**Author’s response to reviews**

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

**Authors:**

Tetsuo Kobayashi (kotetsuo@dent.niigata-u.ac.jp)

Satoshi Ito (s-ito@water.ocn.ne.jp)

Akira Murasawa (rasenami@poppy.ocn.ne.jp)

Hajime Ishikawa (med@ra-center.com)

Hiromasa Yoshie (yoshie@dent.niigata-u.ac.jp)

**Version:** 1 **Date:** 10 Jan 2019

**Author’s response to reviews:**

Dear Dr. Maria Hodges,

Thank you for your review for our manuscript (BRHM-D-18-00078). In response to your E-mail decision letter (dated on January 9, 2019), we have now prepared the revised manuscript entitled: "Tofacitinib reduced periodontal inflammation 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:

This manuscript is said to be the first describing a response to tofacitinib in periodontal disease in 2 patients with RA. This is of interest given the similarities in the pathogenesis of these 2 diseases and the potential for immunosuppression with DMARDs such as tofacitinib to increase periodontal disease to the extent that it is driven by microorganisms such as P. gingivalis.

Answer:

Thank you very much for your review and comments.

Comments:

There were improvements in periodontal markers following commencement, likely to a clinically significant degree. Interestingly, the same cannot necessarily be said of the RA response to tofacitinib. The changes in RF and CCP titres are not likely to be clinical significant and the changes in other clinical and serological parameters, apart from the patient global assessment were underwhelming, perhaps due to the otherwise good control of RA at initiation of the tofacitinib.

Answer:

We agree with your excellent suggestion that tofacitinib was efficacious in improving gVAS, which has now been added in the Discussion to reflect your point (Discussion section, Page 5, lines 2-3 of Discussion paragraph 1).
Comments:

For example, in case 1, it is stated that tofacitinib was started due to secondary failure of adalimumab yet the joint scores and CRP were normal or low (high SDAI driven by high PGA). These low scores at initiation prevent comparisons between response in RA disease activity (bar PGA) and responses in PD parameters being drawn. The responses in IL-6 and TNF are more convincing and consistent with a biological benefit in RA with tofacitinib.

Answer:

In response to your excellent suggestion, we apologize for not having fully explained the RA condition caused by the secondary failure of adalimumab. Her CRP levels were actually raised before the re-visit of our rheumatic center (3.45 mg/dL). But for some reason, it was decreased to 0.1 mg/dL but her gVAS was worsened to 51 (Table 1). We have now added the detailed information on the case 1 (Case presentation section, Page 3, lines 8-15 of Case presentation paragraph 1).

Comments:

The authors state "Case 1 showed an increasing trend in not only the disease activity of RA but also the periodontal inflammation at baseline despite having received ADA therapy for 42 months". No data prior to the baseline measurements are reported so this statement is not supported by evidence in this manuscript.

Answer:

We agree with your excellent suggestion that no periodontal data before and after treatment with ADA in Case 1. We have thus deleted this paragraph (Discussion section in the first manuscript, Page 5, paragraph 3 of Discussion).

Comments:

The concluding statement that tofacitinib has a beneficial effect on PD may be "through its inhibitory effects on the serum proinflammatory cytokines" is speculative and more research is required to understand the relationship between PD and use of tofacitinib.

Answer:

We agree with your excellent suggestion, and have now altered the sentence to reflect your point (Abstract, Page 2, lines 2-3 of paragraph 3; Conclusions section, Page 5, line 2).
Reviewer 2

Comments:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Answer:

Thank you very much for your review and comments.