



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 71392

Title: Higher infliximab and adalimumab trough levels are associated with fistula healing in patients with fistulising perianal Crohn's disease

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03662809

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: Australia

Manuscript submission date: 2021-09-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-14 12:29

Reviewer performed review: 2021-09-18 22:16

Review time: 4 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The manuscript deals with an interesting topic concerning the effectivity of two anti-tumor necrosis factor-alpha agents in healing perianal fistulas that are usually presented in patients with Crohn's disease. Although there are other articles in the literature dealing with the use of anti-TNF for the treatment of fistulas, the current work stands out for being the largest study to assess the relationship between adalimumab trough levels and clinical fistula healing. I would like to make the following comments and suggestions: 1. In the abstract, methods session, data about the antibodies against infliximab and adalimumab measurement was missing. 2. In the methodology section, page 6, item "Study Design and Patient Population", I suggest the authors to include the information on the moment when the blood collection was performed, taking into account the schedule of the anti-TNF injections. Moreover, I also suggest to provide more details concerning the type of samples that were used (is it serum?). 3. The Montreal Classification should be added to the patient's characteristics table to better describe the patients included in the study. In addition, information on previous surgeries could also be included in this table. 4. How long was the time between diagnosis (fistula) and the blood collection? 5. Was a clinical intervention performed after the trough levels results? 6. Previous studies have already demonstrated the advantage of acidifying samples pre-anti-drug antibodies ELISA, with the aim of breaking down the antibody immune complexes, which prevent an effective binding to the kit, thus increasing its sensitivity and avoiding false negatives. Did the authors perform this pre-treatment for the measurement of anti-drug antibodies? If not, I suggest them to include and discuss this information in the discussion section. 7. In the results



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section, page 9, third line "Five patients had been changed from infliximab to adalimumab or vice versa and were included in both the infliximab and adalimumab groups". Can't the fact that these patients had already presented some loss of response to the medications influence the result? This information could have been mentioned in the discussion. 8. The assays for measuring the trough levels were different. Was there any difference in the results while comparing the tests that were used? 9. Table 1 shows the patient demographics and disease characteristics. Were those variables between the groups statistically analyzed? Were the group under infliximab treatment and that one under adalimumab homogeneous considering their demographics and disease characteristics? Overall, it is a well written manuscript, but it needs revision.



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Reviewer's code: 03967085

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Chief Doctor

Reviewer's Country/Territory: Bulgaria

Author's Country/Territory: Australia

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Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The authors share their experience on anti-TNF agents in CD patients in Australia. The aim is stated clear. The authors stated clearly what study found and how they did it. The title is informative and relevant. The references are relevant and recent. The cited sources are referenced correctly. Appropriate and key studies are included. The introduction reveals what is already known about this topic. The research question is clearly outlined. The research question also justified given what is already known about the topic. The process of selection of the subjects was clear. The variables are well defined and measured appropriately. The study methods are valid and reliable. There are enough details provided in order to replicate the study. The data is presented in an appropriate way. The text in the results add to the data and it is not repetitive. Statistically significant results are clear. It is clear which results are with practical meaning. Results are discussed from different angles and placed into context without being overinterpreted. The conclusions answer the aim of the study. The conclusions are supported by references and own results. The limitations of the study are not fatal, but they are opportunities to inform future research. Specific comments on weaknesses of the article and what could be improved: Major points - none Minor points - none



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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 02941507

Position: Editorial Board

Academic degree: FACG, FEBG, MD, PhD

Professional title: Associate Professor, Staff Physician

Reviewer’s Country/Territory: Greece

Author’s Country/Territory: Australia

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Reviewer performed review: 2021-09-25 16:49

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

In this retrospective study the authors assessed the relationship between adalimumab trough levels and clinical fistula healing in patients with fistulising CD. They showed that higher infliximab and adalimumab trough levels were associated with perianal CD fistula healing, with higher rates of healing in higher tertiles of infliximab and adalimumab levels, thus confirming the existed evidence that fistula healing improves with higher anti-TNF trough levels. However no association with fistula closure was observed. The authors included 114 (66 infliximab, 48 adalimumab) patients of whom 72.7% achieved fistula healing and 27.3% fistula closure. Concerning the results of adalimumab administration they showed that 77% achieved fistula healing and 35.4% fistula closure. However, in a previous abstract published on January 2020 the same group of authors included 123 patients (IFX = 72; ADA = 51) of whom 75.0% on maintenance IFX achieved fistula healing and 30.6% achieved fistula closure. (B Gu, K Venkatesh, A J Williams, W Ng, C Corte, S Ghaly, W Xuan, S Paramsothy, S Connor. P586 Higher infliximab and adalimumab trough levels are associated with fistula healing in patients with fistulising perianal Crohn's disease. Journal of Crohn's and Colitis, January 2020;14:S490-S491). What is the explanation for these differences?