Impact of adalimumab on disease burden in moderate-to-severe ulcerative colitis patients: The one-year, real-world UCanADA study

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Point-by-point Response to Reviewers' and Editorial Office's Comments

Dear Editorial Office Director/Editor-in-Chief and Reviewers, thank you for your review and for identifying this manuscript as current, interesting, well written and clear, as well as a well-designed study.

Your comments have been carefully considered, and the actions taken are summarized in the point-by-point response below.

Comment	Response	Changes
Reviewer #1 – Specific Comments to Authors		
1. *I only would suggest to specify how long must the washout period have been for the patient to be enrolled in the study.*	For the washout period, as mentioned in the manuscript, "an appropriate washout period took place per routine practice", for this observational study. The information collected during the study in relation to the washout period was either 'Yes' or 'No'; the length of washout periods was not measured. However, routine practice for a washout period varies usually between 2 to 3 months, which has been added to the manuscript.	**The following was added to the *Materials and Methods* section under *Study design and patients*:** "If a patient was previously treated with vedolizumab or any anti-tumor necrosis factor (-TNF) agent (except adalimumab), an appropriate washout period took place per routine practice, **which period varied usually from 2 to 3 months**."

Comment	Response	Changes
2. *Moreover, only patients who had primary failure to biologics were excluded, while patients with secondary loss of response did not. Patients who underwent multiple therapies may start a new therapy with greater psychological burden than patients biologic-naive. This should be at least briefly discussed in the Discussion section. I do not have any further comment.*	Agree with the comment. See proposed changes.	**The following sentence was added to the Discussion section:** **"In the present observational study, while patients who had a preliminary failure to biologics were excluded, patients with secondary failures were included, which may have led to the inclusion of patients with greater psychological burden than biologic-naïve patients."**
Reviewer #2 – Specific Comments to Authors		
1. *The authors state that "using a mixed model for repeated measures using observations from all follow-up visits with the baseline value included in the model as a covariate". Please provide the standard error bar charts or margins plot which create from the proper modeling equation and account for correlation of data. Additionally, please clarify the details of which analysis rely on e.g., marginal model or conditional model.*	Thank you. Additional information has been added to the Materials and Methods. Please note that 'Least squares means, *p*-value and 2-sided 95% CI of the difference between the two groups defined by the clinical effectiveness were determined', which results are provided in Supplementary Table 10. Also, additional details on the analysis of secondary objective to determine the correlation between effectiveness rates and PRO measures is now provided in the Supplementary material section.	**For clarity, the following was added in the Materials and Methods section under Study size and statistical methods:** **"All models with repeated measures included a random intercept with the effectiveness variable (fixed, forced-in), visit (fixed, forced-in), baseline value of the PRO measure (fixed, forced-in) and other covariates. Cross-sectional regression models included an intercept with the effectiveness variable (forced-in), baseline value of the PRO measure (fixed) and other covariates. Least squares means, p-value and 2-sided 95% CI of the difference between the two groups defined by the clinical effectiveness were determined. Additional details on the statistical analysis used to determine the correlation between effectiveness (clinical response and remission) rates and PRO measures are provided in the Supplementary material section."**
2. *Not to mention the great possibility of bias, some of which are nicely indicated in the Discussion.*	Agree.	**Please see addition to the discussion section under Comment #2 from Reviewer #1.**

Comment	Response	Changes
	As mentioned, the possibility of bias has been indicated in the discussion under limitations of the study.	
3. *How the authors deal with possible missing not at random in nearly 40% drop out participants. Additionally, the great number of drop out participants might affect to power of analysis and conclusion. How the authors deal?*	In this observational study, three methods were applied to account for missing data in the study: as observed, last observation carry forward (LOCF) and non-responder imputation (NRI), which are presented as sensitivity analyses for the primary endpoint. Missing data is mentioned in the limitations of the study. With regards to the proportion of drop outs, it is also mentioned in the discussion section "*This study consisted of a small cohort of patients, and only 48 (48%) patients completed the study. However, the results between the ITT population and completers population were fairly consistent*."	**No changes. Already mentioned/presented in the manuscript are the as observed, LOCF, NRI methods to account for missing data.** **Also mentioned in the manuscript is the fairly good consistency between the ITT population and the completers population.**
4. *Finally, since I am not a native English user, I did not check for grammatical errors thoroughly. This should be done by an appropriate language reviewer.*	Thank you. Four of the co-authors are English native, based in Canada, an anglophone country. We are confident that the proposed revised manuscript meets the language requirements, i.e., Grade A.	**The revised manuscript was carefully reviewed by all the English-native authors, focusing on grammar and language polishing. Minor changes were made.**
<u>Editorial Office's Comments – Science Editor</u>		

Comment	Response	Changes
5. *The manuscript has been peer-reviewed, and it' s ready for the first decision.* 6. *Language Quality: Grade B (Minor language polishing)* 7. *Scientific Quality: Grade B (Very good)*	Thank you for the review. Language and science have been addressed as suggested.	**As suggested, the manuscript was revised for polishing the language, specifically by the 4 English-native Canadian authors.** **Communications were received from the Editorial Office on June 19, 2022, stating "By the way, you don't need to find a language company to edit the manuscript."**
Editorial Office's Comments – Company editor-in-chef		
8. *I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.*	Thank you for the review and conditional acceptance.	**Please see all the proposed changes to address the reviewers' comments**
Figures: 9. *Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".* 10. *Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.* 11. *Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author*	The requested changes were made and PPT file provided. Copyright ©The Author(s) 2022 was added to the PPT file.	**Changes were made as instructed**

Comment	Response	Changes
needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.		
12. *Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.*	The tables format was reviewed to comply with the requirements	**Tables have been reviewed to meet the requirements**