Editorial Office

World Journal of Clinical Cases

Re: Manuscript No. 40132: Revision of Manuscript

Title: Treat-to-target in Crohn's disease: Will transmural healing become a therapeutic endpoint?

August 17 2018

Dear Dr. Ying Dou, Science Editor, Editorial Office,

I thank you very much for giving me the opportunity to submit a revised version of my manuscript and for your suggestions.

I am grateful to the reviewers for reading my manuscript and for their helpful comments/suggestions. As indicated in my point-by-point responses below, I have addressed all reviewers' comments. The manuscript has been duly revised accordingly.

I feel that the novel version of the manuscript has considerably improved and do hope that this revised version of the manuscript will be found suitable for the *World Journal of Clinical Cases.*

I am looking forward to your answer.

Yours sincerely,

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Response to Editor's comments on the edited manuscript file

Editor's comment:
Please revise the manuscript according to the review report and my comments. And answer all of the reviewers' comments carefully (point-to-point).

Response:
The manuscript has been revised carefully according to the reviewers' reports and the Editor comments. The answers to all reviewers' comments are found below (point by point).

Editor's comment:
Please provide all authors abbreviation names and manuscript title here (under the Core Tip).

Response:
My abbreviated name and the manuscript title were added there.

Response to reviewers' comments

Reviewer 1 (03729678)

Scientific quality: Grade C (Good), Language evaluation: Grade B Minor language polishing, Conclusion: Minor revision.

Specific comments to authors:

DE Serban made a narrative review of literature of 11 articles (7 published as full papers and 4 as abstracts only) dealing with the question whether one should or not include transmural healing (vs mucosal healing evaluated by endoscopy) in the treatment strategy of Crohn's disease. Overall, the message is that transmural healing is sometimes not reached in patients with mucosal healing and that it seems that the prognosis of CD is better when this goal is reached than when it is not.

Response: I thank the reviewer for this comment. That is indeed the message.

1. The author provides many details of the studies with some repeats which could be avoided in order to shorten the text.

Response: I thank the reviewer for the important suggestion. I inserted many data, since there was no limit of the number of words. Details have now been removed from the text and there are no repeats. The text was considerably shortened, containing now only two thirds of the original manuscript.

2. Introduction: in the first line, the author states that "CD represents a chronic transmural inflammatory condition of the gastrointestinal tract" does the author mean that CD lesion are always transmural ? this would be in contradiction with the result of her analysis

Response: According to the definition and diagnosis of Crohn's disease (CD), lesions are always transmural (before therapy), which differentiates CD from the other major form of inflammatory bowel diseases – ulcerative colitis. I insert here only some of the most representative references (besides those which were already written in my original manuscript), since there are thousands. From older to the most recent:

a. Lennard-Jones JE. **Classification of inflammatory bowel disease.** Scand J Gastroenterol 1989, 24(suppl 170), 2-6.

b. Freeman HJ. **Natural history and long-term clinical course of Crohn's disease.** World J Gastroenterol. 2014;20:31–36.

c. Bouguen G, Levesque BG, Feagan BG, et al. **Treat to target: a proposed new paradigm for the management of Crohn's disease.** Clin Gastroenterol Hepatol. 2015;13:1042–1050.e2.

d. Gomollón F, Dignass A, Annese V, et al, **ECCO. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016**: Part 1:

Diagnosis and medical management on behalf of ECCO. J Crohns Colitis 2017;11:3–25.
e. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. **ACG Clinical Guideline: Management of Crohn's Disease in Adults.** Am J Gastroenterol. 2018 Apr;113(4):481-517.

The fact that CD is transmural before therapy is not in contradiction with the results of my review. The aim of the therapy in CD is to heal the lesions. As mentioned in my review, the current goal is mucosal healing (MH). But, according to the results of my review, healing of the transmural wall appears to lead to significantly better long-term outcomes. If the whole wall is healed, then there are no more lesions. This does not mean that before therapy CD is not transmural. I insert a fragment from an editorial by Maconi G *et al*, which was included in the original references of my review and dated from 2017 (Maconi G, Armuzzi A. Beyond remission and mucosal healing in Crohn's disease. Exploring the deep with cross sectional imaging. *Dig Liver Dis* 2017;**49**:457–8):
"Whether MH in CD reflects the complete healing of the damaged bowel wall, is uncertain and still matter of debate. Hence, a new concept of deep healing, involving the whole intestinal wall in CD, the transmural healing (TH), has been developed. This is the normalization of the thickening of the bowel walls, assessed by cross sectional imaging, which should reflect the complete resolution of the bowel damage. The TH has been considered as an end point parameter by few studies, so far".

The reason I wrote this review was to point out that TH is better and, thus, to clarify the debate.

I hope that my response answers properly this comment.

3. The author could discuss the limits of the cross sectional studies to make the distinction between active disease and fibrosis.
Response: Distinction between active disease and fibrosis was not addressed specifically in the studies included in my review. Only one study included assessment of fibrosis (Orlando *et al*) and that study had already been discussed in my review. In any case, **regardless of the nature of the study, distinction between active inflammation and fibrosis is still an unsolved issue, even for experts,** because **there is almost a complete overlap between inflammation and fibrosis.** In order to support my affirmation, I insert a fragment from a very recent paper by one of the most eminent experts in intestinal fibrosis across the world, Florian Rieder (Rieder F. Managing Intestinal Fibrosis in Patients With Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2018 Feb;14(2):120-122).
"One of the most significant challenges in this field is that the current techniques to detect **fibrostenosis are insufficient, as they are not validated or not accurate enough to be reliably used in clinical practice.** The most advanced techniques presently available in this area are **delayed enhancement magnetic resonance (MR)**

imaging and magnetization transfer MR imaging, but these techniques are not validated. Currently under exploration are ultrasound-based techniques such as ultrasound elastography. Other attempts have been undertaken to diagnose fibrosis, or the fibrotic component of a stricture, using endoscopy, biopsies, or biomarkers, but **none of these techniques are accurate enough to be used**. Diagnosis of a fibrotic component of a stricture is difficult in Crohn's disease patients because **there is almost a complete overlap between inflammation and fibrosis;** separating these 2 processes is one of the biggest obstacles for developing future antifibrotic therapy."

I hope my response answers properly this comment.

Reviewer 2 (00069458)

Scientific quality: Grade C (Good), Language evaluation: Grade B Minor language polishing, Conclusion: Major revision.

Specific comments to authors:

This narrative review aimed to critically review and summarize the available literature relating transmural healing (TH) to long-term outcomes.

Major points: 1. Abstract, introduction and discussion are too long and should be shortened.
Response: I thank the reviewer for this important remark. As mentioned before, I added a lot of data, for which I worked hard to put together. Since there was no limit of words, I considered the information provided as essential for the topic of my review. Following the reviewer's suggestion:
a. The Abstract was shortened. It contains now 209 words (minimum is 200).
b. The Introduction was shortened by approximately one third.
c. Discussion was reduced also with approximately one third and carefully re-written.
I believe that any further shortening would result in a loss of the fundamental ideas that I wanted to point out in order to benefit the readers. I hope that the shortened version is more accurate.

2. Discussion shouldn't include any results.
Response: I thank the reviewer for this comment. Results were either moved to the "Results" paragraph or removed completely from the manuscript.

3. Data presented only in an abstract form should better be excluded.
Response: I thank the reviewer for this suggestion. I had included the abstracts, as I wanted to include all data that were published to date and since there were only seven full manuscripts; abstracts were not easy to find. Following the reviewer suggestion, abstracts were completely removed in the revised manuscript.