CEDARS-SINAI MEDICAL CENTER

January 4, 2017

Members of the Editorial Board

World Journal of Gastroenterology

REF: Manuscript NO: 31541-manuscript revision

Dear Editor,

Please find attached a revised version of our manuscript entitled ***"Insights on the use of biosimilars in the treatment of inflammatory bowel disease"*** for your consideration for publication in *World Journal of Gastroenterology*. We thank you and the reviewers for the thorough assessment of our work and the very helpful suggestions and comments – and are delighted to see that the paper was overall well-received and was invited for revision following the first decision.

We have performed additional revisions and believe that all peer reviewer comments are addressed. We are pleased with our edits, including further clarification of the goals of biologic therapy in managing IBD and additional clinical data to support our statements on immunomodulators and immunogenicity. Please find on the following pages a detailed point-by-point reply to each individual comment.

All authors have read the manuscript and approved it. This manuscript has not been submitted or published in any form in any journal. The authors declare no competing financial interests.

We hope that you will find our revised manuscript of great interest for the readers of *World Journal of Gastroenterology*. Again, thank-you very much for inviting this manuscript revision, and we hope we have satisfied all queries made by the reviewers.

We look forward to hearing from you.

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Sincerely yours,

David Q. Shih, MD, PhD, FACP
Associate Director of Basic Research,
F. Widjaja Foundation, Inflammatory Bowel & Immunobiology Research Institute,
Cedars-Sinai Medical Center

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Point-by-point reply to the reviewers' comments

Reviewer 00009417:

1. "A short table should be given comparing biologics and biosimilars."

Reply:

We thank the reviewer for the favourable response to our manuscript. As suggested, we have added a simple table (Table 1) that compares and contrasts some of the important aspects of biosimilars, including cost and approval process. We hope that this will facilitate understanding of biologics and biosimilars for readers.

Reviewer 02568706:

1. "The notion that the high cost of biologics have triggered the development of biosimilars is an over-simpliciation. The expiration of patent would trigger a biosimilar if a profit is foreseen, regardless of the cost of the RMP."

Reply:

We thank the reviewer for the comments made about the MS. We agree that patent expiration is the main driver of biosimilar development and understand that our previous statements reflected an over-simplified conclusion. As such, we have revised our manuscript to reflect this. Our edits are highlighed on page 3 of the MS, paragraph 3, line 1.

2. "Other important factors that influence pharmacokinetic profile include patient weight (BMI), as well as the extent and severity of disease (p.5)."

Reply:

We have included these additional factors in our description of pharmacokinetic profile. Our edits are highlighted on page 6 of the MS in the pharmacokinetic profile section.

3. “The section on immunogenicity ignores the key IBD studies such as SONIC. Moreover, azathioprine is ued but not mentioned (p.6). Also the COMMITT Study is not discussed using MTX.”

Reply:

As suggested, we have included important results from the SONIC, COMMITT, and UC SUCCESS studies in order to support our statement regarding concomitant use of immunomodulators and immunogenicity. Our edits are highlighted in page 6 of the MS, paragraph 2 of the immunogenicity section.

4. “Important information is missing regarding the magnitude of the RA trials (PLANETRA, PLANETAS) on p.9”

Reply:

We agree that important information about these studies was missing. Per the comments, we have revised the MS to include this information. Our edits are highlighted on page 10 of the MS, paragraph 1 of the Infliximab-dyyb section.

5. “The authors hae addressed potential concerns about the interchangeability of infliximab and inflectra. However, in the future, pharmacists may be able to switch to one of a number of biosimialrs over the course of years of disease. Since these molecules are not identical, what are the potential risks and implications of exposure to MULTIPLE biosimilars?”

Reply:

We thank the reviewer for this comment. In our revision, we acknowledge the lack of studies concerning multiple switching, cross-switching, and reverse switching. Furthermore, we have included an updated statement by ECCO reflecting their stance on biosimilar switching. These edits are highlighted on page 10 of the MS, paragraph 3 of the interchangeability section.

Reviewer 00503587:

1. “The authors state twice that biologic drugs are useful for symptom management in IBD. Whilst this may be true, the current concepts of managing IBD go well beyond simply reducing symptoms or focusing just on symptoms. These sections should be expanded and corrected accordingly.”

Reply:

We thank the reviewer for all comments made about the MS. We agree that our previous statements pertaining to the goal of biologic therapy was an oversimplication. As suggested, we have updated our MS to include mucosal healing and prevention of long-term complications as additional goals of managing IBD with biologics. These edits are highlighted in line 3 of the abstract and page 3 of the MS, paragraph 2 of the introduction.

2. “The authors comment on anti-IL biologic (page 3 and later in the MS). This description should be corrected.”

Reply:

We appreciate the reviewer’s comment. After reviewing the comment, we noticed that this is likely confusion and we have expanded the description. The corrected statement is highlighted on page 3, paragraph 2 of the introduction, lines 15-16, and page 4, paragraph 3 of “What are biologics?” section.

3. “In multiple locations the authors list items in brackets. These should include “and” between the second last and last items.

Reply:

We thank the reviewer for this suggestion. We have corrected and added “and” to all appropriate brackets used in our manuscript. These edits are highlighted on page 3, 4, 6, 7, 8, and 9 of the MS.

4. “The last sentence in the second paragraph on page 5 is incomplete and requires attention.”

Reply: After reviewing the sentence, we agree that it was incomplete. We have revised this sentence appropriately. Our edits are highlighted on page 5 of the MS, paragraph 3 of the "What are biosimilars?" section.

5. "The first sentence of the second paragraph on page 10 is excessively long and does not read well. Please revise accordingly.

Reply: After reviewing, we agree that this sentence is written in an incoherent way. We have simplified this sentence to make it easier for readers to understand and follow. This edit is highlighted on page 10 of the MS, paragraph 1, lines 1-3 of the Infliximab-dyyb section.

6. "In the subsequent paragraph on page 10, the authors use the word decrease in comparison between the two interventions reported. This word is not the best word in this context; suggest to change to 'demonstated significantly lower clinical…"

Reply: Per the suggestion, we have revised this statement. This edit is highlighted on page 10 of the MS, paragraph 1, line 5 of the Infliximab-dyyb section.

7. "Unfortunately, this version of the MS contained many track changes and comments from the authors. These items should all be removed from a MS submitted for peer review – particularly as this impedes review and readability of the MS."

Reply: We express regret for including all of the previous "track changes and comments." They have been removed from our revised version of the manuscript. We appreciate the comment.