

December 10rd, 2023

Dear Editor of World Journal of Gastrointestinal Surgery,

Thank you for your valuable recommendations. These suggestions are of great help to our manuscript entitled “ Is Proactive Therapeutic Drug Monitoring of TNF- α Monoclonal Antibody Superior to Maintenance Management in Inflammatory Bowel Disease? Systematic review and network meta-analysis” (NO: 89368). We marked the edited text in red.

We examined and revised the manuscript carefully to make all of the statements clear and concise. Our group has worked diligently and seriously to address the reviewer comments. The responses to each comment are listed as follows on behalf of all coauthors. I have made these revisions and carefully refined our manuscript following these comments. We responded point-by-point to each comment. The English language in the manuscript has been edited by a native speaker with Editorial Certificate(twice) uploaded with supplementary material.

Thank you again for your kind suggestions. Your careful and detailed comments were extremely helpful for us in revising our manuscript. Best regards.

Yours Sincerely,

The corresponding author

Yingshi Zhang

To reviewer 1

Comments 1: Dear authors, After reviewing this study, I have no major concern to this study but have two minor issues. 1. The conclusion of result section had poor correlation to the above discussion. Please modify the discription.

Response: Sincerely thank you for your valuable comments. Latest cutting-edge research result have been added in the Discussion part, and the paragraph order has also been adjusted. The revised part were: “**Moreover, proactive optimisation of maintenance dosing might prolong time to loss of response in some patients[37]**” and “**A recent latest cutting-edge research result demonstrated that proactive TDM, targeting higher exposure concentrations ($> 5 \mu\text{g/mL}$), can improve disease remission rates and enhance durability of the anti-TNF biologics. The effective management of anti-TNF therapies in children with IBD requires evidence-based precision dosing strategies, including routine TDM and proactive pharmacodynamic assessments[40]. Therefore, TDM may be the most useful in patients undergoing monoclonal antibody monotherapy.**” in the Discussion part, page 13-14.

Comment 2: Some grammar errors were found in the main text.

Response: Sincerely thank you for your valuable comments. This manuscript have been re-edited with language certificate form www.aje.com(NO.8D91-B4EA-CBC2-5A8E-D141)

To reviewer 2

Comment: Fangyuan Zheng et al is a systematic review and network meta-analysis to determine the efficacy and safety of proactive therapeutic drug monitoring (TDM) of TNF- α mAbs in patients with IBD and to determine which subtype of IBD patients were more suitable for proactive TDM intervention. The review searched randomized trials (RCTs) and observational studies in PubMed, Embase, and Cochrane engines to compare proactive TDM of TNF- α monoclonal with reactive TDM or empiric therapy. Pairwise and network meta-analyses were used to determine the IBD patient subtype that led to clinical remission and to determine the need for surgery. The review yielded 13 studies after exclusion, and the baseline indicators were balanced. They found that the

studies with a significant increase in patients that reached clinical remission included Adalimumab (ADA) and randomized trials (RCT) subgroups and showed a significant decrease of patients that needed surgery in proactive vs. reactive and Infliximab (IFX)+ADA subgroups, and the overall risk of adverse events was reduced from pairwise meta-analysis. Moreover, network meta-analysis outcomes suggest that patients with IBD treated with ADA are more likely to undergo TDM, especially in comparison with patients with reactive treatment. The study concluded that IBD patients treated with ADA are more suitable for proactive TDM and have obvious advantages compared with reactive TDM and recommend proactive TDM in IBD patients treated with ADA. This systematic review and network meta-analysis is well analyzed by PRISMA guidelines and registered with the PROSPERO website. Appropriate five figures, two tables, and forty-four citations supported by additional supplementary data available at WJG online.

Response: Sincerely thank you for your valuable comments.

To Science editor

Comment 1: Please provide the Biostatistics statement.

Response: Sincerely thank you for your valuable comment. The Biostatistics statement have been uploaded with the online submission system.

Comment 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. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation

for each figure. Such as Figure 1 title. A: ; B: ; C: ..

Response: Sincerely thank you for your valuable comment. All figures were original image created for the manuscript, and there is no copyright dispute. Besides, all Figures cited in the original manuscript already in the form of PPT.

Comment 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..

Response: Sincerely thank you for your valuable comment. All figures were original image created for the manuscript, and there is no copyright dispute.

Comment 4: Please don't include any *, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP <0.05, bP <0.01 (P > 0.05 usually does not need to be

denoted). If there are other series of P values, $cP < 0.05$ and $dP < 0.01$ are used, and a third series of P values is expressed as $eP < 0.05$ and $fP < 0.01$.

Response: Sincerely thank you for your valuable fourth comment. The issues has been revised in this manuscript as described above.

Comment 5: Abbreviations other than special types of words such as COVID-19 and SARS-CoV-2 are not allowed in the article title, and no more than 18 words are allowed. The title cannot start with "the, a, an". .

Response: Sincerely thank you for your valuable fifth comment. We have shortened the manuscript title to: “ Is tumor necrosis factor- α monoclonal therapy with proactive therapeutic drug monitoring optimized for inflammatory bowel disease? network meta-analysis”

Comment 6: Please provide all fund documents.

Response: Sincerely thank you for your valuable sixth comment. The fund documents have been uploaded as supplementary.

Comment 7: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text (and directly before the References).

Response: Sincerely thank you for your valuable reminder. The “Article Highlights” part have been added at the end of main-text.

Comment 8: Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address

Response: Sincerely thank you for your valuable reminder. The doi and PMID Number, or website address have been added in the reference list.

To Company editor-in-chief

General comments: I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>, or visit PubMed at: <https://pubmed.ncbi.nlm.nih.gov/>.

Response: Sincerely thank you for your valuable comment. We ran the PUBmed search again and updated two newer, influential articles in the discussion section.

The revised part were: **“Moreover, proactive optimisation of maintenance dosing might prolong time to loss of response in some patients[37]”** and **“A recent latest cutting-edge research result demonstrated that proactive TDM, targeting higher exposure concentrations (> 5 µg/mL), can improve disease remission rates and enhance durability of the anti-TNF biologics. The effective management of anti-TNF therapies in children with IBD requires evidence-based precision dosing strategies, including routine TDM and proactive pharmacodynamic assessments[40]. Therefore, TDM may be the most useful in patients undergoing monoclonal antibody monotherapy.”** in the Discussion part, page 13-14. And maybe it's my permission, RCA website I can't log in, I'll keep trying.