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Letter

Febuxostat Use and Safety in Patients With Hyperuricemia

To the Editor:

I read the paper by Deng et al,[1] in which the authors conducted a metaanalysis to evaluate whether febuxostat use increased the risk of developing cardiovascular (CV) events, cardiac death, and all-cause mortality. The adjusted relative risk (RR) of febuxostat use for all-cause mortality was 0.87 (95% CI 0.57–1.32). In addition, the adjusted RRs of febuxostat use for CV disease (CVD) mortality and events were 0.84 (95% CI 0.49–1.45) and 0.98 (95% CI 0.83–1.16), respectively. Further, there was no dose-response relationship between febuxostat dose and CV events. The accompanying editorial[2] accepted the study outcomes, presenting safety of febuxostat use for CV events and mortality in patients with hyperuricemia. I have 2 concerns about their study.[1]

First, there are 2 clinical trials to compare the safety of allopurinol and febuxostat: the CARES trial and the FAST trial.[3,4] White et al concluded that "febuxostat was noninferior to allopurinol with respect to rates of adverse CV events. All-cause mortality and CV mortality were higher with febuxostat than with allopurinol."[3] Mackenzie et al[4] also concluded that febuxostat was "non-inferior to allopurinol therapy with respect to the primary CV endpoint," but the long-term use of febuxostat did not increase mortality or serious adverse events (AEs) compared to allopurinol.[4] Choi et al compared the 2 studies and described that "the CARES trial showed internal inconsistency between primary MACE and CVD mortality end points, whereas FAST findings were internally consistent."[5] Fundamentally, there are big differences in the CVD comorbidities of the target patients with gout in the 2 trials. Patients with major CVD within the past 6 months at baseline were excluded in the FAST trial, and the same exclusion was applied within the past 60 days at baseline in the CARES trial. Taken together, both trials present important information regarding safety in gout pharmacotherapy. The mortality risk in patients with severe CVDs should be assessed according to the CARES trial outcomes, with the understanding of the limitation of internal consistency. In patients with mild-to-moderate CVDs, the mortality risk should be assessed according to the FAST trial outcomes.

Second, Gao et al[6] conducted a metaanalysis to summarize the CV safety of febuxostat for the treatment of gout, and the pooled odds ratios (95% CIs) of febuxostat compared with allopurinol for the composite of urgent coronary revascularization and stroke were 0.84 (95% CI 0.77–0.90) and 0.87 (95% CI 0.79–0.97), respectively. Although they observed that febuxostat was not significantly associated with an increased risk of mortality and serious CV AEs compared with allopurinol, there was a risk reduction in CV safety in patients with febuxostat use. Further randomized controlled trials should be conducted to specify the levels of safety in gout pharmacotherapy for patients with hyperuricemia.

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The author declares no conflicts of interest relevant to this article.

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REFERENCES

1. Deng H, Zhang BL, Tong JD, Yang XH, Jin HM. Febuxostat use and risks of cardiovascular disease events, cardiac death, and all-cause mortality: metaanalysis of randomized controlled trials. J Rheumatol 2021;48:1082-9.
2. Charlton A, MacMullan PA. Is febuxostat use associated with increased risk of cardiovascular disease events? The answer is crystal clear. J Rheumatol 2021;48:965-6.
3. White WB, Saag KG, Becker MA, et al; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200-10.
4. Mackenzie IS, Ford I, Nuki G, et al; FAST Study Group. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020;396:1745-57.
5. Choi HK, Neogi T, Stamp LK, Terkeltaub R, Dalbeth N. Reassessing the cardiovascular safety of febuxostat: implications of the febuxostat versus allopurinol streamlined trial. Arthritis Rheumatol 2021;73:721-4.
6. Gao L, Wang B, Pan Y, Lu Y, Cheng R. Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: a systematic and meta-analysis. Clin Cardiol 2021;44:907-16.