Revision of Manuscript 62457

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Dear editors,

dear reviewers,

First of all I like to thank the Editors and reviewers that the submitted manuscript has the chance to be accepted for publication after revision according to your appreciated suggestions.

Based on the comments of the Science Editor, the current manuscript is not considered as a Frontier article. Accordingly, I have to declare that the manuscript is a retrospective series.

Related to the retrospective study design with collection and analysis of regular clinical data (data analysis for quality assurance with follow-up; data collection not for primary study purpose), a letter of the local ethical committee (institutional board review) is attached to the submitted revision of my manuscript.

A. Point-by-point responses to the issues raised in the peer-review reports:

Reviewer #1:

No specific revisions were recommended.

Reviewer #2:

This a very interesting article on a very hot topic for Crohn's disease with ano-perineal fistula and a long follow up. I have a few questions and remarks: There is many debates about the criteria for healing: either the Present's criteria and/or MRI

criteria. The paragraph in the discussion about the definition of healing should be added into the methods. Table 2 should be added as a paragraph in the method section to be more apparent. Did you do the PDAI score? Recent data showed that fibrin glue injection or other local method are disappointing. One of the predictor of response is the medical treatment. It is suprizing that no patient had a combinaison of anti-TNF and immunomodulators. How do you explain this? How many patients had their medical treatment change after the stem cell treatment? Patients with major medical changes after injection should not be considered in remission thanks to the stem cell treatment. In addition, patients with abscess should not be considered in remission even a long time after injection. Did they have MRI to diagnose a fistula? Or did they have medical change for the Crohn's disease because of the abcess? I do not think that figure 1 and 2 bring important information. The discussion is too long. You could shorten the paragraph about the COVID as we understand the higher difficulties to perform a protocol during this period.

According to the reviewer`s suggestions I revised several aspects in the manuscript:

The complex of "criteria for healing" and "definition of healing" was specifically addressed in the "Methods" section. Accordingly, Table 2 was added as a paragraph in the "Methods" section. Therefore, the former paragraphs on study population, prospective data evaluation and study design were re-written and summarized as two paragraphs (Study population; Study design and outcome evaluation) including Tables 1 and 2 and criteria of healing; moreover, Parks classification was added int paragraph of study population to ensure a more ascertain description of complex fistula (see also suggestion of reviewer #3). Additionally, the section "Follow-up" was revised

The role of "healing" and "remission" in patients with occurrence of perianal abscess was specifically addressed and discussed; moreover, aspects of medical therapy and/or change in medical therapy due to abscess were added. In detail, the significance of perianal abscesses (incidence 36.4%) was specifically discussed in terms of associated recurrence or persistence and medical therapy. Furthermore, the challenges related to abscess during follow-up (e.g. local problem vs. systemic disease) were added to the discussion. Finally, the information that no patient with abscess had change of medical treatment was included.

As suggested, Figures 1 and 2 were deleted.

There was no patient who has a combination of anti-TNF and immunomodulators.

Focussing on discussion, the discussion was revised and shortened in general. In detail, the paragraph related to COVID pandemia was significantly shortened.

Unfortunately, I did not use the PDAI score; therefore, no data on PDAI score can be provided. I will include the score for further protocols or surveillance.

Furthermore, I did not use MRI as standard tool for monitoring all patients; consequently; I cannot provide MRI data for the whole collective. MRI was only performed in three patients. As this was a retrospective series on routine clinical data (quality control), there was no routine administration of MRI.

Following the suggestions of the reviewer including re-analysis and taking into consideration that patients with the occurrence of abscess cannot be defined "in remission", a healing rate of 63.6% was assessed.

Reviewer #3:

The application of adipose-derived mesenchymal stem cells (Darvastrocel) to study the therapeutic effect of patients with perianal fistula Crohn's disease is a very innovative and practical study. The only limitation is that the number of case specimens is small, and we look forward to further progress in the future for the multi-sample and multi-center clinical research.

According to the reviewer`s suggestions I revised several aspects in the manuscript:

Related to the study population, the definition of complex fistula was specifically revised in the "Methods" section. Fistulas were determined according to Parks classification to enable a more ascertain definition (paragraph: study population).

The fundamental limitations of the study – small patients`collective, retrospective series and absence of a control group – were added to the "Discussion" section.

B. Point-by-point responses to the issues raised in the Editorial Office`s comments:

According to the Editorial Office`s suggestions, the following aspects in the manuscript were revised:

Science Editor:

As suggested, the "Article Highlights" section has been added to the manuscript.
All references have been checked; all references are relevant to the manuscript and have been created according to the WJG recommendations.

As there is no statistical evaluation within the manuscript, a statistical review or certificate is not necessary.
The manuscript (including ethical standards) has been reviewed by the local ethical committee. As this is a retrospective series with data collection of routine clinical data (quality assurance, anonymous data), there was no specific institutional review approval necessary. The letter of the local institutional board (local ethical committee) has been attached to the submission.

Editorial Office Director:

A PDF of the letter of the local etical committee (Institutional Review Board) will be uploaded with the revised manuscript.

Finally, I like to thank the Editorial team and the reviewers for their work.
I would be grateful if the revised version could be accepted for publication in WJG.

Best regards,
Oliver Schwandner, FASCRS