RESPONSE TO THE REVIEWER

World Journal of Clinical Cases Manuscript No 91615

Discontinuation of therapy in inflammatory bowel disease: Current views

Dear Reviewer,

We thank you for your comments regarding manuscript 'Discontinuation of therapy in inflammatory bowel disease: Current views' in *World Journal of Clinical Cases*. We appreciate the time and effort that you dedicated providing feedback on our manuscript and are grateful for the comments and valuable improvements to our paper. Please see below, for a point-by-point response to your comments and concerns.

Reviewer #1

Point 1:

The article is not original per se but it is quite interesting. It is a generic review on the important topic of discontinuing the maintenance therapy in IBD Clinical settings. The quality of the article is overall low, but with some improvements it may be considered for publication. Please clarify: in the biologic therapy chapter (as well as in the Fig. 1), you mention low serum anti-TNF levels are linked to decreased risk of relapse. Did you intend low serum anti IFX antibody instead?

Answer

Thank you for your valuable comments and encouragement. Regarding the note about anti TNF levels, in our manuscript we have stated:

'Lower serum anti-TNF levels and mucosal healing appeared linked to a decreased risk of relapse following anti-TNF discontinuation', using reference number 54.

Namely, Gisbert et al. in their article have stated as follow:

'From another perspective, low anti-TNF trough levels (<2lg/mL) at discontinuation were predictive of maintaining remission, suggesting that patients had sustained remission regardless of (futile) continued anti-TNF administration and were therefore also less likely to experience aflare-up once therapy is discontinued'.

Based on this finding we made our statement in the manuscript.

54. Gisbert JP, Marn AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. Aliment Pharmacol Ther. 2015;42:391-405.

We hope you will find our revised version suitable for publication in the World Journal of Clinical Cases. We are looking forward to hearing from you in the near future.

Reviewer #2

I enjoyed reading this narrative review of the outcomes, pros and cons of treatment de-escalation in IBD. In general, this is a well-presented and readable review. Whilst it does not add a substantial amount to the already large body of literature in this area, it is a useful and concise update as to the current situation. This obviously remains an important and somewhat contentious area and the author's conclusion are balanced. There are several areas that may benefit from further detail or amendments.

Answer:

Thank you for your comments. We hope that the corrections will further improve the manuscript.

<u>Point 1</u>

1. The abstract is very vague on exact details. Could more specific details on risk factors or relapse rates with individual agents be included? This is likely to entice more readers.

Answer

Thank you for your suggestion. Abstract was modified according to your comment.

Point 2

2. Throughout the paper, the authors accept that reintroduction of therapy is effective in recapturing disease control. However, they quote success rates of ~ 66% to support this. It could easily be argued that one third of patients with chronic debilitating failing to recapture remission is actually a substantial proportion and retreatment may not be as effective as the authors would perhaps have us believe?

Answer

Thank you for this noticing this. We agree with your opinion. Although about two thirds of patients are expected to have satisfying response after reintroduction of therapy, still more than 30 % will experience therapy failure. We added and highlighted this fact in Conclusion section according to your valuable comment.

Point 3

3. In the modern era, where sequencing of advanced therapies is often the reality and many patients will have received more than one advanced therapy, may clinicians are likely to be interested in how this disease behaviour may alter decisions about de-escalation, do the authors have an advice or data on this cohort? Most of the data seem to relate to TNFi as 1st advanced therapy. Are there data specific to de-escalation of subsequent lines of therapy? Many clinicians would probably assume that these are higher-risk patients, based on duration or behaviour and perhaps the same parameters apply? It would be helpful to try and separate if different pathways should be applied for subsequent lines of advanced therapies?

Answer

Thank you for this interesting remark.

Indeed, multiple lines of advanced therapy are increasingly becoming a reality in the treatment of inflammatory bowel disease. Therefore, the interest of clinicians regarding eventual data on the challenges of de-escalation of therapy in such patients is understandable.

Unfortunately, there are no relevant studies dealing with the mentioned situations. Previous experience indicates the possibility of drug withdrawal when it comes to combined therapy. It is mainly a combination of immunomodulators and biological therapy, with mostly positive experiences when it comes to the withdrawal of immunomodulators from the combination, as emphasized in the section on immunomodulators and biological therapy.

Indeed, the most data on de-escalation of therapy refer to anti-TNF therapy, given that it has been available for the longest time. Data on other, advanced therapeutic lines, such as IL12/IL23 antagonists, α4β7integrin or small molecule therapy, are very scarce. The reasons probably lie in the fact that these are recently introduced therapeutic lines. As stated in the paragraph regarding biological therapy, the results of a retrospective analysis of the risk of relapse after the vedolizumab withdrawal showed that two-thirds of the patients had relapse within the first year after discontinuation of vedolizumab, with retreatment success in two-thirds of patients. Experience with reintroduction of tofacitinib has also been mentioned in the text (OCTAVE Open study).

We agree that such group of patients are higher risk ones. In our opinion, decision regarding possible withdrawal should be based on known predictive factors and clinical impression.

Point 4

4. The figures given in the introduction of only onset IBD are confusing. If ¼ are diagnosed before 20, is the 1/5 referred to at aged < 10, one fifth of the 25% (so 5% overall) or 20% overall (which seems to only leave 5% in the adolescent group (which seem incorrect?).

Answer

Thank you for this note.

Indeed, about 25% of patients with IBD are diagnosed before 20. However, 20% of children with IBD are diagnosed before 10, and 5 % before year 5. We have rearranged this part in Introduction section thanks to your observation.

Point 5

The inference on the section about 5ASA therapies, especially "topical" therapies would seem to be about 5ASA as sole therapies, not when already combined with other agents? It would be worth being really explicit here about which studies are sole therapy compared to combo-therapy.

Answer

Thank you on this notice. Regarding the section about 5-ASA therapy, in part of topical therapy mentioned studies (references 27-32) involved topical monotherapy. We added this fact to the manuscript in the section 5-Aminosalicylates.

Point 6

6. I think on page 7, the authors mean rectal therapies when covering "topical" therapies? All 5ASA drugs probably work topically whether given rectally or as controlled-release oral forms. Please clarify.

Answer

Thank you for this comment. We agree with your argumentation. We added 'rectal' in the section regarding 5-aminosalicylates.

Point 7

7. Use do not rather than didn't -page 10 line 12.

Answer

Thank you for this comment. It is corrected.

Point 8

8. On page 13, there is a paragraph seemingly about ustekinumab therapy. This appears to concern the use of ustekinumab in psoriasis rather than IBD? The long-term behaviour of psoriasis is likely very different from IBD and hence I am not sure what relevance this has to

IBD. Either this section should be removed or some comparator data included on the rates of psoriasis disease recurrence with other agents (TNFi, ciclosporin etc).

Answer

Thank you. We agree with your suggestion. After detailed inspection, we removed this part from the manuscript.

Point 9

9. The authors correctly identify the use of fecal calprotectin as a marker to predict relapse of IBD. However, they noticeably fail to provide any guidance on what action should be taken on these results? It is perfectly reasonable to monitoring the calprotectin but should treatment be re-instated just for the raising calprotectin.

Answer

Thank you for this valuable remark. Further explanation has been added regarding follow up period after withdrawal in 'Monitoring after withdrawal from therapy and predictive factors of relapse' section. In our opinion frequent checking of CRP and fecal calprotectin are needed after withdrawal of therapy, since it has been noticed that arise of these two factors can precede clinical relapse. This is important in predicting optimal timing of endoscopic revision.

Editorial office

Dear Editors,

We thank you for your generous comments regarding manuscript 'Discontinuation of therapy in inflammatory bowel disease: Current views'. We are grateful for the opportunity to submit our manuscript for publication in *World Journal of Clinical Cases*. We appreciate the time and effort that you dedicated providing feedback on our manuscript and are grateful for the comments and valuable improvements to our paper. We hope you will truly consider publishing this manuscript. Please see below, for a point-by-point response to your comments and concerns.

Science Editor

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

2 Scientific quality: The author submitted a study of discontinuation of therapy in inflammatory bowel disease. The manuscript is overall qualified.

(1) Advantages and disadvantages: The reviewer has given positive peer-review reports for the manuscript. Classification: Grade D and Grade C; Language Quality: Grade B and Grade B. The article is not original per se but it is quite interesting. Whilst it does not add a substantial amount to the already large body of literature in this area, it is a useful and concise update as to the current situation. This obviously remains an important and somewhat contentious area and the author's conclusion are balanced. There are several areas that may benefit from further detail or amendments. The abstract is very vague on exact details.

Thank you for your opinion and comments. We have added new text to the Abstract section in order to make it more attractive to the readers.

(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.

Thank you for this remark. We have rearranged manuscript by adding new content according to yours and the reviewer's comments.

(3) Table(s) and figure(s): There are 1 Figure and 1 Table should be improved. Detailed suggestions for each are listed in the specific comments section.

Thank you. Reviewers' comments have been taken into account.

(4) References: A total of 65 references are cited, including 14 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.

Thank you for this comment. Language polishing has been performed.

4 Specific comments:

(1) Please provide the filled conflict-of-interest disclosure form.

Disclosure form has been provided.

(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: .

Figure 1 has been provided in PPT form. We verify that Figure 1 is original image created for the purpose of this manuscript.

(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.

Figure 1 is original picture.

(4) Please provide the PMID numbers and DOI to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

PMID numbers and DOI have been added to reference list. All authors have been listed.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Transfer to another BPG Journal

Thank you for this opportunity.

Company Editor-in-Chief

I recommend the manuscript to be published in the World Journal of Clinical Cases.

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 Reference Citation Analysis (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/.

Thank you for your suggestion and encouragement. Manuscript has been furtherly improved. We are grateful for new opportunity that has been given to us.

We hope you will find our revised version suitable for publication in the World Journal of Clinical Cases. We are looking forward to hearing from you in the near future.

Your sincerely,

Assoc. Prof. Josko Bozic, MD, PhD