$). A significant difference was also observed in the changes in serum uric acid from baseline between the febuxostat and allopurinol groups (mean difference −0.92 mg/dL, 95% CI −1.29, −0.56 mg/dL; heterogeneity $\chi^2 = 6.24$, $I^2 = 52\%$, $P < 0.001$).

Conclusion: Febuxostat might be more renoprotective than allopurinol.

Keywords: Chronic kidney disease, Febuxostat, Gout, Hyperuricemia, Meta-analysis

Introduction

Hyperuricemia has been reported to be related to rapid progression of renal function in patients with chronic kidney disease (CKD) [1]. Hyperuricemia induces renal vasoconstriction via activation of the renin–angiotensin system and endothelial dysfunction and augments interstitial inflammation and fibrosis [2,3]. Serum uric acid concentration shows a linear relationship with renal function: an 11% increase in risk per 1 mg/dL increase

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in uric acid [4]. Furthermore, individuals with hyperuricemia (> 9 mg/dL) have a 3 times higher risk for chronic kidney disease [5].

Allopurinol is the most widely used urate-lowering agent in gout patients [6]. It protects against renal deterioration in patients with proteinuria and even improves renal and cardiac functions in patients with renal and cardiac diseases [7,8]. However, the metabolite of allopurinol is excreted predominantly by the kidneys [6] and induces hypersensitivity syndrome. Hence, alternative therapeutic options may have a significant effect on the future of successful gout management, particularly in patients with renal impairment [6].

Febuxostat is a novel xanthine oxidase inhibitor that is safe for CKD patients due to its hepatic elimination. It is used as an alternative medicine for patients who are intolerant to allopurinol [9]. Several studies [10–12] have reported the renoprotective effects of febuxostat, and recently, febuxostat has been reported to improve renal function in patients with CKD stage 3 [13]. However, its renoprotective effect has not been sufficiently investigated.

Observational studies and randomized controlled trials (RCTs) have shown that allopurinol retards renal progression. Febuxostat is also effective in lowering uric acid and possesses renoprotective effects. However, which drug is more effective in renoprotection remains unclear because of insufficient direct comparison between the two drugs. We aimed to perform a systematic review and meta-analysis of RCTs to assess the renoprotective effects and urate-lowering effects between the two drugs in patients with hyperuricemia.

Methods

We used the databases below to comprehensively search for studies evaluating the renoprotective effects of febuxostat compared with allopurinol. This study was based on the Cochrane methods for Systematic Reviews of Interventions [14] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Data and literature sources

PubMed-MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and KoreaMed were searched for human-only studies published until May 2015. For electronic database searches, we used 'febuxostat' as the keyword. The search was not limited by language, year of publication, or type of diseases. The full search strategy in Supplementary table 1 was developed for MEDLINE and was adapted for the other electronic databases. After the initial electronic search, we manually searched the bibliographies from the identified studies (Fig. 1).

Study selection and data extraction

Results of the various searches were independently reviewed by two reviewers (S. Kim and S.Y. Han). Titles and abstracts were reviewed, and, if additional information was required, the full text was reviewed. Any difference in the reviewers' selection of studies was resolved by discussion.

Studies were eligible for inclusion if they 1) were allocated at random (by chance alone) to receive one of several clinical interventions; 2) compared febuxostat to allopurinol; 3) followed participants for at least 1 month after randomization for medication; and 4) reported any of the following renal outcomes: changes in estimated glomerular filtration rate (eGFR), serum creatinine, albuminuria, and serum uric acid. Studies were excluded in participants with dialysis, kidney transplantation, and malignancy.

The two authors (S. Kim and S.Y. Han) blindly extracted data from the included studies using the predefined data extraction form. The following variables were extracted: 1) demographics (e.g., age, gender, dose of agents); 2) study design; and 3) changes in serum creatinine, eGFR, albuminuria, and serum uric acid. If data were missing or additional information was required, the author of the original paper was contacted via email.

Assessment of methodological quality

The methodological quality of included studies was independently assessed by two authors (S. Kim and S.Y. Han) using the risk of bias assessment tool developed by the Cochrane Bias Methods Group [16]. Any discrepancy between the authors was resolved through discussion or review by a third author (H.J. Kim). Judgments of risk of

bias are presented in Fig. 2. The risk of bias across studies was assessed using GRADE (Supplementary table 2).

Statistical analysis

The primary outcomes of this study were the changes in eGFR in the febuxostat and allopurinol groups. The secondary outcomes were the changes in serum creatinine, albuminuria, and serum uric acid in the febuxostat and allopurinol groups. The results of the studies were analyzed with Review Manager program ver. 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, Denmark). Data were pooled using DerSimonian–Laird random-effects models in a meta-analysis when they were similar to justify combining results, both clinically and statistically. For all continuous outcomes, we used weighted mean differences with 95% confidential intervals (CI) or standardized mean difference with 95% CI depending on the similarity of scales measuring an outcome. Heterogeneity of the results was tested using the chi-square test with a P value < 0.10 indicating significant heterogeneity and an I^2 statistic with a value > 50% indicating substantial heterogeneity. In the case of substantial heterogeneity, the result was explored, including subgroup analyses or sensitivity analyses, in an attempt to explain the heterogeneity. Publication bias was not assessable because of the limited number of publications retrieved.

Results

Selection and description of studies

Database searches identified 3,815 articles. Of these, 514 publications were excluded for duplication, and 3,257 publications were excluded because they did not fulfill the selection criteria based on their titles and abstracts. We obtained full manuscripts for the remaining 49 articles. In scrutinizing the articles, we identified 4 potentially relevant studies [11,12,17,18]. The other 45 publications were excluded for the following reasons: 12 full-text articles were unavailable, 4 were duplications, 4 were commentaries, 21 inappropriately described the outcome, and 4 were not RCTs. Fig. 1 shows a flowchart of the study selection process. Characteristics of included and excluded studies are presented in Supplementary tables 3 and 4.

Four studies from 3 countries were included in our systematic review (Table 1) [11,12,17,18]. The studies were published between 2013 and 2014. The risk of bias assessment is summarized in Fig. 2. One trial [17] included participants with higher urine uric acid excretion regardless of renal function but excluded participants with gout. One trial [18], a *post-hoc* study, included only gout

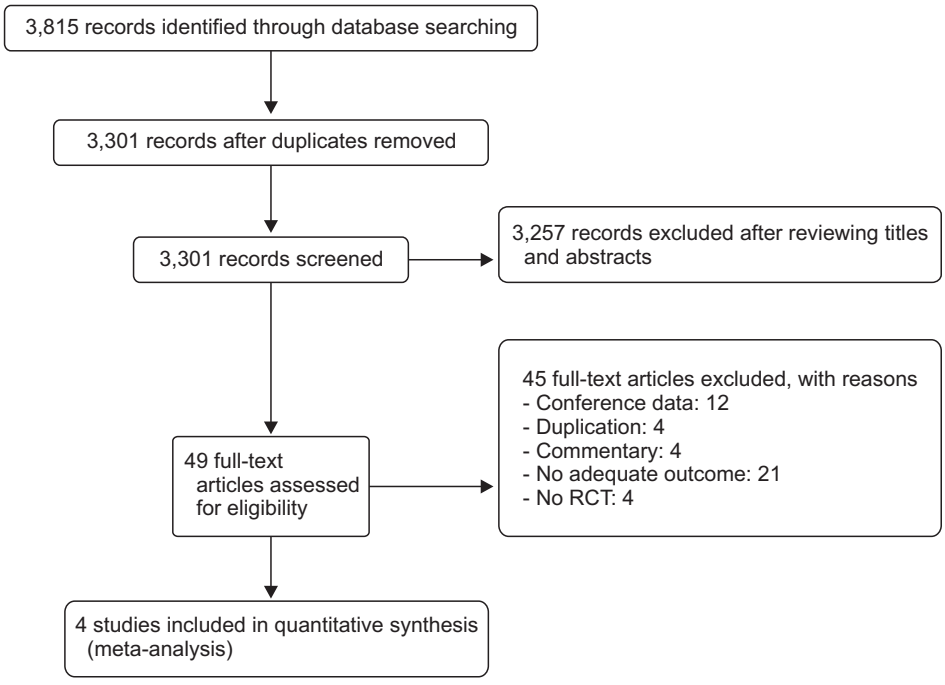

Figure 1. Flow diagram of study selection.
RCT, randomized controlled trial.

Table 1. Study and population characteristics

Study	Population	Study design	Follow-up duration (mo)	Intervention (febuxostat)					Control (allopurinol)			
				Subgroup	Sample size (n)	Age (yr)	Gender, men	sUA baseline, (mg/dL)	Sample size (n)	Age (yr)	Gender, men	sUA baseline (mg/dL)
Goldfarb et al, 2013 [17]	United States (multiracial)	RCT, phase II, double-blind, multicenter	6	Total	33	49.1 ± 9.6	27 (81.8)	6.2 ± 1.63	33	46.5 ± 9.9	31 (93.9)	6.3 ± 1.49
Kim et al, 2014 [18]	Korean	RCT, phase III, double-blind, multicenter, *post-hoc*	1	Total	106	NA	70 (100)	NA	36	48.3 ± 11.8	36 (100)	9.5 ± 1.0
				40 mg group	35	49.6 ± 11.9	NA	9.7 ± 1.1				
				80 mg group	35	49.1 ± 12.4	NA	9.5 ± 1.3				
				120 mg group	36	51.2 ± 9.9	NA	9.5 ± 1.0				
Sezai et al, 2013 [11]	Japanese	RCT, single-blind, single center	6	Total	71	67.4 ± 9.7	58 (81.7)	8.6 ± 0.96	69	66.4 ± 10.8	57 (82.6)	8.6 ± 0.98
Tanaka et al, 2015 [12]	Japanese	RCT, open label, single center	3	Total	21	70.1 ± 9.5	19 (90.5)	7.75 ± 0.84	19	66.1 ± 7.0	16 (84.2)	8.18 ± 1.11

Data are presented as data only, mean ± standard deviation, or number (%).
NA, not available; RCT, randomized controlled trial; sUA, serum uric acid.

Figure 2. Judgements of risks of included studies.
+, yes; -, no; ?, uncertain.
*Washout period was not described.

patients with normal renal function; the analysis in this trial was based on results of all participants of an original study, and thus, it was considered an RCT. One trial [11] included participants who underwent cardiac surgery with hyperuricemia and mild to moderate renal dysfunction. One trial [12] included CKD stage 3 patients with hyperuricemia but excluded active gout patients.

Febuxostat was the intervention agent and allopurinol was the control agent in all trials. The dose of allopurinol varied between 50 and 300 mg/day in the control group. Obtaining outcome data was difficult because renal outcomes were not the primary focus in the three studies, and all studies lacked renal outcomes.

Serum creatinine and eGFR

Four trials reported data on serum creatinine levels at the 3- to 6-month follow-up appointment. No significant differences existed in the change in serum creatinine from baseline between the febuxostat and allopurinol groups (mean difference −0.03 mg/dL, 95% CI −0.08, 0.02 mg/dL; heterogeneity $\chi^2 = 6.85$, $I^2 = 56\%$, $P = 0.26$) (Fig. 3).

Four trials reported data on eGFR at the 1 or 3 month follow-up appointment. Among these trials, one was a subgroup study. A significant difference was found in the change in eGFR from baseline between the febuxostat and allopurinol groups at the 1 month follow-up (mean difference 1.65 mL/min/1.73 m^2, 95% CI 0.38, 2.91 mL/min/1.73 m^2; heterogeneity $\chi^2 = 1.25$, $I^2 = 0\%$, $P = 0.01$ for 1 month follow-up). However, no significant difference existed at the 3 month follow-up (mean difference 1.42 mL/min/1.73 m^2, 95% CI −2.78, 5.62 mL/min/1.73 m^2;

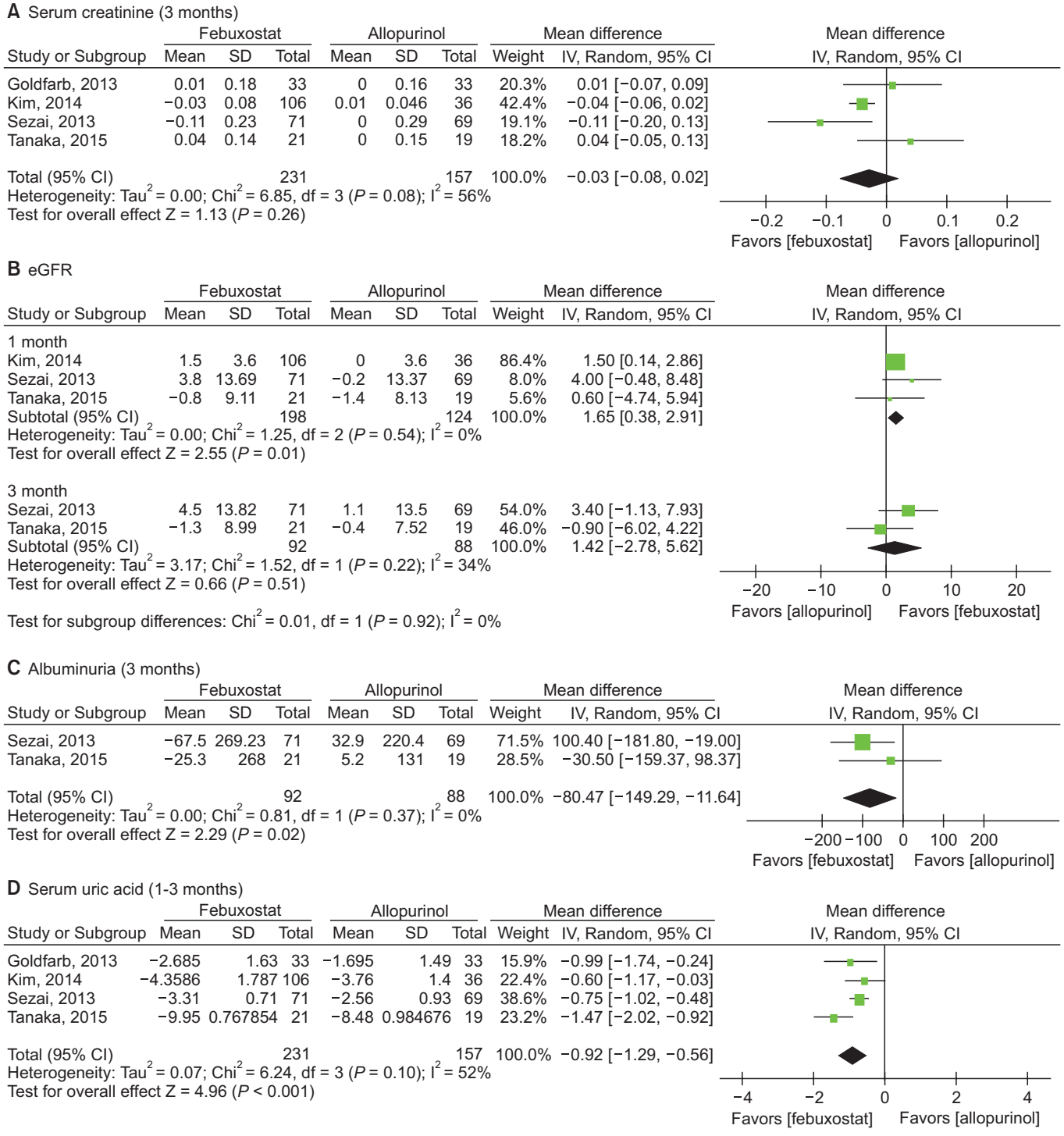

Figure 3. Comparison of renoprotective effects of febuxostat and allopurinol.
CI, confidence interval; df, degree of freedom; eGFR, estimated glomerular filtration rate; IV, inverse variance; SD, standard deviation.

heterogeneity $\chi^2 = 1.52$, $I^2 = 34\%$, $P = 0.66$) (Fig. 3). These results showed that febuxostat increased eGFR significantly more than allopurinol at 1 month.

Albuminuria

A significant difference was found in the change in the albuminuria level at the 3-month follow-up from base-

line between the febuxostat and allopurinol groups (mean difference −80.47 mg/gCr, 95% CI −149.29, −11.64 mg/gCr; heterogeneity $\chi^2 = 0.81$, $I^2 = 0\%$, $P = 0.02$) (Fig. 3) in two trials.

Serum uric acid

All four trials reported data on serum uric acid levels at the 1- to 3-month follow-ups. The change in serum uric acid levels (follow-up value minus baseline value) was significantly larger in the febuxostat group than in the allopurinol group (mean difference −0.92 mg/dL, 95% CI −1.29, −0.56 mg/dL; heterogeneity $\chi 2 = 6.24$, $I^2 = 52\%$, $P < 0.00001$) (Fig. 3).

Discussion

We performed a systematic review and meta-analysis to show the renoprotective effects of febuxostat in patients with hyperuricemia. Febuxostat showed significant antiproteinuric and uric acid lowering effects at 3 months with preserved eGFR at 1 month. However, eGFR and serum creatinine levels were not different at 3 months between the two groups. This result could be attributed to the limited number of studies analyzed. Another possible cause of insignificant changes in eGFR can be related to the significantly decreased eGFR values of the report of Tanaka et al [12] as compared to the increased levels of eGFR in the allopurinol group. The difference in eGFR levels may be the results of differences in blood pressure. Blood pressure was significantly lower in the febuxostat group than that in the allopurinol group. Other studies showed that eGFR was increased at 6 to 12 months. In observational studies, febuxostat increased eGFR as treatment duration was prolonged. Sakai et al [19] showed that eGFR recovered slowly after febuxostat treatment in hyperuricemic CKD patients who were resistant to allopurinol, while Tsuruta et al [20] reported that the changes in eGFR were significant 12 months after febuxostat was changed from allopurinol. Considering that eGFR and albuminuria are the most important renal function markers, febuxostat may be more renoprotective than allopurinol.

Hyperuricemia is associated with chronic kidney disease [21]. In animal studies, hyperuricemia induces glomerular hypertension and afferent arteriolar thickening, resulting in interstitial inflammation and fibrosis [22,23]. The largest study reviewed included 177,570 patients enrolled in the United States Renal Data System database followed over 25 years. Subjects within the highest quartile of serum uric acid had a hazard ratio of 2.14 for CKD—a level of risk that ranked third after proteinuria and severe obesity [24]. We are aware of the three recently published systematic reviews about uric acid-lowering effects in chronic kidney disease [25–27]. Wang et al [27] conducted a search up to December 2011 and included studies with patients with hyperuricemia regardless of kidney function. They reported that urate-lowering agents were associated with a decrease in serum creatinine and an increase in eGFR, showing the beneficial effects of urate-lowering agents on slowing the progression of renal function. Bose et al [25] conducted a comprehensive English literature search up to December 2012. They included studies of patients with normal or mildly decreased GFR of kidney transplant recipients, but they could not draw conclusions due to a lack of robust data. Kanji et al [26] performed a search up to June 2013. They included studies of patients with baseline eGFR < 60 mL/min/1.73 m^2 or serum creatinine > 1.55 mg/dL for men and > 1.18 mg/dL for women. They suggested that using allopurinol in clinical practice to delay CKD progress would be premature because of the lack of good quality studies. However, these three systematic reviews did not include febuxostat as an intervention agent. Our meta-analysis focused on the effect of febuxostat vs. allopurinol as a urate-lowering agent. Febuxostat was more renoprotective than allopurinol.

Allopurinol is widely used as a urate-lowering agent in gout patients [6]. The renoprotective effects of this agent have been reported in several studies in CKD. However, allopurinol is not widely used for renoprotection because of its mild to severe adverse effects including life-threatening hypersensitivity syndrome. These adverse effects are more common in CKD patients. Febuxostat can be used as an alternative to allopurinol. The main route of febuxostat elimination is in the liver, followed by excretion of metabolites in the urine and feces. The area under the time–concentration curve is increased by a factor of 1.8 in patients with severe renal dysfunction, but no dose adjustment is required in mild-to-moderate renal impairment [6]. In one systematic review, febuxostat showed more urate-lowering effects and less adverse effects than

allopurinol in participants with normal and abnormal renal functions [28]. Some studies [10–12] have also reported the renoprotective effects of febuxostat. Although febuxostat is effective in lowering uric acid and safe in CKD, it is still unclear whether its renoprotective effect is superior to allopurinol. We concluded that febuxostat would be more renoprotective than allopurinol.

The strengths of this review are that it represents a comprehensive overview of the evidence and risk of bias assessment and includes only RCTs. The limitations are as follows. First, we included only four studies. Second, the follow-up period was only 1 to 6 months; this period is extremely short to evaluate the changes of biological laboratory markers. Third, the renal functions of the patients were not homogeneous. The mean eGFR was different among the studies. Fourth, the quality of the included studies was variable. This review included a small number of single-center trials with relatively short and variable duration of follow-up, as well as clinical heterogeneity in trials evaluating baseline kidney function and proteinuria. One study [12] was an open-label trial, and one study [17] did not report eGFR. A sensitivity analysis could not be performed because of the small number of studies. The suboptimal quality of the included trials limited our ability to draw robust conclusions. Finally, the lack of data on the adverse effects of febuxostat and allopurinol limits our ability to make solid conclusions regarding the renoprotective abilities of the two drugs.

In conclusion, through our meta-analysis, we found that febuxostat was more renoprotective than allopurinol. Currently, routine prophylaxis of asymptomatic hyperuricemia is not recommended in the current guidelines. Urate-lowering therapy is only used for patients with clinical evidence of crystal deposition including gout and urolithiasis [29]. Although more RCTs on renoprotective effects of febuxostat are encouraged, febuxostat can be considered as an alternative to allopurinol in patients with hyperuricemia.

Conflicts of interest

All authors have no conflicts of interest to declare.

Supplemenary materials

The supplementary materials of this study are available at https://doi.org/10.23876/j.krcp.2017.36.3.274.

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