

Point-by-Point Response

Name of Journal: *World Journal of Gastroenterology*

Manuscript Title: *Disease Clearance in Ulcerative Colitis: A New Therapeutic Target for the Future*

Invited Manuscript ID: 91825

Respected Editor and Reviewer #1,

We would like to thank you for your encouraging and positive assessment of our manuscript. We appreciate the consideration and expertise you have dedicated to the review process. We have carefully reviewed your comments and have incorporated the necessary revisions to the manuscript. We hope these modifications will meet your criteria for approval. The proposed changes and our responses are as follows in a point-by-point manner:

Comment 1: First of all the quality of the language is surprisingly uneven through the manuscript. A thorough correcture reading by an expert in english is recommended.

Reply: Our manuscript is thoroughly reviewed by an expert English editing service after we incorporated all the changes suggested in the report for peer reviewer #1. The manuscript was thoroughly edited by the American journal experts (Springer Nature). Accordingly, we have attached proof of non-native speakers of English editing certificate to our re-submission package.

Comment 2: Abstract: What is meant by "experimental platforms for ulcerative colitis"?

Reply: Thank you for your comment. Our rationale of mentioning experimental platforms for ulcerative colitis was to highlight that over the past few decades the murine models for studying ulcerative colitis have vastly improved allowing improved

understanding of disease pathophysiology resulting in diversification of pharmacological therapeutic targets. Accordingly, we have specifically clarified this in the abstract and introduction. This now reads “Advancements in murine modeling systems”.

Comment 3: Introduction: "colonic inflammation in the rectum" should read "chronic inflammation..."

Reply: Thank you for your suggestion. We have made this change, and it now reads “ UC is characterized by chronic inflammation in the rectum and can progress continuously to the proximal colon”.

Comment 4: An incidence rate is normally given as the number of new cases/100,000/year. It cannot be given as "20% of caees". Just write the actual incidence rate.

Reply: Thank you for your comment. We have now removed the sentence describing 20% of cases and included only the prevalence and incidence rates per 100,000 population in the US. This section now reads “In the United States, the epidemiological burden of UC is comparable with global trends, with an incidence and prevalence of 6.3 per 100,000 and 378 per 100,000 people, respectively”.

Comment 5: Pharmacoeconomic data is provided. This is of value but the information should be placed after the sentence describing the increasing disease and economic burden.

Reply: We thank peer reviewer #1 for this targeted suggestion. Accordingly, we have placed the pharmacoeconomic data after the sentence describing the increasing disease and economic burden. This section now reads “In addition to the significantly increasing

disease burden, the progressive and debilitating nature of UC results in a significant economic burden owing to increased direct and indirect costs associated with health care utilization^[8]. Pharmacoeconomic data from the Crohn's and Colitis Foundation of America (CCFA) estimated that the annual economic costs are between US\$14.6 and US\$31.6 billion^[9]".

Comment 6: "higher biologic needs" does not make sense. Should be "higher needs for biologics"

Reply: We have adapted this comment into our revised manuscript. This section now reads "Furthermore, disease progression predisposes patients to greater needs for biologics, as well as greater risk for extraintestinal manifestations, pseudopolypsis, anorectal dysfunction, gut dysmotility, surgeries and hospitalizations".

Comment 7: I think I know what is meant by "sub-therapeutic agents" but it should simply be named "Due to the availability of only less potent drugs" It can be debated whether Janus kinase inhibitors can be considered to be safe.

Reply: We have incorporated these changes. The section now reads "Due to the availability of only less potent drugs, the natural disease course has not been fully elucidated. Over the past few decades, advancements in murine modeling systems have yielded novel mechanisms of disease onset and progression."

Additionally, we included a latest study assessing comprehensively the safety of Janus Kinase inhibitors versus all advanced therapies across IBD and other immune mediated conditions. This now incorporates evidence of debated safety of this class of medication. The section now reads "Janus kinase inhibitors (JAKis), provide a cost-effective means of targeting natural disease history^[19]. No significant difference in overall safety

outcomes was observed between UC patients receiving JAKis and patients receiving other active treatments [20]. Therefore, the safety of JAKis can also be debated.”

Comment 8: The manuscript is providing some evidence for the value of disease clearance. For that reason the sentence "The impact of achieving simultaneous clinical, endoscopic and histological remission on disease outcomes remains limited" is obviously wrong.

Reply: We agree with this suggestion that it is important to stay focused with respect to ulcerative colitis. Our initial idea behind stating this sentence was that even though most studies for disease clearance are retrospective studies or post-hoc analyses. Therefore, we have edited this section to accurately represent that these sets of emerging evidence support disease clearance as a therapeutic target in UC. This section now reads “Emerging evidence supports the impact of attaining simultaneous clinical, endoscopic and histological remission on disease outcomes.”

Comment 9: Disease clearance in ulcerative colitis: The inflammation in Crohn’s disease is transmural. This is not the case in ulcerative colitis. The present manuscript deals with UC and the data regarding Crohn’s disease and the value of transmural healing is out of context and shouldn’t be included.

Reply: Thank you for your suggestion. Our understanding of including CD disease clearance data was to highlight that apart from other medical conditions, disease clearance has already gained interest in CD. However, we agree that since the scope of the manuscript is only ulcerative colitis and that we should only include evidence of ulcerative colitis. Therefore, we have removed this CD related information. The relevant section has been updated from the grammar point of view to keep consistent with contextual flow. This section now reads “ DC has also demonstrated use in aiding

therapeutic positioning in biologic drug efficacy comparator trials^[43]. To avoid confusion in patients, DC should not be used synonymously with the term “cure”.

Comment 10: Why incorporate disease clearance in ulcerative colitis ? "Non-inflammatory colonic alterations" should be defined.

Reply: We agree with the peer reviewer’s suggestion and have described these alterations in a manner which is easy to grasp for the avid reader. Accordingly, we have added a new basic science studies in the references adequately describing these perturbances. This section now reads “Chronic inflammation alters colonic physiology and anatomical integrity, resulting in abnormal colonic motility, a reduction in goblet cells, aberrant barrier function and sequelae of intestinal fibrosis^[49-52]. The extent and location of these changes contribute to persistent PROs despite adequate disease control^[44, 53, 54]”.

Comment 11: "Clinically silent patients" should read "Patients in clinical remission"

Reply: We have made the required modification to “ Patients in clinical remission are less likely to seek medical attention, thus increasing their risk of developing sequelae related to unchecked smoldering inflammation”.

Comment 12: "Histologic healing is associated with a threefold increase in CRC risk" This is definitely not true.

Reply: We agree that this is stated incorrectly by us. Evidence supports that histologic inflammation is associated with an increased risk of colorectal cancer. We have extensively re-written this section which now reads “ Histologic inflammation has also been deemed an independent risk factor for the development of colorectal cancer (CRC)^[7]. A 3- to 5-fold increase in the risk for CRC has been observed in patients with persistent histological activity ^[72]. The severity of histologic inflammation correlates

with progression to advanced neoplasia^[72]. Reversal of histologic disease has been shown to reduce the risk for CRC”

Comment 13: Evidence supporting disease clearance in ulcerative colitis - I would suggest to add "as a therapeutic target":

Reply: Thank you for the suggestion. We have accordingly made this change and the relevant section now reads “ *Evidence supporting disease clearance in ulcerative colitis as a therapeutic target*”

Comment 14: "This underlines the importance of initiating early treatment" I agree but it should be added that it also underlines the need for the development of more efficient drugs.

Reply: We have incorporated this idea of developing more efficient drugs in the relevant section and have included a relevant high impact study reference to support this idea. The section now reads “Furthermore, this finding indicates the need for developing more efficient drugs^[84].”

Comment 15: Future avenues and utility in clinical landscape: It is stated that dual therapy can increase the likelihood of achieving DC. This may be so but it has not been proven. The literature is scarce on the value of dual therapy which should be pointed out.

Reply: We agree with this suggestion and have included this in our section with the most relevant reference. This section now reads “. The likelihood of achieving DC may be increased by dual therapy and by discovering biomarkers of drug response. Evidence pertaining to the value of dual therapy remains limited, with few prospective large-scale studies conducted to date^[91]. Therefore, the role of dual therapy in inducing DC remains unknown.”

Comment 16: I think the figures are too simple and they do not add much to the understanding of the message of the manuscript. The figures can be omitted.

Reply: Thank you for your suggestion. We omitted both figures. However, we made a new figure 1 which summarizes disease clearance and it's clinical impact on ulcerative colitis patients. This figure is now included in this revised manuscript and formatted as per the journal requirements.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Comment: As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Reply: The manuscript was thoroughly edited by the American journal experts (Springer Nature). Accordingly, we have attached proof of non-native speakers of English editing certificate to our re-submission package.

5 ABBREVIATIONS

Comment: In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/ definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: Abbreviations are not permitted. Please spell out any abbreviation in the title.

(2) Running title: Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract.

Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

(4) Key Words: Abbreviations must be defined upon first appearance in the Key Words.

(5) Core Tip: Abbreviations must be defined upon first appearance in the Core Tip.

Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text.

Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (*H. pylori*)

(8) Figures: Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text.

Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the

Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

(9) Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

Reply: We have reviewed the manuscript and have ensured that abbreviations format is followed through the main text. Likewise the abbreviation for STRIDE and disease clearance have been used appropriately as per the journal requirements. These are highlighted in yellow at the first instance of mention in the text.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

1 Conflict of interest statement: Academic Editor has no conflict of interest.

2 Scientific quality: The author submitted a study of disease clearance in ulcerative colitis. The manuscript is overall qualified.

Reply: Thank you very much for your kind and encouraging review.

(1) Advantages and disadvantages: The reviewer have given positive peer-review reports for the manuscript. Classification: Grade B; Language Quality: Grade B. In order to improve treatment and control of patients suffering from ulcerative colitis a thorough discussion of treatment outcomes is of relevance. By providing a review regarding the concept of disease clearance the authors of the present manuscript do so. For that reason

the paper is highly relevant for the readers. However some issues should be dealt with before the manuscript is ready for publication.

Reply: We have incorporated all peer reviewer comments and made the requested changes. The manuscript is also now polished with the English language editing certificate also attached to this re-submission package.

(2) Main manuscript content: The author clearly stated the purpose of the study and the research structure is complete. However, the manuscript is still required a further revision according to the detailed comments listed below.

Reply: Thank you very much for your positive comments. The details in the comments section have been incorporated by us.

(3) Table(s) and figure(s): There are 2 Figures should be improved. Detailed suggestions for each are listed in the specific comments section.

Reply: We have removed both figures and made one new figure summarizing the whole concept of disease clearance and it's clinical impact.

(4) References: A total of 88 references are cited, including 32 published in the last 3 years. The reviewer didn't request the authors to cite improper references published by him/herself.

3 Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Reply: The manuscript is also now polished with the English language editing certificate also attached to this re-submission package.

4 Specific comments: (1) Please provide the filled conflict-of-interest disclosure form.

Reply: I have filled the conflict of interest disclosure form and included in this re-submission package.

(2) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C:

Reply: We have provided the new figure 1 file in PPT format with all components of the figure in decomposable form. The figure title is also edited as per requirements. Kindly note that both old figures were created from scratch by us using the software Biorender. The issue with biorender remains that it does not allow download of figures in a decomposable form. In addition to the peer reviewer comments regarding the figures ,we believe a single figure summarizing the whole concept of the manuscript would be more beneficial for the readers.

(3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published, and correctly indicate the reference source and copyrights. For example, **“Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation:** Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc^[6]”. And please

cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Reply: All figures in the manuscript are created by us.

5 Recommendation: Conditional acceptance.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Thank you very much for the positive review. We have incorporated all changes and formatted the manuscript as per the journal requirements. We hope these changes meet your requirements for full approval of the manuscript for publication in your esteemed journal.

We look forward to hearing from you!

Sincerely,

Syed Adeel Hassan, MBBS/MD