

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled " Efficacy and safety of adalimumab in comparison to infliximab for Crohn's disease: A systematic review and meta-analysis" (Manuscript NO.: 74609, Meta-Analysis). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made corrections which we hope meet with approval. The main corrections in the paper and the responses to the reviewer's comments are as follows (the replies are highlighted in orange):

Responds to the reviewer's comments:

Reviewer #1:

1. Why was ODDS RATIO chosen and not Risk difference or mean difference?

Response: Although we defined response and remission by CDAI or HBI, most studies did not give CDAI or HBI value before and after treatment, only the number of patients who achieved response or remission after treatment. Therefore, we have chosen ODDS RATIO, not risk difference or mean difference.

2. Heterogeneity needs to be defined in the methods according to Higgins. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019) [Internet]. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane; 2019. Available from: www.training.cochrane.org/handbook

Response: An I^2 estimate $> 50\%$ and a P -value < 0.05 were regarded markers of significant heterogeneity, and its causes were investigated.

3. Why was the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) not carried out? I recommend performing and redoing the analyses.

Response: Thank you for your suggestion. It was necessary to evaluate the quality of our conclusion. We carried out GRADE evidence. All outcomes were judged as “low” because all included literature was observational studies. The results were shown in Table 3.

4. "These results were consistent with the results of most published studies" Which? Quote them.

Response: These results were consistent with results of references 5, 6, 7, 8, 9, 10, 11, 12, 15, 16 and 17. They found clinical outcomes were similar in patients treated with IFX or ADA as induction and maintenance therapy for CD. We have quoted them.

5. “Few research compared clinical benefit between IFX and ADA only in biological non-naïve CD patient” Which? Quote them.

Response: The study by Macaluso *et al*^[10] compared clinical benefits between IFX and ADA in the biological non-naïve CD patient subgroup. We have quoted them. In addition, this analysis was done in the study by Zorzi *et al*^[6], Tursi *et al*^[15], Bau *et al*^[14], Otake *et al*^[5] and Doecke *et al*^[16].

6. Funnel Plot charts are not required if you have followed PRISMA's recommendations.

Response: The number of included studies in every outcome was less than 10, and it was not necessary to conduct a funnel plot. However, the egger's test was not strictly required for the number of studies, so we used the funnel plot and the egger's test to detect possible publication bias.

7. In the Forest Plot charts you put the author and year and after that, put the year again. Fix this.

Response: We apologized for our negligence and fixed this.

8. In Figure 5, if the study does not present data like Kaniewska, it should not be metanalyzed.

Response: Although the study by Kaniewska *et al*^[11] found no severe adverse events, the sample size of this study was not small and should not be neglected.

Reviewer #2:

1. Crohn's disease is fundamentally heterogeneous disease and the therapeutic efficacy of Crohn's disease differs between the types of disease e.g., location of disease, existence of stenosis and/or fistula, or perianal involvement. Although I understand it will be difficult to reanalyze after stratification of disease types, the authors should consider the impact of these factors on your data.

Response: Thank you for the valuable suggestion. We should consider the impact of these factors on our data. However, it was important to remember that this was a meta-analysis based on cohort study. Direct head-to-head studies comparing the long-term outcomes of IFX to ADA in CD are sparse. The mismatching of groups is an inherent potential weakness of retrospective studies. We again reviewed included studies. There was no significant difference between IFX and ADA groups in the location of disease and the existence of stenosis and/or fistula of included studies. We believe that these factors have similar effects on IFX and ADA groups and more studies on this subgroup of patients are needed.

Patients with perianal involvement were included in all studies. However, IFX patients had more perianal diseases in the studies of Benmassaoud *et al*^[7], Varma *et al*^[8], Narula *et al*^[9] and Cosnes *et al*.^[12] Clinicians tended to choose IFX over ADA in patients with more severe disease activity or phenotypes (perianal disease) due to its intravenous administration and weight-based dosing schedule. Although the study population contained a significant number of patients with perianal disease, no sub-analysis of perianal disease outcomes was provided. We

attempted to adjust for these differences using subgroup analysis and led to the same conclusions (Supplemental Table 2). Furthermore, there had research focusing on this subset of patients. Ji *et al*^[18] found the cumulative rate of nonrecurrence or aggravation of fistula was no significant difference in the ADA group and IFX group at 24 months (62.5% vs 83.9%, $P = 0.09$). High-quality clinical data for fistulizing CD are lacking. Current evidence suggested that IFX and ADA had similar effects in patients with perianal disease.

2. I assume immunomodulators would be used more in infliximab cases than adalimumab cases and the effect of immunomodulators on the efficacy of infliximab for Crohn's disease might differ based on the timing of administration (from the beginning or later add on), especially in the rate of loss of response. Can the authors make this point clear by distinguishing the patients with immunomodulators based on the timing of their administration?

Response: The finding that combination therapy with an immunomodulator is superior with IFX but not with ADA was reported in Kestens *et al*^[4], Benmassaoud *et al*^[7], and Doecke *et al*^[16] studies. The possible reason is that IFX combined with IM treatment reduces its immunogenicity. However, clinical efficacy of ADA combination therapy did not differ from that of ADA monotherapy (71.8% vs 68.1% at Week 26, $P = 0.63$)^[21]. Therefore, more patients in the IFX group combined with IM treatment than in the ADA group in the Narula *et al*^[9] study. No change was found in results after sensitivity analysis (Supplemental Table 1). Although immunomodulators would be used more in IFX cases than ADA cases, this does not disturb our analysis.

Patients were on concurrent immunomodulation at anti-TNF induction to improve the efficacy of the induction of the remission and discontinued concomitant therapy mainly due to adverse effects or intolerability (from the beginning). When loss of response occurs,

concomitant therapy is resumed (later add on). Only Cosnes *et al*^[12] study used immunomodulators later. No different results were found after sensitivity analysis was performed (Supplemental Table 1). In conclusion, the timing of combination with immunomodulators also does not impact results, including the rate of loss of response.

3. Can the authors describe the effect of bowel resection (prior and after treatment) on these analyses?

Response: Many patients underwent bowel resection before anti-TNF treatment. In the Zorzi *et al*^[6], Benmassaoud *et al*^[7], Cosnes *et al*^[12] and Doecke *et al*^[16] studies, some patients received surgery after anti-TNF treatment. The bowel resection was conducted due to loss of response or an escalation in symptoms or disease activity. The final outcome of this subgroup of patients was not provided in the original article. The bowel resection before or after treatment may affect the results, so subgroup analysis was conducted. All results were consistent with the main analysis except for total overall adverse events (Supplemental Table 3). In the subgroup of prior surgery before treatment, IFX and ADA had similar overall adverse events. We can not explain it. Larger and long-term comparison studies will be necessary. In summary, bowel resection before and after treatment has little impact on the analysis.

4. The authors showed the data of these comparisons in anti-TNF therapy naïve as well as non-naïve cases. Can the authors clarify the type of first anti-TNF therapy (infliximab → adalimumab, infliximab → infliximab, adalimumab → infliximab, adalimumab → adalimumab, other anti-TNF therapy → infliximab or adalimumab)? This is important to understand ineffectiveness of secondary anti-TNF therapy.

Response: It's unknown why some CD patients lost response to anti-TNF treatment. When naïve patients didn't respond to anti-TNF therapy, one strategy in optimizing the use of biologics is therapeutic drug monitoring, which involves measuring serum drug concentration and anti-drug

antibodies (ADAbs). If drug concentration is subtherapeutic or undetectable and ADAbs are undetectable, this can be caused by nonimmune-mediated pharmacokinetic failure, and patients might benefit from dose escalate (IFX→IFX, ADA→ADA). If ADAbs is detectable, then it suggests that drug clearance is increased due to immune-mediated mechanisms and switching to a drug in class with the same mechanism of action but other molecular structures may be the preferred pharmacologic option (IFX→ADA, ADA→IFX. other anti-TNF therapy → IFX or ADA). It is necessary to clarify the type of first anti-TNF therapy to understand ineffectiveness of secondary anti-TNF therapy. We again reviewed the studies and found In Zorzi *et al*^[6] study, 13 patients in the IFX group had previous exposure to anti-TNFs (10 with IFX, 3 ADA). In these patients, anti-TNFs were discontinued due to clinical remission, no response or loss of response. 17 patients in the ADA group had previous exposure to IFX. Reasons for IFX discontinuation were clinical remission, infusion reaction or no response. In Doecke *et al*^[16] study, 46 patients in the IFX group had previous exposure to anti-TNFs (38 with IFX, 8 ADA). 76 patients in the ADA group had previous exposure to anti-TNFs (40 with IFX, 36 ADA). The exact reason for switching treatment is not clear. The outcome of this subgroup of patients was not provided. Besides, most of the studies did not identify specifically the type of first anti-TNF therapy in anti-TNF therapy non-naïve cases. We are sorry to fail to clarify this point. Future studies need to address the question.

5. There are some typos.

Response: We have corrected the typos.

Responds to the science editor's comments:

1. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using

PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: We provided decomposable figures. However, we don't know if these pictures meet the requirements. If there is something that needs to be changed, please contact me.

2. The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

Response: We have added "Article Highlights" section accordingly.

3. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Response: We revised our reference list accordingly, but there are still have 4 references from the Aliment Pharmacol Ther. These references are all original study included the meta-analysis, so we can not remove these.

4. Please provide decomposable Tables (in which all components are movable and editable), organize them into a single Word file, and submit as "74609-Tables.docx" on the system. The tables should be uploaded to the file destination of "Table File.

Response: We provided decomposable tables. As the reviewer suggested, we carried out GRADE evidence and added table 3.

Thank you for all your comments. Additionally, we thanked WORDVICE for editing this manuscript. We hope our work can promote a better understanding of our research.

We tried our best to improve the manuscript and made some changes in the manuscript.

We appreciate for Editors'/Reviewers' warm work earnestly and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours,

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