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EDITORIAL

Febuxostat and the Black Box Blues

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We met the US Food and Drug Administration's (FDA's) recent decision to include a black-box warning on febuxostat's label with disappointment (1). This decision was based largely on the results of the cardiovascular safety of febuxostat and allopurinol in participants with gout and cardiovascular comorbidities (CARES) trial (2), an FDA-mandated phase 4 study to follow up a possible signal in the initial phase 3 data. For reasons we have described before (3) and will recapitulate here, the authors of the CARES report suggested that febuxostat use is associated with increased cardiovascular (CV)–related death, but the conclusion was undercut by the study's own data. First, because the study compared febuxostat with allopurinol but included no control arm, the febuxostat result is interpretable only relative to allopurinol; at most, the study directly supports a relative benefit of allopurinol, not an independent risk of febuxostat. Moreover, the CARES trial applies directly only to patients at high risk of CV, whom the study enrolled, yet given the nature of its process, the FDA apparently felt obliged to issue its black-box warning for all patients with gout, raising a concern that may not apply to patients at low risk of CV and potentially "throwing out the baby with the bathwater."

Through no fault of the trial's designers (and despite their best efforts to follow up lost subjects), the CARES trial was also hobbled by a high drop-out rate, with a majority of patients not completing the trial, leaving the FDA to make decisions on what was essentially an incomplete data set. Indeed, when additional, nonadjudicated deaths among lost subjects who were identified by a search company were included, any difference in risk of death between allopurinol and febuxostat became nonsignificant. As to the specifics, only a small fraction of the deaths in question occurred while patients were on the study drug. In fact, roughly 90% of the reported deaths occurred after the study drugs (allopurinol and febuxostat) had been discontinued; although it is difficult to impute causality to a variable no longer present, the FDA clearly felt obliged by its process to do so.

Although patients enrolled in the CARES trial were at high risk of CV events, it employed no uniform protocol with respect to the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Although randomization yielded equal numbers of patients taking aspirin in both treatment groups, there was a twofold higher CV mortality rate for those patients randomly assigned to febuxostat not taking aspirin compared with those who were on allopurinol without aspirin. In contrast, patients who were taking aspirin experienced no increased rates of CV mortality while on febuxostat versus allopurinol. For NSAIDs, the opposite result was seen: patients randomly assigned to febuxostat who were simultaneously taking NSAIDs experienced a twofold CV mortality increase compared with allopurinol users taking NSAIDs, whereas no difference in CV mortality was seen among the febuxostat and allopurinol users not taking NSAIDs. In applying the wisdom of hindsight, perhaps it would be better (if such a study were to be performed again) if all patients at high risk of cardiovascular disease (CVD) received indicated cardioprotective aspirin and were instructed to avoid CV risk–inducing NSAIDs. In any event, these observations suggest that even if there is a CV risk of febuxostat relative to allopurinol, it may be mitigated through proper patient selection and appropriate, guideline-based CV management (4). Indeed, if the study had protocolized aspirin use and NSAID avoidance, the FDA might have had the opportunity to provide guidance on risk minimization instead of recommending avoidance of febuxostat.

Weakening the supposition that febuxostat increases the risk of CV death, several other studies show no such association. A recent meta-analysis found an increased rate of CV-associated death across 10 prospective trials but only when CARES study data were included (5). Moreover, in a recently published retrospective study of US Medicare claims data in which 24 936 febuxostat initiators were compared with 74 808 allopurinol investigators (roughly 100-fold the number of CARES enrollees), the incidence of myocardial infarction or stroke (primary outcome) did not differ between the two groups. Secondary outcomes, such as all-cause mortality, also did not differ between the two groups, except for a slight decrease in heart-failure exacerbation in the febuxostat group. These observations persisted in subgroup analyses of patients at high risk of CVD, similar to the entry criteria for the CARES trial (6). Although well-designed prospective clinical trials

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have the potential to provide specific, superior, and causal data that retrospective studies may not, the FDA's own recent emphasis on incorporating "real-world evidence" into their decision-making processes suggests that, at the least, they should have explicitly addressed these results (7), particularly because they apply to low-risk patients, who were not directly addressed in the CARES trial.

Because the CARES study presents a limited case for febuxostat as an independent risk factor for CV mortality and given that a safety alert had already been in place for nearly a year, perhaps the FDA could have taken a "wait-and-see" approach, because further data were about to be published on the very subject. On March 7 2019, the results from the prospective randomized controlled trial, Febuxostat for Cerebral and Cardiorenovascular Events Prevention Study (FREED) (N = 1070), were published, which showed that febuxostat did not increase CVD, CV mortality, or all-cause mortality in a group of elderly patients with hyperuricemia (without gout) at high risk of CVD; the comparator group in this study received low-dose allopurinol or no treatment (8). If this study was not considered sufficient evidence, the FDA could have chosen to await the Febuxostat versus Allopurinol Streamlined Trial (FAST) (N = 6142), a prospective randomized trial that enrolled patients with hyperuricemia and gout who were at high risk of CV events (9). FAST (performed specifically to investigate the CV safety of allopurinol and febuxostat) studied a population comparable with the CARES cohort and will be helpful at either confirming or refuting the conclusions drawn from the CARES trial. Patient recruitment was completed in late 2017, and results are expected shortly.

The FDA's job is, no doubt, a difficult one. It must ensure public safety and, in so doing, err on the side of minimizing harm. While waiting for more definitive data, it would certainly have been appropriate for the FDA to continue to encourage caution, and it would have been reasonable for physicians to consider allopurinol as a first-line agent as a generally prudent approach. But febuxostat remains an important tool for treating a disease with very few other options, and we are concerned that this black-box warning (and all the attendant sensationalism that may surround it) may lead many patients in need of this therapy to not receive it, leading, ironically, to poor outcomes and possibly even higher mortality. The black-box warning may also dampen enthusiasm to conduct studies that might eventually answer the question properly. Regardless of what the soon-to-be-published FAST study concludes, first impressions are difficult to undo, and black-box warnings are rarely removed, so the stigma that now surrounds febuxostat (deserved or not) may stick.

AUTHOR CONTRIBUTIONS

Drs. Abeles and Pillinger drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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