Author’s response to reviews

Title: Effects of tofacitinib on the clinical features of periodontitis in patients with rheumatoid arthritis: two case reports

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Author’s response to reviews:

Dear Dr. Tim Shipley,

Thank you for your review for our revised manuscript (BRHM-D-18-00078R1). In response to your E-mail decision letter (dated on January 17, 2019), we have now prepared the revised manuscript which is now entitled: "Effects of tofacitinib on the clinical features of periodontitis in patients with rheumatoid arthritis: two case reports" by T. Kobayashi et al.

We have carefully considered and addressed all suggestions/recommendations of your expert reviewers in the revised paper. Our point-by-point reply is also uploaded with this letter.

We feel that our manuscript has been considerably improved by the changes suggested by you and your expert reviewers.

We look forward to hearing from you regarding our re-submission.

Respectfully yours,

Tetsuo Kobayashi, DDS, Ph D.

General Dentistry and Clinical Education Unit,
Our point-by-point reply to the reviewers’ comments:

Reviewer 1

Comments:

The authors have addressed each of my comments but have not acknowledged my concerns about their claim that tofacitinib improved the clinical features of RA when in fact neither case had more than low disease activity at baseline and there were not in fact consistent improvements in DAS28, SJC, TJC. Comments elsewhere in the manuscript claiming improvement in clinical disease activity should be rephrased to acknowledge the low disease activity at baseline and inconsistent findings in measures of disease activity eg in the abstract which states: "Both cases showed improvement not only in the disease activity and symptoms of RA".

Answer:

Thank you very much for your review and comments. We agree with your excellent suggestion, and have now altered the sentence to reflect your point as follows:

-Improvements were also observed in the serum levels of IL-6 in both cases as well as in the serum levels of TNF-α and anti-cyclic citrullinated peptide immunoglobulin G in one case and of rheumatoid factor and matrix metalloproteinase-3 in the other case. Patients who received tofacitinib exhibited an inconsistent clinical response, likely due to the low disease activity of RA at the start of the administration (Page 2, Abstract Case presentation).

-Improvements were also observed in the serum levels of TNF-α and anti-CCP IgG in one case and in those of RF and MMP-3 in the other case. Patients who received tofacitinib exhibited an inconsistent clinical response, likely due to the low disease activity of RA at the start of the administration (Page 5, Discussion paragraph 1).
Likewise, the Discussion implies that tofacitinib reduced RF and CCP, serum TNF and IL-6 in both cases. In fact only IL-6 was reduced in both cases as I don't think the reduction in TNF in case 2 can be construed as a significant reduction. Reductions in RF and CCP did not occur in both cases either.

Answer:

We agree with your excellent suggestion, and have now altered the sentence to reflect your point as follows:

-Improvements were also observed in the serum levels of TNF-α and anti-CCP IgG in one case and in those of RF and MMP-3 in the other case. Patients who received tofacitinib exhibited an inconsistent clinical response, likely due to the low disease activity of RA at the start of the administration (Page 5, Discussion paragraph 1).

Comments:

I have made an assumption that the changes in some of the periodontal measures at least are clinically significant but this is not explicitly stated in the manuscript. Can the authors state confirm whether the improvements in periodontal measures are clinically significant and specifically state this in the manuscript?

Answer:

According to your excellent suggestion, we have now added the sentence that the improvements in periodontal conditions were clinically significant as follows:

-improvements in the clinical periodontal conditions resulted in significant changes in both case definitions from baseline to reassessment (from moderate to no periodontitis for case 1 and from moderate to mild periodontitis for case 2) according to the criteria of the CDC/AAP [13] (Page 5, Discussion paragraph 2 last sentence).

Comments:

Hence the manuscript should present this as a study of the effects of tofacitinib on the clinical features of periodontal disease with a suggestion of improvement in antibodies (RF in one case and CCP in the other case), serum IL-6, TNF in one case and MMP-3 in the other case (in patients receiving tofacitinib for RA with inconsistent clinical response in RA likely due to the low disease activity to start with).
there were improvements in these markers. Likewise, if improvements in PD measurements were clinically significant, this can be stated. If not, the conclusion should be toned down to: tofacitinib did not exacerbate PD disease despite possible immunosuppressive effects.

Answer:

According to your excellent suggestion, we have now changed the title as “Effects of tofacitinib on the clinical features of periodontitis in patients with rheumatoid arthritis: two case reports (Page 1, title), and also altered the sentence you suggested as follows:

-Improvements were also observed in the serum levels of IL-6 in both cases as well as in the serum levels of TNF-α and anti-cyclic citrullinated peptide immunoglobulin G in one case and of rheumatoid factor and matrix metalloproteinase-3 in the other case. Patients who received tofacitinib exhibited an inconsistent clinical response, likely due to the low disease activity of RA at the start of the administration (Page 2, Abstract Case presentation).

-Improvements were also observed in the serum levels of TNF-α and anti-CCP IgG in one case and in those of RF and MMP-3 in the other case. Patients who received tofacitinib exhibited an inconsistent clinical response, likely due to the low disease activity of RA at the start of the administration (Page 5, Discussion paragraph 1).

In addition, we have added the sentence that the improvements in periodontal conditions were clinically significant as follows:

-improvements in the clinical periodontal conditions resulted in significant changes in both case definitions from baseline to reassessment (from moderate to no periodontitis for case 1 and from moderate to mild periodontitis for case 2) according to the criteria of the CDC/AAP [13] (Page 5, Discussion paragraph 2 last sentence).

Comments:

Importantly, were the periodontal assessments blinded to the use of a new DMARD (tofacitinib) between baseline and later assessments? If not, the major conclusion of the manuscript that tofacitinib improved periodontal inflammation is undermined and cannot be drawn.

Answer:

In response to your excellent suggestion, rheumatologists and periodontists were blinded regarding the rheumatologic and periodontal conditions as well as the administration of tofacitinib. These have now been included in the Discussion (Page 5, Discussion paragraph 2, the
second sentence). Therefore, we concluded that tofacitinib has a beneficial effect on periodontitis.

Comments:

It would also have been useful to demonstrate the changes in the manuscript in response to my comments, using tracked changes.

Answer:

We apologize for the inconvenience, and have now indicated all changes in the manuscript with blue-colored and underlined letters.