

20 March 2014

Dear Editor:

**Title:** Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis

**Authors:** Lisa M. Lundquist, Sabrina W. Cole, Martha L. Sikes

**Name of Journal:** *World Journal of Orthopedics*

**ESPS Manuscript NO:** 8580

I would like to thank you and the *World Journal of Orthopedics* reviewers for your helpful comments on our manuscript entitled "Tofacitinib for treatment of rheumatoid arthritis". I have attached the revised manuscript (8580-edited) with all revisions highlighted in yellow. Specific revisions are outlined in **bold font** below.

*Reviewer: 02527882*

In this article, the mechanism of action and adverse event/safety profile of Tofacitinib are well described. I would suggest changing the title to "A Review of Pharmacology of Tofacitinib in the treatment of RA" and editing the manuscript to focus on the pharmacology aspect.

**Author response: Title changed to: "Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis" to be more descriptive. Since safety and efficacy trials are highlighted, the manuscript does not focus solely on pharmacology.**

The description under "Efficacy studies" is rather repetitive and has already been included in Table 1. I would suggest deleting major portion of this part of manuscript. This would also help reduce the length of manuscript and make it more focused and readable.

**Author response: Efficacy studies section streamlined.**

Core tip: Tofacitinib, a Janus kinase (JAK) inhibitor, is the first oral non-biologic disease-modifying antirheumatic drug (DMARD)... Please revise this statement. Tofacitinib is not the first oral non-biologic DMARD approved for RA. Leflunomide and Sulfasalazine would fall in this category.

**Author response: Statement revised.**

*Reviewer: 505024*

The subject matter is interesting. However, I have the following major concerns: Abstract should summarize what is described in the paper, which is the pharmacology, safety and efficacy of tofacitinib. That should then be followed by approval status, not about guideline recommendations. Information, such as tofacitinib is a pan JAK inhibitor and RA synovium has increased expression of JAK-STAT pathway, etc, should included in the abstract.

**Author response: Abstract revised. Guideline recommendation removed.**

The efficacy data should not be simply described as in original publications. The unique feature of each study should be mainly discussed, for example, the study durations were different, were there any different results with different terms of observations? The p value should be inserted in the table 2. The numbers alone do not mean anything to readers.

**Author response: Efficacy studies section streamlined.**

Incidence rate for each adverse event should be described. It is better to do integrated analysis of all study data.

**Author response: Incidence data were provided for adverse events. It was not the authors' intent to complete a systematic review or a meta-analysis, so integrated data analysis was not done.**

What are the authors position about the therapeutic agent? What is the advantage comparing with other agents?

**Author response: The oral route of administration is noted as the advantage.**

*Reviewer: 02523327*

Well-written review about the role of tofacitinib in managing rheumatoid arthritis. Some minor revisions are needed to make the manuscript suitable for publication. In the abstract the authors should give more details about the mechanism of action of tofacitinib

**Author response: Abstract revised.**

Specify that the manuscript is not a systematic review

**Author response: It was not the authors' intent to complete a systematic review or a meta-analysis. Journal format for 'Topic Highlight' does not require.**

In the section "efficacy studies" several data are repetitive, since their presence in table 1. I suggest to reduce this part in the text;

**Author response: Efficacy studies section streamlined.**

P values are needed in table 2

**Author response: P-values added to Table 2.**

*Reviewer: 02570690*

Thank you for your paper. It provides a reasonable general overview of the studies on this drug in rheumatoid arthritis. General comments: It is probably incorrect to label tofacitinib as a 'non-biologic' DMARD. There has been considerable controversy with regards to this drug which is synthetic but acts like a biologic and a suggested terminology as adopted by EULAR is 'targeted synthetic DMARD'

**Author response: Terminology revised to 'targeted synthetic DMARD'.**

The authors have explained the pharmacology of the drug well. In the paper the authors should mention that though approved by USA FDA, approval has been rejected (twice) by EMA (European Medicines Agency)

**Author response: EMA rejection information added.**

The authors should clarify, for the non- rheumatologist, what DAS28-4ESR (i.e. disease activity score using a 28 joint count, ESR and patient global assessment) is

**Author response: Authors provided information in first paragraph of 'Efficacy Studies' section in first submission.**

References should be written in full as they appear on PubMed. As an example, reference 15 "Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate." is actually "Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study."

**Author response: References revised.**

Efficacy studies: Even though this is not a formal systematic literature review or meta-analysis, the authors should mention their search strategy

**Author response: Journal format for 'Topic Highlight' does not require.**

Only a study description and a comment that "results were statistically significant" should be further qualified in each instance by the magnitude of benefit so as to be of use to the reader. for e.g. for the Oral Solo trial, instead of writing "All patients who received tofacitinib had statistically significant improvement in ACR20, ACR50, and ACR70 response criteria and HAQ-DI scores at month 3", the authors should mention, for e.g. ACR20 response was 59.8% in the 5 mg tofacitinib group, 65.7% in the 10mg group and 26.7% in the placebo group, etc. If possible odds ratios with CIs, numbers need to treat/ harm etc. should be provided.

**Author response: Details are provided in Table 2. For streamlining and avoidance of duplication of data, the text does not include.**

The authors should also comment on study results rather than just stating them. As an example, in the above study, there were no differences in the DAS28 in the placebo and tofacitinib groups and it will be of interest to the reader as to why this robust index of disease activity was no different for an apparently effective drug? Following on from the above comment, rather than only stating study findings, the authors should try to – at least briefly- critique studies to make it more worth while for the reader (e.g. radiographic score at 6 months as the primary outcome- why not at 12 months?) Either in the table or elsewhere the authors should mention secondary outcomes.

**Author response: Secondary outcomes are mentioned throughout the text.**

Again, from my previous comment, there is little point in only providing the 6 month radiographic score, as especially the 12 and to a slightly lesser extent the 24 month scores are important. Indeed on looking at the full length papers, these scores have been analysed but have not been mentioned in the paper

**Author response: The authors reported primary and secondary outcomes in Table 2 and the text. If the ORAL study investigators evaluated efficacy past the primary and secondary endpoints, these data were not included in this manuscript.**

The authors should give either plots with odds ratio/ figures of efficacy (and safety) data to enhance readability

**Author response: Incidence data were provided for efficacy and safety. It was not the authors intent to complete a systematic review or meta-analysis. Readability would not be improved by 6 separate safety and efficacy figures for each ORAL trial.**

Safety and tolerability studies I am not sure what the authors intend to say when they write "only two deaths" for a chronic illness like RA where there should be no medication related deaths The general impression is the authors have undercalled adverse events. As an example, the authors mention "Although infections were reported in patients receiving tofacitinib, the reports were mainly mild to moderate in severity" and "no opportunistic infections were reported"- but both the Oral Solo and Tof. vs. adalimumab studies have mentioned events that seem opportunistic, for e.g. herpes zoster, liver abscess, pyelonephritis, etc The authors should also preferably give numbers (e.g. risk ratios with CIs) for adverse events in the main text

**Author response: Wording was changed to state report of two deaths in clinical trials. The statement of no opportunistic infections reported was specific to results from the phase 2 trials. The wording has been clarified in the text to indicate as such. The specific opportunistic infections observed in phase 3 trials are noted in the table. As noted above, it was not the authors' intent to complete a systematic review and the text provides a summary of adverse effects observed in clinical trials. Specific rates are included in the table. Additionally, study authors did not consistently report inferential statistics for safety endpoints.**

*Reviewer: 02705576*

This is a concise review of the clinical program for the drug. Please consider if the trial names are well-known enough to cite (as in easily found on clinicaltrials.gov and in the literature) or if you wish to also use the lead author's name.

**Author response: Authors determined the trials names are well-known, described in the first paragraph of the efficacy section, and referenced to guide the reader to additional information, if needed.**

Also, be consistent with NSAIDs as a term, rather than splitting out "NSAIDs and cox-inhibitors". In the US there is no separate therapeutic category dividing the two.

**Author response: NSAIDS and Cox2 inhibitors were separated in Oral Step trial, which is why the authors have chosen to keep them separated in this manuscript.**

I appreciate the opportunity for our manuscript to be considered for publication in *World Journal of Orthopedics*, and I look forward to hearing from you soon.

Sincerely,



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