Author's response to reviews

Title: Effect of febuxostat to prevent reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study

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Author's response to reviews: see over
Professor Doug Altman  
Editor-in-Chief, Trials  

September 27, 2013  

Re: Submission of the revised study protocol for the manuscript #1011386667103203  

Dear Professor Altman:  

I highly appreciate your cordial e-mail dated August 30, 2013, which included valuable comments from Reviewer 1. In response to your request, I prepared a list of Ethics Review Boards (ERBs) that approved our study—the FEATHER Study. Please note that the study is ongoing, and the number of participating medical institutions varies. As of today, the number of the institutions has increased by 2 to become 67 as compared with the number listed in my last e-mail. Since the study was approved by the same ethical bodies at some medical institutions, the number of ERBs (58) does not coincide with the number of the institutions (67). Since I already uploaded the lists of Steering Committee members, Executive Committee members, and Independent Data and Safety Monitoring Committee members as “Appendix” at the time of manuscript submission, I expressed the appendix as “Appendix I” in order to refer to the new list of ERBs as “Appendix II” for the revised manuscript.  

I carefully read the comments and prepared the replies on a comment-by-comment basis on the subsequent pages. Furthermore, I extensively rephrased the original manuscript as per Reviewer 1’s insightful suggestions and enriched its contents by adding a battery of medical literature providing experimental and clinical findings to make the revised manuscript more convincing, readable, and comprehensible. As per your instruction, furthermore, I also highlighted the changes (modifications/additions/typo corrections) that I made in the revised manuscript to facilitate identification by you and the reviewer.  

I do expect you and the reviewer find the revised manuscript acceptable for publication in your journal.  

Sincerely,  

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Reviewer 1’ comments

MAJOR COMPULSORY REVISIONS

TITLE

The title in the manuscript is presently: “The effect of febuxostat to prevent reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study”. I suggest changing it to: “The effect of febuxostat to prevent reduced renal function deterioration in patients with hyperuricemia complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study”.

Reply: I heartily appreciate your comment. In consideration of your very insightful suggestion and of the expression in the current guideline [Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012. Nihon Jinzo Gakkai Shi 2012, 54:1031-1189 [article in Japanese], I rephrased the title as follows: “The effect of febuxostat to prevent a further reduction in renal function in patients with hyperuricemia, who have never had gout but are complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study

BACKGROUND

• 3rd paragraph, last line. – The authors wrote “we consider it important to clarify the clinical relevance of conducting pharmacotherapy for cohorts…” I do not understand that sentence.
• 3rd paragraph. – By “pharmacotherapy”, are the authors meaning “pharmacodynamics and/or pharmacokinetics”?

Reply: I highly appreciate your valuable comments. The study conducted by Whelton et al. [reference #17 in the revised manuscript] provided us with a clue helpful for designing our study to be conducted in patients with hyperuricemia with reduced renal function. Since their study was a post-hoc analysis on the 5-year extension open-label study of a Phase II randomized clinical trial of febuxostat (FOCUS study), we do not have any intention to mean “pharmacodynamics” or “pharmacokinetics” by the term “pharmacotherapy.” However, your comments adverted me that the sentences are meaningless and incoherent to the preceding sentences. Therefore, I completely rephrased these sentences as follows: “Therefore, we presumed that continuous lowering of SUA concentrations might deter a further reduction in renal function in patients with hyperuricemia and/or gout and recognized the importance of prospectively evaluating the long-term effect of SUA reduction on renal function in hyperuricemic patients with impaired renal function.” I expect you find these new sentences comprehensible and coherent. I also tried to ensure the consistent and coherent usage of the terms “urate”, “subjects”, and “control”
throughout the revised manuscript. Furthermore, I highlighted the changes (modifications/additions/typo corrections) that I made in the revised manuscript to facilitate identification by you and the editor-in-chief/editors.

METHODOLOGY

- Blinding, 5th line. – I do not understand the sentence “Furthermore, changes in SUA concentration under blinding should be addressed…”

Reply: I appreciate your kind comment and found that the sentences are meaningless. I completely rephrased the sentences as follows: “Furthermore, the following actions should be taken to ensure the safety of the patient when SUA levels change as described below:” I also added the following sentence to the Blinding heading because it was missing in the submitted manuscript: “Laboratory tests at respective medical institutions should exclude the measurement of SUA concentration and urinary urate concentration from the assessment items.” Because of the very imprecise descriptions on “blinding” of laboratory results = “concealing of the measured values of serum and urinary urates” in the submitted manuscript, I nearly entirely restructured Table 2 in the revised manuscript in order to facilitate readers to identify the items that should be measured at each institution’s or central laboratory.

- Randomization. – I do not understand what is meant by “assignment method”; are you talking about stratification? If this is the case, it means that there are six strata (site, age, gender, serum level of uric acid, proteinuria and complication of diabetes.) This is a lot of strata…!

Reply: I am sorry for the confusing expression. I rephrased the expression to “the dynamic allocation using the following 6 background factors…” I understand that the dynamic allocation method (a procedure to assign patients sequentially for the secured balance of background factors) is not a stratification method but is a procedure by which patients are dynamically assigned/allocated, in our study at a 1:1 ratio, to receive febuxostat or placebo.

- Statistical methods and sample size.
- 1st paragraph, last line: I do not understand at all the sentence “Multiplicity will be considered for these tests”.

Reply: I am sorry for the imprecise expressions. I extensively rephrased the sentences to make them more comprehensible as statistical descriptions as follows: “In patients with CKD stage 3, the intergroup difference in the eGFR slope should be compared between the febuxostat group and the control group according to Student’s t-test. Subsequently, patients with stage 3a and
patients with stage 3b should be extracted to conduct the stratified analysis between these two subgroups. The problem of statistical multiplicity should be avoided when conducting these statistical analyses.”

• The discussion of the medical literature can be improved. For example, there should be some RCTs done in USA since the FDA approved febuxostat; these RCTs should be discussed. It might be a good idea to provide more information on the mechanisms of action of febuxostat and on its side effects.

Reply: In response to your valuable suggestions, I extensively renovated medical literature to enrich the contents of the entire revised manuscript. I checked the recent literature on RCTs in the USA as per your suggestions and found that the only RCT conducted after the approval of febuxostat in the United States is an article published by Becker et al. “Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, Lademacher C. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther. 2010;12: R63.” I discussed the article in the Discussion Section of the revised manuscript as follows: “A 6-month, large-scale, randomized, controlled study of febuxostat 40/80 mg or allopurinol 300 mg (200 mg in moderate renal impairment) was conducted in 2,269 patients with gout and SUA ≥ 8.0 mg/dL [48]; the study indicated 1) the equivalent UL efficacy and comparable safety for febuxostat 40 mg daily and allopurinol 300/200 mg daily, 2) the significantly greater efficacy of febuxostat 40 mg daily in lowering SUA than allopurinol in patients with mildly or moderately impaired renal function, 3) comparable safety at the doses examined, and 4) the favorable tolerability of febuxostat 40 mg daily, especially for gout patients with mild or moderate renal impairment.” Moreover, I enriched the text with respect to the mechanisms of action and side effects of febuxostat as follows: “Following the > 40-year period during which allopurinol—marketed in 1966—was available as the only XO inhibitor, febuxostat was approved in 2009 in the USA for the chronic management of hyperuricemia in patients with gout. Oxypurinol, the active metabolite of allopurinol, exerts the XO-inhibitory activity (the Kd value: 0.54 nmol/L) by binding to the reduced form of XO—Mo(IV)—through strong covalent bond [32]. However, covalent bond disappears and oxypurinol is released because Mo(IV) is reoxidized with time and returns back to the oxidized form of XO—Mo(VI) whose half-life is 300 min at 25°C—, and enzyme activity thus recovers [33]. Febuxostat presents striking contrast to oxypurinol because of its strong binding to enzyme proteins through multiple interactions, e.g.,
ionic bond, multiple hydrogen bonds, and hydrophobic interactions. Therefore, febuxostat does not depend on the oxidized or reduced form of XO and is strongly bound to both the oxidized and reduced forms of XO, thus inhibiting the enzyme for a long period of time and translating into its obvious therapeutic advantages [34]. Furthermore, febuxostat has high enzyme selectivity because of minimal effects on enzymes other than XO involved in the purine and pyrimidine metabolism [12,35]. Moreover, rat models, in which oxonic acid is used to induce hyperuricemia [36,37], indicate that hyperuricemia provokes a diversity of pathophysiological changes, e.g., activation of the renin-angiotensin system, decreased creatinine clearance, and severe arteriopatgy of the afferent arteriole [36-38]. Experimental studies afforded evidence that allopurinol and febuxostat, when used before the development of irreversible histological damage in the vasculature and glomeruli, can reverse these adverse changes, thereby preventing renal function reduction [39,40]. In addition, mild to moderate renal impairment has little effect on the pharmacodynamics and pharmacokinetics of febuxostat [41,42]. These experimental and clinical findings drove us to investigate the effect of early ULT with febuxostat on hyperuricemia complicated by renal impairment in clinical settings.”

• Strengths and limitations of the trial can be better discussed.

Reply: I do appreciate your kind suggestions and carefully prepared the sentences in the Discussion Section in order to clearly describe the strengths of our study as follows: “The present study, designed as a randomized placebo-controlled study of febuxostat 80 mg daily more effectively lowered SUA concentrations than did allopurinol 300 mg daily. In an 8-week randomized, double-blind, allopurinol-controlled clinical trial in 244 patients with gout, febuxostat 40 mg daily showed the significantly more potent urate-lowering effect than allopurinol 200 mg daily [47]. A 6-month, large-scale, randomized, controlled study of febuxostat 40/80 mg or allopurinol 300 mg (200 mg in moderate renal impairment) was conducted in 2,269 patients with gout and SUA ≥ 8.0 mg/dL after approval [48]; the study indicated 1) the equivalent UL efficacy and comparable safety for febuxostat 40 mg daily and allopurinol 300/200 mg daily, 2) the significantly greater efficacy of febuxostat 40 mg daily in lowering SUA than allopurinol in patients with mildly or moderately impaired renal function, 3) comparable safety at the doses examined, and 4) the favorable tolerability of febuxostat 40 mg daily, especially for gout patients with mild or moderate renal impairment. The large-scale randomized controlled clinical studies of febuxostat conducted to date [45,46,48] reported treatment-related adverse events (AEs), the majority of which were mild to moderate in severity (e.g., liver function test abnormalities,
diarrhea, headache, joint-related signs and symptoms, and rashes); the major serious AEs were cardiovascular disorders, nonspecific bacterial infections, coronary artery disease, ischemic coronary artery disorders, etc. Hence, there is a battery of experimental and clinical evidence to design a randomized controlled study in hyperuricemic patients with moderate renal impairment (30-59 mL/min/1.73 m$^2$).” In addition, I prepared the study limitations as a new heading as follows: “Hyperuricemic patients, who do not have gout and who are complicated by CKD stage 3 only, are being enrolled in the present study. Therefore, no clinical evidence will be obtained for patients with severer CKD—stage 4 or 5. Furthermore, patients who participate in a double-blind, randomized, placebo-controlled, clinical study have understanding of medicine and clinical studies. Hence, selection bias cannot be ruled out.”

ETHICS

- Proof of ethics approval: OK.

Reply: I appreciate your comment.

FUNDING

- Proof of funding: OK.

Reply: I appreciate your comment.

MINOR ESSENTIAL REVISIONS (not for publication).

- General suggestions.
- The quality of the English must be improved: some sentences are difficult to understand and some of them are meaningless.

Reply: I highly appreciate your critiques and made every effort to make the revised manuscript more comprehensible and readable.

- Reference 5. – The word “Community” in the title is capitalized; is this right or wrong?

Reply: It was a simple typo. I corrected the letter and appreciate your indication.

DISCRETIONARY REVISIONS.

- None.
CONCLUSION OF THE REVIEWER.

- The rationale is strong: hyperuricemia is indeed a cause of kidney failure and there is evidence that febuxostat, a nonpurine xanthine oxidase inhibitor, can decrease significantly the blood level of uric acid.

Reply: I do appreciate your encouraging comment.

- The study is relevant: the prevalence of hyperuricemia in Japanese male adults is 21.5%!

Reply: It is an epidemiological figure reflecting the reality in Japan.

- The hypothesis makes sense: administration of febuxostat to hyperuricemic patients already with chronic kidney failure will slow down or stop the progression of the kidney failure.

Reply: I highly appreciate your inspiring comment. We do expect that our study will contribute to the progress in medical science.

- The research question is clear: in adults with hyperuricemia and kidney failure (stage 3), can febuxostat improve glomerular filtration rate and decrease the serum level of uric acid?

Reply: I highly appreciate your comment.

- The design of the study is very good and should bring out data that will answer the research question.

Reply: I highly appreciate your comment.

The science detailed in this paper is good. However, the issues that I raised must be addressed by the authors and the English must be improved before this manuscript can be considered ready for publication by the journal TRIALS.

Reply: I extensively rephrased the original manuscript as per your positive suggestions and enriched its contents by adding a battery of medical literature providing experimental and clinical findings to make the revised manuscript more convincing, readable, and comprehensible. I do expect you find the revised manuscript acceptable for publication in TRIALS.