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EDITORIAL

Advances in gout: some answers, more questions

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See related research by Becker et al., http://arthritis-research.com/content/12/2/R63

Abstract

In a previous issue of the journal, Becker and colleagues present efficacy and safety data from a large study comparing febuxostat to allopurinol. The study showed non-inferiority of febuxostat 40 mg/day in lowering serum urate compared to allopurinol 200 to 300 mg/day. More importantly, the study showed a similar frequency of important cardiovascular adverse events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) for febuxostat 40 mg/day (0%), febuxostat 80 mg/day (0.4%) and allopurinol groups (0.4%). Other cardiac adverse event rates (unstable angina, coronary revascularization, cerebral revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic event, congestive heart failure, and arrhythmia) were also similar for febuxostat 40 mg/day (1.3%), febuxostat 80 mg/day (1.2%) and allopurinol groups (0.9%). A meta-analysis of safety data from published studies is presented.

For many decades, urate-lowering therapy consisted of allopurinol, a xanthine-oxidase inhibitor and uricosurics, such as probenecid, sulfinpyrazone and benzbromarone. Febuxostat, another xanthine inhibitor, was approved in 2009 in the US, Canada, Japan and the European Union for the treatment of hyperuricemia in gout patients. Gout is associated with high medical comorbidity and deficits in health-related quality of life. In a previous issue of *Arthritis Research and Therapy*, Becker and colleagues [1] describe a non-inferiority randomized controlled trial (RCT) of febuxostat compared to allopurinol in 2,269 patients with gout. Several findings of this important study merit discussion.

The cornerstone of gout treatment is achievement of a target serum urate <6 mg/dl. This therapeutic goal is based on the solubility of urate at 37°C (6.8 mg/dl), levels below which have been associated with lower risk of gout flares and tophi [2-4]. A target serum urate was achieved in significantly more patients in the febuxostat 80 mg group (67%) compared to the 40 mg group (45%) and the allopurinol group (42%; 300 mg daily or 200 mg daily in moderate renal impairment); the 40 mg febuxostat dose was not inferior to allopurinol [5]. First, the superiority of febuxostat 80 mg/day to allopurinol 300 mg/day in achieving serum urate <6 mg/dl in this study confirms similar findings from previous RCTs of febuxostat using this or higher doses of febuxostat (120 and 240 mg daily) [5-7]. This study provides evidence for non-inferiority of a febuxostat 40 mg dose compared to allopurinol in achieving a target serum urate <6 mg/dl. One important fact to bear in mind, however, is that the allopurinol dose should be optimally titrated between 100 and 800 mg/day in clinical settings (or even higher doses in some cases according to experts) to achieve a target serum urate <6 mg/dl, and all febuxostat studies to date have used 200 or 300 mg allopurinol as the comparator. Therefore, these studies do not answer an important question: is febuxostat superior to a titrated dose of allopurinol in the treatment of hyperuricemia in patients with gout? We know now that allopurinol doses of ≤300 mg/day fail to adequately treat hyperuricemia in 50% of gout patients [8]. It should be noted that, in practice, many physicians do not adequately titrate allopurinol and fail to follow serum urate to achieve the target level [9-10]. Thus, there is limited 'real world logic' in such a study design strategy.

Second, this study provides safety data as one of its important secondary outcomes. This finding has high relevance since cardiovascular adverse outcomes were an early safety signal in the first large febuxostat RCT, with four deaths in the two febuxostat groups and no deaths in the allopurinol group [5]. In the current study, febuxostat was well-tolerated and not associated with significantly more cardiovascular adverse events compared to allopurinol [1]. Cardiovascular adverse events as defined by the Adjudicated Antiplatelet Trialists Collaboration (APTC; cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) occurred in 0% of patients in the febuxostat 40 mg group, 0.4% in the febuxostat 80 mg group and 0.4% in the allopurinol group, without a

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Table 1. Serious adverse events, cardiovascular adverse events and mortality in randomized controlled trials of febuxostat

Study	Duration	Febuxostat 40 mg/day	Febuxostat 80 mg/day	Febuxostat 120 mg/day	Allopurinol 200/300 mg/day	Placebo
Cardiovascular adverse events						
Schumacher *et al.* [7]	1 month	-	5/267 (2%)[a]	5/269 (2%)	1/268 (0.4%)	1/134 (0.7%)
Current study [1]	6 months	APTC: 0/757 (0%) Non-APTC: 10/757 (1.3%)	APTC: 3/756 (0.4%) Non-APTC: 9/756 (1.2%)	-	APTC: 3/756 (0.4%) Non-APTC: 7/756 (0.9%)	-
Death						
Schumacher *et al.* [7]	1 month	-	0/267 (0%)[a]	0/269 (0%)	0/268 (0%)	0/134 (0%)
Becker *et al.* [6]	1 month	0/37 (0%)	0/40 (0%)	0/38 (0%)	-	0/38 (0%)
Current study [1]	6 months	1/757 (0.1%)	1/756 (0.1%)	-	3/756 (0.4%)	-
Becker *et al.* [5]	1 year	-	2/256 (1%)	2/251 (1%)	0/253 (0%)	-
Serious adverse events as defined in each study[b]						
Schumacher *et al.* [7]	1 month	-	11/267 (4%)[a]	9/269 (3%)	7/268 (3%)	2/134 (1%)
Becker *et al.* [6]	1 month	0/37 (0%)	1/40 (2.5%)	2/38 (5.5%)	-	0/38 (0%)
Current study [1]	6 months	19/757 (2.5%)	28/756 (3.7%)	-	31/756 (4.1%)	-
Becker *et al.* [5]	1 year	-	11/256 (4.3%)	21/251 (8.4%)	19/253 (7.5%)	-

[a]One out of 134 (1%) had cardiovascular adverse events, 5 out of 134 (4%) had serious adverse events and none of the patients died in the 240 mg febuxostat group in the study by Schumacher and colleagues [7]. Adjudicated Antiplatelet Trialists Collaboration (APTC) events were defined as one or more of the following: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Non-APTC cardiovascular events included unstable angina, coronary revascularization, cerebral revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic event, congestive heart failure, and arrhythmia. [a]Serious adverse events were defined as follows in each study: no definitions were provided in the Schumacher and colleagues [7], Becker and colleagues [6] or the current study [1]; Becker and colleagues [5] defined a serious adverse event as '…an event that was life-threatening or that resulted in death, hospitalization or prolongation of hospitalization, persistent disability or incapacity, or a congenital anomaly or birth defect.'

statistically significant difference; non-APTC events (unstable angina, coronary revascularization, cerebral revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic event, congestive heart failure, and arrhythmia) occurred in 1.3%, 1.2% and 0.9%, respectively. A review of RCTs of febuxostat showed that cardiovascular adverse events were reported in 1.3 to 2% of febuxostat-treated patients versus 0.4 to 0.9% of allopurinol-treated patients, and death occurred in 0 to 1% of febuxostat-treated patients versus 0 to 0.4% of allopurinol-treated patients (Table 1). These differences were not statistically significantly different in each study.

A meta-analysis of data provided in Table 1 was performed by combining the 40 mg, 80 mg and 120 mg daily doses of febuxostat into a single category. The relative risk of cardiovascular adverse events (APTC and non-APTC combined) in febuxostat compared to allopurinol (200/300 mg) was 1.7 (95% confidence interval (CI) 0.4, 7.0) and compared to placebo was 2.5 (95% CI 0.3, 19.4), with neither statistically significant (since the 95% CI included one). The relative risks for mortality and serious adverse events was 1.0 (95% CI 0.1, 12.8) and 0.9 (95% CI 0.5, 1.7), respectively, for febuxostat compared to allopurinol; for febuxostat compared to placebo, these were not estimable (no deaths occurred in either group) and 2.5 (95% CI 0.7, 9.0), respectively. Although none of these comparisons were statistically significant, there was a non-significant trend towards more serious adverse events in febuxostat compared to placebo, but no difference when compared to allopurinol. A limitation of this meta-analysis is the presence of significant heterogeneity (as assessed by I^2 statistic of >50%): cardiovascular adverse events (I^2, 48%), mortality (I^2, 58%) and serious adverse events (I^2, 41%). A 5-year open-label study [3] of patients taking febuxostat 40 to 120 mg found 18% (21 of 116) suffered serious adverse events and 5% (6 of 116) suffered cardiovascular adverse events. Another limitation is that outcomes were assessed at different time points for adverse events due to varying lengths of RCTs.

The data regarding safety presented in this study are important. Associations of hyperuricemia with cardiovascular risk are well known [11]. In addition, recent evidence also suggests that gout is an independent risk factor for overall cardiovascular mortality [12] and for myocardial infarction, after adjusting for hyperuricemia-associated risk [13]. So, why would febuxostat, a medication that lowers serum urate (a cardiac risk factor),

increase cardiac adverse events? There are perhaps two important issues that need to be addressed before we seek answers to this question: first, is the cardiovascular risk increased with febuxostat treatment compared to allopurinol or other urate-lowering agents, as was suspected with the initial RCT [5]? And second, is urate-lowering below a certain level (<4 or <3 mg/dl or some threshold) undesirable since lowering urate too much or too rapidly may create oxidative stress that could predispose to cardiovascular outcomes? We need well-designed large database or registry post-marketing surveillance studies with validated, adjudicated cardiovascular outcomes to answer these important questions. While randomized studies of febuxostat with safety as the primary outcome would also be helpful, clinical trials often are of insufficient size, duration of follow-up, or have patients with insufficient generalizability to address such questions. It is possible that 'J' or 'U' shaped curves similar to ones observed for blood pressure and stroke risk [14] and diastolic blood pressure and cardiovascular outcomes in patients with coronary artery disease [15] may apply to serum urate and cardiovascular risk as well. In this exciting era of availability of new gout treatments and high-quality epidemiological and outcomes studies in gout, several existing questions will (need to) be answered and several new ones will likely emerge.

Abbreviations

APTC = Adjudicated Antiplatelet Trialists Collaboration; CI = confidence interval; RCT = randomized controlled trial.

Competing interests

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