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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 62766

Title: Relationship between clinical remission of perianal fistulas in Crohn's disease and serum adalimumab concentrations: A multi-center cross-sectional study

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04025482
Position: Peer Reviewer
Academic degree: MD
Professional title: Assistant Professor
Reviewer's Country/Territory: Slovenia
Author's Country/Territory: France

Manuscript submission date: 2021-02-11

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-13 09:54

Reviewer performed review: 2021-02-13 16:55

Review time: 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for the opportunity to review this interesting paper. The main message of the paper is that higher ADL concentrations were associated with fistula healing – in particular the new message is that these concentrations are much higher than generally accepted. The strength of the paper is the very robust evaluation of fistulas, backed up with strong evaluations (Present's criteria, PDAI, absence of seton and proctological assessment) – something rarely reported in the literature – the authors should congratulated for this. Specific comments: - Please avoid ADL concentrations "needed" - it is just association please correct to »associated« or similar - Abstract: »Serum ADA concentrations tended to be higher in patients whose treatment was optimized than in those whose treatment was not optimized (14 [5–16] μg/mL vs. 10 [4–13] μg/mL, p=0.20) and in patients receiving combination therapy than in those receiving ADA alone (12 [5–16] μg/mL vs. 11 [5–14] μg/mL, p=0.11)." – none of the reported comparisons are significant – would suggest to remove from the abstract (can comment in discussion) - Abstract: A target concentration that is associated with remission has not yet been determined by a prospective study – this was not studied by the authors – should be removed from the abstract - Please add definitions of outcomes reported in the abstract already in the abstract: i.e. define clinical remission of fistula in the abstract (important to reach broader readership) - Fig 1: please make it clear and self-explanatory (name the axes, remove abbreviations - Fig: the same as for Fig 1. Also add titles: - please change the y axis to proportions (%) – the number of pts with achieved remission can still be added to the top of the column. - Please work on the figure appearance - Discussion: o You mention no correlation of drug concentration to adverse events – this is important

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as would enable clinicians to use higher dose of tnf-inhibitors – perhaps you could make and extra paragraph and discuss this in line with other literature on this topic (e.g. infliximab some suggest no link to infections/ DOI: 10.1080/00365521.2018.1486882, DOI: 10.1093/ibd/izy066 …….but others do not: • DOI: 10.1016/j.cgh.2020.03.018) – should deserve a separate paragraph since you stress the safety of high ADL concentrations in both, the first and the last paragraph. o 3rd paragraph: you suggest to measure drug concentrations if no remission – but you also suggest that higher concentrations are needed for fistula healing – since the ceiling concentration was not reached I think it is difficult to rely on certain drug level (i.e. we do not have a concentration to target as you conclude –so why measuring drug levels at all (perhaps only to exclude immunogenicity issue) o "We identified a trend but not a significant difference in serum ADA concentrations according to healing status (11 [7–14] μg/mL vs. 10 [4–16] μg/mL, p = 0.69)." – with medians so close and p completely insignificant it is difficult to say that this is trend – I would suggest change this (perhaps the ADA concentrations that would associate with this very robust endpoint were not reached with 40 mg weekly dose in this cohort – this could be one explanation for this result (i.e. what do you think about off-label dose of ADL 80mg weekly to reach this more difficult endpoint?)

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Reviewer's code: 02997260
Position: Peer Reviewer
Academic degree: PhD
Professional title: Senior Researcher
Reviewer's Country/Territory: Lithuania
Author's Country/Territory: France

Manuscript submission date: 2021-02-11

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-15 06:42

Reviewer performed review: 2021-02-17 16:05

Review time: 2 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Overall the manuscript is well prepared and provides useful clinical information. The main manuscript imperfection is the ADA concentration measuring because its time point was not the same through the centers. Some centers had performed ADA concentration measurements during induction, while others – during treatment. This circumstance undoubtedly influences the ADA values. To ensure that it is the ADA concentration and not the duration of treatment that affects PAFs remission, I suggest supplementing the study with regression analysis. It will strengthen the conclusions of this study.