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Febuxostat versus allopurinol for renoprotection; a mini-review on recent concepts

Hossein Mardanparvar[1,2*]

Abstract
Both febuxostat and allopurinol inhibit xanthine oxidase to reduce uric acid levels, febuxostat is more selective and potent in its mechanism of action, does not require dose adjustments based on kidney function, and does not affect other enzymes involved in nucleic acid synthesis.
Keywords: Febuxostat, Allopurinol, Chronic kidney disease, Reactive oxygen species, Xanthine oxidase, Oxidative stress, Chronic renal failure
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Introduction

Febuxostat is a selective xanthine oxidase inhibitor that binds to the molybdenum-pterin active site of the enzyme, inhibiting both the oxidase and dehydrogenase activities (1). This characteristic allows it to effectively lower serum uric acid levels without inhibiting other enzymes involved in purine and pyrimidine synthesis and metabolism (2). On the other hand, allopurinol is a non-selective inhibitor that binds to the oxidized form of xanthine oxidase, inhibiting only the oxidase activity (3). It does not inhibit the dehydrogenase activity, which is the primary form of the enzyme under normal conditions (4). Febuxostat binds to the active site of xanthine oxidase with high affinity, leading to potent inhibition of both forms of the enzyme, since allopurinol binds competitively to the oxidized form of xanthine oxidase, which is less potent compared to febuxostat binding mechanism (1,5). Additionally, by inhibiting both forms of xanthine oxidase, febuxostat can reduce the formation of reactive oxygen species that contribute to vascular inflammation and damage, while, allopurinol only inhibits the oxidase activity, which means it does not directly affect reactive oxygen species formation (6,7). Moreover, allopurinol can indirectly impact RNA and DNA synthesis by inhibiting multiple enzymes in purine and pyrimidine metabolism. In contrast, febuxostat only inhibits xanthine oxidase and does not directly affect nucleic acid synthesis (8,9). These differences in mechanism of action contribute to the distinct therapeutic profiles of febuxostat and allopurinol in managing hyperuricemia and gout (8-10). Febuxostat is known for its potency in lowering serum uric acid levels and its potential renoprotective effects, while allopurinol is associated with a higher risk of hypersensitivity reactions but is effective in preventing acute gout attacks (11). This mini-review sought to examine renoprotective efficacy of febuxostat versus allopurinol for renoprotection.

Search method

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; Febuxostat, allopurinol, chronic kidney disease, reactive oxygen species, xanthine oxidase, oxidative stress and chronic renal failure

Febuxostat versus allopurinol in clinical studies

Febuxostat appears to provide better renoprotection compared to allopurinol in patients with chronic kidney disease (CKD) (12,13). The previous large-scale observational study by Hsu et al showed that febuxostat users had a 35% lower risk of progressing to long-term dialysis compared to allopurinol users among patients with pre-dialysis stage 5 CKD. Febuxostat users also had a lower overall rate of dialysis or death (14). The prior meta-analysis by Lin et al, showed that

febuxostat had reno-protective efficacy in chronic renal

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[1]Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2]Guissu Research Corporation, Bandar Abbas, Iran
***Corresponding Author:** Hossein Mardanparvar, Email: h.mardanparvar@hums.ac.ir

Implication for health policy/practice/research/ medical education

Febuxostat is a more selective and potent inhibitor of xanthine oxidase, inhibiting both the oxidase and dehydrogenase activities, while allopurinol is a less selective inhibitor that only targets the oxidase activity. This allows febuxostat to more effectively lower uric acid levels and potentially provide additional benefits related to reducing oxidative stress.

failure patients (11). Additionally, the study by Lee et al in patients with stage three CKD and hyperuricemia, demonstrated that febuxostat group had significantly higher mean eGFR values and longer renal survival time and free from renal disease progression compared to the allopurinol and control groups (13). In another study, however Park et al showed, allopurinol attenuated CKD progression compared to febuxostat (15). Likewise, the meta-analysis by Wang et al, detected, febuxostat may offer a more beneficial therapeutic option for managing chronic renal failure in hyperuricemic individuals (16). The recent study by Yang et al, also showed that, febuxostat 40 mg was more effective than allopurinol 100 mg in reducing serum uric acid levels in CKD patients (13). Meanwhile, a large randomized trial by Becker et al, demonstrated that 53% of the 80 mg febuxostat group and 62% of the 120 mg febuxostat group reached the primary endpoint of serum urate below 6 mg/dL, compared to only 21% in the allopurinol 300 mg group (14). However, some studies found no significant difference between febuxostat and allopurinol in terms of changes in renal function. For instance, the study by Nagaraju et al, detected that febuxostat was superior at diminishing hyperuricemia than allopurinol; nevertheless, no significant difference in the progression of chronic renal failure was seen (15). Recently, Yamamoto et al, in a multicenter randomized controlled trial on chronic renal failure individuals with hyperuricemia found not benefit of intensive uric acid-lowering treatment to ameliorate the level of albuminuria (16). More recently, Yang et al in a meta-analysis exhibited that, administration of febuxostat is connected with an abridged risk of renal events and a slow decline in kidney function. Furthermore, they found the urine albumin to creatinine ratio reduced in febuxostat receivers. They concluded that, this agent is an effectual medication for slowing the development of renal function disturbance in individuals with gout (17). These results show the necessity to larger randomized trials and long-term follow-up studies to establish whether febuxostat has a promising consequence on the progression of chronic renal failure.

Conclusion

Febuxostat may provide superior renoprotection and preservation of kidney function compared to allopurinol in patients with chronic renal failure, particularly in more advanced stages. Febuxostat appears more effective at lowering uric acid levels and slowing the decline in renal function over the long-term. However, more large-scale, long-term studies are still needed to definitively compare the renal outcomes between these two urate-lowering therapies.

Conflicts of interest

The author declares that he has no competing interests.

Ethical issues

The author has adhered to ethical standards in research practices (including the avoidance of plagiarism, data fabrication, and double publication).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author utilized Perplexity to refine grammar points and language style in writing. Subsequently, the author thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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