

Dear Reviewers,

First of all, we appreciated the manuscript review, as well as, the provided feedback. Please, find below your suggestions and comments addressed.

Reviewers' code: 03027040

"As conventional therapies are usually related to specific side effects, it could be interesting to add if any adverse events and side effects were analyzed in the included studies, especially in long term therapy for maintenance of remission"

Thank you for the suggestion provided; however the focus of this systematic review was the effectiveness of conventional therapy, therefore we did not search for adverse events and side effects in the included studies.

Reviewers' code: 02549032

1. The authors include both CD and UC in this review. It would be advisable to separate these two diseases, as the instruments for measuring disease activity are different.

Thank you for your contribution. The tables were split by disease (CD or UC) in the new version of the manuscript.

2. The authors used as study outcomes: <<clinical remission>> and <<clinical response>>. The difference is not clarified. Clinical response means clinical induction? or maintenance therapy? after initial control of active disease? Both can be overlapped. This is confusing.

Thank you for sharing your concern with us. It is a matter of evaluating clinical response and clinical remission in the active phase of the disease, therefore, induction of response and clinical remission; in the case of maintenance, we will have maintained clinical response or maintained clinical remission. The definition of these terms changes according to the individual study. Hence, in our systematic review, it is being considered the definition of each individual study, which was added to the new version of the manuscript. Please, note that below each table the respective definitions were described, if applicable.

3. Although the issue of <<Conventional therapy in moderate-severe IBD>> is interesting the paucity of studies and the negative result of this review made the publication of this review difficult in the present form. Instead a short letter to the editor should be advisable with the conclusion of necessity of further studies with also mucosal healing as endpoint.

We appreciate your feedback. Our study was previously presented as a poster in the 2017 Advances in IBD Congress and, at that moment, as we

verified some important issues that could guide IBD management, we considered relevant to have a full manuscript of that.
Please, find a letter to the Editor in the attached documents.

4. Some minor grammatical mistakes eg: <<In page 12, 2nd paragraph a grammatical mistake <<rately referenced by treatment guidelines. Therefore, we believe that tacrolimus use should..>>.

Thank you for your input, we had the manuscript reviewed for language and have corrected any mistakes discovered.

Sincerely,

PhD Flávio de Castro Feitosa

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Letter to the Editor:

Dear Editor,

We are submitting our article entitled “Conventional therapy for moderate to severe inflammatory bowel disease (IBD): a systematic literature review” for possible publication in the prestigious *World Journal of Gastroenterology*. In our paper, we verified some important issues that could guide IBD management.

It is known that many patients with IBD, particularly with Crohn’s disease, are moderate to severe at presentation, and despite the emergence of biological therapy, conventional therapy continues to be used in those patients, mainly in countries where biologicals are not covered by insurance. Thus, in our systematic review, we aimed to investigate the efficacy of the so-called conventional therapy (biologicals not included) in patients with moderate to severe disease; such a study turns out to be relevant in view of the fact that most of the reviews, so far, deal with mild/moderate cases or simply do not mention the disease severity.

Our results showed that little high-quality evidence is available on conventional therapy for moderate to severe IBD patients, especially for clinical remission maintenance and objective data, such as mucosal healing and fecal calprotectin. We also observed some positive results for tacrolimus in the treatment of ulcerative colitis.

In conclusion, our systematic review demonstrated that further studies with high quality and real-world evidence are needed to definitely and convincingly prove the effectiveness of conventional therapy in moderate to severe IBD.

We do hope our work will contribute to clarify the role of conventional therapy in moderate to severe IBD patients, and encourage researchers to carry on appropriate trials and studies to define the best therapeutic strategies in such patients.

Sincerely,

Adérson O.M.C. Damião, MD, MSc, PhD

First author

Dear Editor,

Please, find below the answers for the following reviewers' request:

"The following questions should be briefly answered:"

What are the new findings of this study? There are few published data on the use of conventional therapy in moderate to severe IBD in the literature

What are the new theories that this study proposes? Maybe there is over use of conventional therapy in moderate to severe IBD patients.

What are the appropriate summarizations of the current knowledge that this study provided? A global picture of conventional therapy studies status in moderate to severe IBD.

What are the original insights into the current knowledge that this study offered? It is possible that conventional therapy is being used with no robust literature evidence to support it.

What are the new hypotheses that this study proposed? Should conventional therapy be use carefully in moderate to severe IBD patients?

What are the new methods that this study proposed? There are no methods proposed in this study.

What are the new phenomena that were found through experiments in this study? There are no experiments in this study.

What are the hypotheses that were confirmed through experiments in this study? There are no experiments in this study.

What are the implications of this study for clinical practice in the future? The rise of new controlled studies to investigate the efficacy of conventional therapy in moderate to severe IBD patients or a decrease in the use of these drugs in moderate to severe IBD patients.

Sincerely,

PhD Flávio de Castro Feitosa

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