Efficacy of febuxostat in hyperuricemic patients with mild-to-moderate chronic kidney disease: a meta-analysis of randomized clinical trials

A PRISMA-compliant article

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Abstract

Background: To investigate the efficacy of febuxostat in hyperuricemic patients with chronic kidney disease (CKD), relevant randomized clinical trials (RCTs) were analyzed.

Methods: We used PubMed, Medline, ISI Web of Science, CBMdisc, and Cochrane Library databases to conduct a systematic literature research. A fixed-effects model was used to evaluate the standardized mean differences (SMDs) with 95% confidence intervals (CIs). We conducted subgroup analysis, sensitivity analysis, and analyzed publication bias, to comprehensively estimate the renoprotective effects of febuxostat in hyperuricemic patients with CKD.

Results: Among 296 retrieved studies, 5 relevant RCTs were included in the meta-analysis. The result showed that serum estimated glomerular filtration rate (eGFR) was improved after febuxostat treatment in hyperuricemic patients with CKD, with an SMD (95% CI) of 0.24 [−0.17 to 0.43] and \( P = .67 \) (fixed-effects model). No heterogeneity was observed across studies (\( I^2 = 0\% \) and \( P = .67 \)). Subgroup analysis suggested that treatment-related reductions in serum eGFR levels were not related to drug doses, intervention times, or region.

Conclusions: The present meta-analysis suggests that febuxostat may slow the progression of mild-to-moderate CKD. Given the limited number of included studies, additional large sample-size RCTs are required to determine the long-term renoprotective effects of febuxostat in hyperuricemic patients with CKD.

Abbreviations: CIs = confidence intervals, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, RCTs = randomized clinical trials, SD = standard deviation, SMD = standard mean differences.

Keywords: chronic kidney disease, efficacy, febuxostat, hyperuricemia, meta-analysis

1. Introduction

Hyperuricemia is a common complication of chronic kidney disease (CKD). In addition, emerging data show that it is an independent risk factor for CKD.¹⁻⁶ Serum uric acid (SUA) is the terminal product of purine metabolism in humans, and is regulated by the kidneys. Because urinary uric acid excretion in CKD patients is reduced, the prevalence of hyperuricemia is higher in this patient population.⁷ Previous studies showed that there is an increased risk of hyperuricemia of 11% per 1mg/dL increase in uric acid.⁸ Furthermore, individuals with hyperuricemia (>9mg/dL) have a 3-fold higher risk of developing CKD.¹⁴

Febuxostat is a new and potent xanthine oxidase (XO) inhibitor. In 2011, it became the first-line urate-lowering therapy for the treatment of hyperuricemia.¹⁹ Hyperuricemia is involved in the pathogenesis of CKD, and might be associated with activation of XO, endothelial dysfunction, and/or tubular injury.¹⁰⁻¹² Moreover, febuxostat ameliorates the progression of CKD by decreasing oxidative stress, and suppressing endothelial dysfunction and tubular injury.¹³ It is primarily eliminated by the liver, and is well tolerated by CKD patients. Moreover, febuxostat may not only by reducing circulating uric acid levels, but also through the other mechanisms, including the reduction of inflammation and oxidative stress and the prevention of glomerular hypertension, afferent arteriolar thickening, and ischemic renal histologic changes, to ameliorate renal damage. In all, febuxostat may be effective for preventing the progression of renal function progress in patients with CKD.

However, the renoprotective effect of febuxostat remains controversial. Although some studies reported positive results,¹⁴⁻¹⁶ others found it had no significant effect on the
progression of renal dysfunction in patients with CKD.\textsuperscript{[17–19]} Furthermore, no systematic studies demonstrating whether renal function is improved after febuxostat therapy in hyperuricemic patients with CKD have been reported.

To determine the renoprotective effects of febuxostat in hyperuricemic patients with CKD, we performed a systematic literature review and meta-analysis of randomized clinical trials (RCTs).

2. Materials and methods

2.1. Search strategy

This study was performed according to the Cochrane Handbook for Systematic Reviews of Interventions,\textsuperscript{[20]} and it published according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.\textsuperscript{[21]} We searched the databases discussed below for studies published up until September 2017 that assessed the renoprotective effects of febuxostat in hyperuricemic patients with CKD.

We searched the following electronic databases for RCTs published no later than September 2017: PubMed, Medline, ISI Web of Science, CBMdisc, and the Cochrane Library. No limits were set on language. The search strategy included the following terms:

\begin{itemize}
  \item (“Renal Insufficiency, Chronic” OR “Chronic Renal Insufficiencies” OR “Renal Insufficiencies, Chronic” OR “Chronic Renal Insufficiency” OR “Kidney Insufficiency, Chronic” OR “Chronic Kidney Insufficiency”) AND (“Hyperuricemia”) AND (“Febuxostat”).
\end{itemize}

2.2. Inclusion and exclusion criteria

The inclusion criteria for the selected studies were as follows: studies that measured SUA and estimated glomerular filtration rate (eGFR) in hyperuricemic patients with CKD undergoing febuxostat therapy as part of randomized controlled trials; studies that reported baseline and follow-up data on the mean and standard deviation (SD) of SUA and eGFR levels, or sufficient information which allowed for the calculation of mean and SD; studies included that eGFR range from 20mL/min per 1.73 m\(^2\); RCTs.

The exclusion criteria were as follows: letters, reviews, animal studies, case reports, and studies without controls; studies that included participants on dialysis, with kidney transplantation, with malignancy, or with eGFR <20 mL/min per 1.73 m\(^2\); studies with participants <18 years old; studies that did not report outcomes related to renal function.

2.3. Data extraction and quality assessment

Study selection and data extraction were performed independently by 2 investigators (Zeng and Tang). Clinical trials that assessed the renoprotective effects of febuxostat in hyperuricemic patients with CKD were selected for review. The 2 investigators blindly collected all recorded information pertaining to general characteristics, doses of febuxostat, duration of treatment, and outcomes (mean and SD values of SUA and eGFR before and after administration of febuxostat). If raw data were not provided, they were extracted from figures and tables as necessary. Any disagreement between the 2 investigators was resolved by a third investigator (Xu) to arrive at a consensus. The quality of the information accessed in RCTs was classified as low, unclear, or high by evaluating the following 7 components: random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and “other bias” according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.

2.4. Statistical analysis

We measured the standardized mean difference (SMD) and 95% confidence intervals (CIs) of eGFR to estimate the renoprotective effect of febuxostat. We estimated statistical heterogeneity among the included studies using the \(I^2\) statistic 0.22 and the \(\chi^2\)-based \(Q\)-statistic. Significant heterogeneity was considered to exist between the studies when \(P < .05\) for the \(Q\)-statistic or \(I^2 > 50\%\). The random-effects model (Mantel–Haenszel method) was used if heterogeneity was detected. Otherwise, the fixed-effects model was used. Subsequently, to identify the sources of heterogeneity, subgroup analysis was carried out for factors including region, and therapeutic dose and duration. Furthermore, restricted maximum likelihood-based random-effects meta-regression analysis was performed to evaluate the aforementioned potential heterogeneity factors. Univariate meta-regression analysis was carried out first, after which the variables that were significant at the 0.1 level were entered into the multivariable model. Sensitivity analyses were performed to evaluate the stability of the results of meta-analysis. Potential publication bias is presented as funnel plots. All analyses were performed using Review Manager Software (RevMan, version 5.2 from the Cochrane Collaboration). Statistical significance was set at \(P < .05\). The appropriateness of pooling data across studies was assessed with the use of Cochran \(Q\) and the \(I^2\) test for heterogeneity.

2.5. Ethical approval

Ethical approval was not necessary because our study was a meta-analysis.

3. Results

3.1. Flow chart of study selection

A total of 296 studies were identified in the initial literature search. A flow diagram of the study selection process is shown in Figure 1. As part of the initial screening of titles and abstracts, we excluded 171 citations, and the 33 articles were to be retrieved for full text review, 28 were excluded: 18 did not report baseline eGFR and/or outcomes related to renal function, 8 did not meet the inclusion criteria, and 2 measured serum creatinine in hyperuricemic patients with CKD undergoing febuxostat therapy. Therefore, 5 randomized, double-blind, controlled trials\textsuperscript{[22–26]} were included in the meta-analysis: 3 RCT studies comparing febuxostat with allopurinol in hyperuricemic patients with CKD\textsuperscript{[23,25,26]} and 2 comparing febuxostat with placebo in hyperuricemic patients with CKD.\textsuperscript{[22,24]}

3.2. Characteristics of included studies

The characteristics of included studies are summarized in Tables 1 and 2. Among the 5 studies eligible for the meta-analysis, a total of 835 subjects were enrolled. Among them, 437 subjects were randomized to receive febuxostat. Three studies were conducted...
in Eastern countries\(^{22,23,26}\) and 2 were conducted in Western countries.\(^{24,25}\) One of the studies (comparing febuxostat vs placebo) did not provide the mean age and SD for each group of patients,\(^{24}\) whereas the others included CKD patients >18 years old. The duration of therapy ranged from 3 to 48 months. Three RCT studies compared febuxostat with allopurinol in hyperuricemic patients with CKD,\(^{23,25,26}\) and 2 compared febuxostat with placebo in hyperuricemic patients with CKD.\(^{22,24}\) The doses of febuxostat ranged from 40 to 240 mg/d. Table 3 shows the risk of bias of randomized trials included in the meta-analysis. Randomization was performed according to a computer-generated random list or by means of a randomly generated number pattern in a majority of the trials.\(^{22-26}\) The randomized trials included in our study were characterized by a low risk of incomplete outcome data and selective outcome reporting. Five randomized trials included in our study were characterized by a high risk of blinding of participants and personnel and outcome assessment.\(^{22-26}\) Moreover, all randomized trials were with an unclear risk of other bias. In conclusion, the quality of these studies was moderate to high.

### 3.3. Pooled analysis

Meta-analysis of data from the 5 eligible studies showed that serum eGFR levels were significantly improved in hyperuricemic patients with CKD compared with the same patient before febuxostat treatment controls (fixed-effects model, SMD = 0.24, 95% CI = [-0.19 to 0.69]; Fig. 2.) and (random-effect model, SMD = 0.24, 95% CI = [0.06-0.43]; Fig. 2.). No heterogeneity was observed across studies (\(I^2 = 0\%\) and \(P = .67\)).

### 3.4. Subgroup analysis

Subgroup analysis was performed according to region (Eastern or Western), duration of therapy (<6 months or >6 months), and dose of febuxostat (<40 mg/d or ≥40 mg/d). In the subgroup analysis, the overall pattern of pooled effect did not vary substantially by the potential sources of heterogeneity, including region and duration of therapy (Table 4). The dose of febuxostat ranged from 40 to 240 mg/d. We performed subgroup analysis for the low-dose (<40 mg/d) and high-dose (≥40 mg/d) febuxostat groups (Fig. 3). According to the results, the low-dose (<40 mg/d) febuxostat group did not show heterogeneity (fixed-effects model, SMD = 0.25, 95% CI = [-0.19 to 0.69], \(I^2 = 0\%\) and \(P = .46\)) as well as the high-dose (≥40 mg/d) febuxostat group (fixed-effects model, SMD = 0.24, 95% CI = [0.03-0.45], \(I^2 = 0\%\) and \(P = .40\)). Furthermore, we conducted subgroup analysis for groups that received different doses of febuxostat (Fig. 4). The outcome of the analysis showed that those who received 240 mg/d febuxostat had increased renoprotective effects (fixed-effects model, test for overall

### Table 1

**Characteristics of the 5 studies in the meta-analysis.**

| Author (year) | Country | CKD criteria | Age (FG vs CG) mean ± SD | Size FG/CG | Types of studies and intervention | Doses (mg/d) | Therapy (mo) |
|---------------|---------|--------------|--------------------------|------------|----------------------------------|--------------|-------------|
| Kenichi (2015)\(^{22}\) | Japan | Rotterdam | 70.1 ± 0.5 vs 66.1 ± 7.0 | 25/20 | RCT comparing the use of febuxostat + placebo in CKD stage 3 or 4 patients | Febuxostat was incremented stepwise to maximum 40 mg/d | 3 |
| Shankar (2017)\(^{23}\) | India | Rotterdam | 52.7 ± 12.7 vs 51.7 ± 13.1 | 54/47 | RCT comparing the use of febuxostat + allopurinol in CKD 3a | Febuxostat: 20–80 mg/d + allopurinol: 100–300 mg/d | 6 |
| Kenneth (2016)\(^{24}\) | UK | Rotterdam | NA | 63/32 | RCT comparing the use of febuxostat + placebo in CKD stage 3 or 4 patients | Febuxostat: 30 mg twice daily | 12 |
| Andrew (2013)\(^{25}\) | American | Rotterdam | 51.9 ± 10.26 vs 52.2 ± 13.61 | 277/274 | RCT comparing the use of febuxostat + allopurinol in CKD stage 3 or 4 patients | Febuxostat: 80 mg/d or 120 mg/d + allopurinol: 240 mg/d + | 48 |
| Chen (2016)\(^{26}\) | China | Rotterdam | 53 ± 16 vs 57 ± 21 | 17/26 | Comparing the use of febuxostat + allopurinol in CKD stage 3 or 4 patients | Febuxostat: 20/40 mg/d + allopurinol: 200 mg/d or 300 mg/d | 6 |

CG = control group, FG = febuxostat group, NA = not available, RCT = randomized controlled trial, SD = standard deviation.
The overall effect indicated that there was no striking heterogeneity among these subgroups (fixed-effects model, SMD = 0.88, 95% CI = [−0.56 to 2.31], \( I^2 = 49\% \) and \( P = .23 \)).

### 3.5. Sensitivity analysis and publication bias

Sensitivity analysis revealed that removal of any one study from the analysis did not subvert the results of the pooled analysis (data not shown). Similarly, excluding 2 studies enrolling both

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**Figure 2.** Meta-analysis of data on serum eGFR in hyperuricemic patients with CKD. CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SMD = standard mean differences.
doses were no >40mg\cite{22,26} did not influence our primary analyses for eGFR (SMD, 0.24; 95% CI, 0.03–0.45; \(P = .02\)), target eGFR level (SMD, 0.24; 95% CI, 0.06–0.43; \(P = .01\)). After exclusion of the long-term follow-up studies\cite{24,25} results were similarly unchanged for eGFR (SMD, 0.23; 95% CI, –0.06 to 0.52; \(P = .12\)) and showed no significant difference. Therefore, the outcome of the pooled analysis can be regarded with a higher degree of certainty. Furthermore, we constructed funnel plots to evaluate publication bias. The funnel plots (Fig. 5) for eGFR showed no publication bias.

### 4. Discussion

The present meta-analysis demonstrated that there was a significant improvement in eGFR after febuxostat therapy (SMD, –0.46; 95% CI, –0.97 to 0.05; \(P = .01\)) in hyperuricemic patients with CKD. The eGFR outcome of the analysis had significant differences. Furthermore, no significant heterogeneity was observed across the included studies. According to subgroup analysis, the febuxostat-treated group (240mg/d) was the group with the greatest amelioration of renal function (test for overall effect: \(P = .01\)). The efficacy of 240mg/d was superior to other doses, and with dose increases, the effect of 240mg/d febuxostat was significantly enhanced.

Hyperuricemia is an independent risk factor for CKD. Large increases or sustained elevations showed that SUA is associated with renal injury.\cite{33} Based on the present meta-analysis and previous observations, decreasing SUA level was associated with significant improvement in the progression of CKD. Therefore, administration of febuxostat may be effective for preventing the progression of renal function progress in patients with CKD.

According to the results of our meta-analysis, febuxostat may be effective in ameliorating renal function progress in CKD. Recent studies indicated that the renoprotective effect of febuxostat may be related to reduction of SUA.\cite{27} Febuxostat may decrease tubulointerstitial impairment and suppress oxidative stress.\cite{11,28} In addition, it was proposed to be involved in the reduction of plasma renin activity, inhibition of oxidative stress, and improvement of endothelial dysfunction.\cite{22,29–33} Furthermore, studies showed that subgroup analysis according to country, duration, and dose did not change significantly after febuxostat treatment in patients with CKD. Moreover, no significant heterogeneity was observed. However, additional studies are necessary to fully understand the precise mechanism of febuxostat in CKD.

The strength of the present meta-analysis is that it is the first comprehensive review to summarize the available evidence for assessing the renoprotective effects of febuxostat in hyperuricemic patients with CKD. In addition, the results are stronger than any single study given that the included RCTs demonstrate homogeneity. We are plausible biological mechanisms to explain the renoprotective effect of febuxostat. Our process for data collection was as complete as possible. Furthermore, subgroup analyses of several relevant factors were carried out. We did not

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### Table 4

| Subgroup meta-analysis of the included studies. |
|-----------------------------------------------|
| Subgroup analysis | Number of studies | Random-effects SMD (95% CI) | \(I^2\) (%) | \(P\) for heterogeneity |
|-------------------|-------------------|-----------------------------|------------|------------------------|
| Country           |                   |                             |            |                        |
| Eastern           | 3                 | 0.23 (–0.06 to 0.52)        | 0          | .75                    |
| Western           | 2                 | 0.26 (0.01–0.50)            | 44         | .18                    |
| Months            |                   |                             |            |                        |
| ≤6               | 3                 | 0.23 (–0.06 to 0.52)        | 0          | .75                    |
| >6               | 2                 | 0.26 (0.01–0.50)            | 44         | .18                    |
| Dose, mg/d        |                   |                             |            |                        |
| ≤40              | 2                 | 0.25 (–0.19 to 0.69)        | 0          | .46                    |
| >40              | 3                 | 15.03 (8.32–21.73)          | 100        | <.00001                |

SMD = standard mean differences.

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**Figure 3.** Meta-analysis of subgroups including low-dose (<40 mg/d) and high-dose (≥40 mg/d) febuxostat groups before and after treatment, using a fixed-effect model. CI = confidence interval, SMD = standard mean differences.
detect significant heterogeneity or publication bias. Based on these factors, this review should provide convincing evidence regarding the renoprotective effect of febuxostat in hyperuricemic patients with CKD.

The present meta-analysis also has limitations. The primary limitation is the limited number of studies analyzed. We only included 5 studies, and could not conduct a meta-regression analysis. In addition, the data (urinary protein, serum creatinine, albumin, and b2MG levels) included in the studies were inadequate, and the mean eGFR was different among them. Therefore, we could not comprehensively evaluate the renoprotective effects. Moreover, other measurements such as smoking status, obesity, and other lifestyle factors should be considered confounding factors because the results of our study were based on unadjusted estimates. Finally, this review included small sample-size, single-center studies with clinical heterogeneity and variable patient backgrounds, which could have resulted in low statistical power and inconsistent results among studies. Four studies\[22,23,25,26\] were open-label trials. Therefore, large sample-size clinical trials should be carried out to further verify the renoprotective effects of febuxostat in hyperuricemic patients with mild-to-moderate CKD.

5. Conclusions

In conclusion, this review represents a comprehensive analysis of the assessment of the renoprotective effects of febuxostat and includes only RCTs. It showed that there was significant improvement of serum eGFR after febuxostat treatment in hyperuricemic patients with CKD. Furthermore, the efficacy of 240 mg/d febuxostat was superior to other doses, and with dose increases, the effect of 240 mg/d febuxostat was significantly increased. The data suggest that febuxostat may ameliorate renal function in early CKD. Additional studies are required to further verify the renoprotective effects of febuxostat in hyperuricemic patients with mild-to-moderate CKD.

Figure 4. Meta-analysis of data on the comparison of different doses of febuxostat before and after treatment in hyperuricemic patients with CKD, using a fixed-effect model. CI = confidence interval, SMD = standard mean differences.

Figure 5. Funnel plot of studies evaluating the association between eGFR and febuxostat in hyperuricemic patients with CKD.
patients with CKD. Considering the limited number of studies analyzed, large sample-size clinical trials are necessary to verify the long-term effects of febuxostat on renal function in CKD.

Author contributions
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