

# The potential renoprotection of xanthine oxidase inhibitors: Febuxostat versus allopurinol

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Hyperuricemia is regarded as a contributor to the progression of chronic kidney disease (CKD) as well as a consequence of CKD. Since approximately 70% of uric acid (UA) is excreted by the kidney, hyperuricemia inevitably develops in individuals with CKD [1]. In a recent survey of National Health and Nutrition Examination Survey (NHANES) data, the odds ratios (ORs) of gout and hyperuricemia were 5.9 and 9.6 among individuals with a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m<sup>2</sup> compared to those with a GFR above 90 mL/min/1.73 m<sup>2</sup> [2].

There is a great deal of basic and clinical evidence that hyperuricemia induces renal injury through various mechanisms and may play a role in the development and progression of CKD. A significant positive association was found between hyperuricemia and the development of CKD among non-CKD patients (summary OR, 2.35) in a meta-analysis based on observational cohort studies [3]. In addition, several trials sought to elucidate the effects of urate-lowering agents on CKD progression. Mostly those trials investigated the effects of allopurinol, a classic xanthine oxidase inhibitor. Although allopurinol has been used widely for the control of serum UA levels, it has infrequent but serious skin side effects. Furthermore, the effectiveness of allopurinol in slowing the development and progression of CKD remains controversial. Indeed, a

systematic review and meta-analysis revealed that allopurinol had no effects on GFR, proteinuria or blood pressure [4].

In this issue of *Kidney Research and Clinical Practice*, Kim et al [5] compared the effects of febuxostat and allopurinol on GFR and proteinuria. Febuxostat, a novel xanthine oxidase inhibitor, is safe and efficacious in patients with stage 3b-5 CKD [6]. The authors performed a systematic review and meta-analysis of randomized controlled trials to compare the renoprotective effect and urate-lowering effect between allopurinol and febuxostat in patients with hyperuricemia. After careful selection among 3,815 initially identified articles, four relevant publications were included in their analysis: One was conducted in Korean gout patients with normal renal function [7], while another was conducted in the USA [8], and the remaining two studies were from Japan [9,10]. Although there was a significant difference in GFR changes at 1 month (mean difference 1.65 mL/min/1.73 m<sup>2</sup>), this difference did not remain statistically significant at 3 months. However, there were significant differences in pre- and post-treatment albuminuria and hyperuricemia levels between the febuxostat and allopurinol groups (mean difference, -80.47 mg/g·Cr and -0.83 mg/dL, respectively). Based on these results, the authors concluded that febuxostat might be more renoprotective than allopurinol.

In general, GFR change is not a sensitive indicator compared to change in proteinuria, thus it would not be the best outcome for short-term research with small number of participants. Of interest, a 4-week trial, in which gout patients with normal renal function were included, showed significantly higher GFR in the febuxostat group compared to a control group (68.13 ± 0.76 vs. 69.96 ± 0.45, *P* = 0.031) [7]. However, there were no significant

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differences between febuxostat and allopurinol users. Similarly, no other trials revealed significant differences between febuxostat and allopurinol in GFR at 1, 3, and 6 months [9,10].

In a study with hyperuricemic patients after cardiac surgery [9], febuxostat use was associated with significant improvement in GFR compared to baseline. In this trial, the albuminuria-lowering effect was more clearly defined in the febuxostat vs. allopurinol group. Since the weight value of this study was so heavy, the pooled effect of febuxostat on proteinuria compared to allopurinol was statistically significant. However, the authors did not investigate whether albuminuria decreased after the use of febuxostat at 1, 3, and 6 months compared to baseline. Therefore, whether urate-lowering treatment with febuxostat mitigates proteinuria remains unclear.

In all of the studies included in this meta-analysis, the urate-lowering effect of febuxostat was significantly higher than that of allopurinol. Thus, the favorable effects of febuxostat on proteinuria appear to be associated with the strength of its urate-lowering effect. If the urate-lowering effects of allopurinol and febuxostat were comparable, the renoprotective effects might not differ between the two drugs.

In addition, it should be noted that the renoprotective effects of febuxostat were compared to allopurinol and not a placebo in this meta-analysis. There is not yet a widely accepted consensus with regard to how we define hyperuricemia at which we should start urate-lowering therapy, and how much we have to decrease serum uric acid level for the better outcomes. Therefore, although evidence suggests that febuxostat has superior urate-lowering and anti-proteinuric effects in CKD patients compared to allopurinol, further investigation to find answers for the basic questions regarding when and how much we should manage hyperuricemia is needed.

### Conflicts of interest

The author has no conflicts of interest to declare.

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