

2019/06/28

Dear Professor, Lian-Sheng Ma,
Founder and Chief Executive Officer
Baishideng Publishing Group Inc.

Title: Manuscript **No.** 48680

“Immune checkpoint inhibitor-induced diarrhea/colitis: Endoscopic and pathologic findings”

Thank you very much for your careful and thoughtful review of our manuscript titled “Manuscript **No.** 48680- **Immune checkpoint inhibitor-induced diarrhea/colitis: Endoscopic and pathologic findings**”.

We have revised our manuscript; the revisions are highlighted using track changes in Microsoft Word (version 16.26), and questions are answered in a point-by-point manner. In addition, under reviewer’s suggestion, we have invited a GI pathologist, Dr. Shiro Adachi, to rewrite the pathology section as a coauthor.

The manuscript has been revised by an academic editing company (**American Journal Experts; <http://www.aje.com/jp/>**).

We sincerely hope that the revised manuscript is acceptable for publication in *the **World Journal of Gastrointestinal Pathophysiology***. We believe that our manuscript is now much improved and that we have resolved several issues that were raised. Our research should be interesting to many readers of the ***World Journal of Gastrointestinal Pathophysiology***.

Thank you in advance for considering our manuscript for publication.

Sincerely,

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Reviewer #1's comments (Reviewer's code: 02444978)

Thank you very much for your comments regarding our manuscript. We hope that the revised manuscript is acceptable for publication in the ***World Journal of Gastrointestinal Pathophysiology***.

Reviewer #2's comments (Reviewer's code: 02540650)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. In the revised manuscript, we asked an editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the grammatical errors.

Our responses to your comments are as follows.

Comments #1. The studied topic is frequently studied, some points are needed to be clear: Sample size is not studied collectively like other studies, studying of each clinical trial sporadically give less statistical significance data.

Response to comment: Thank you for your comment. As you noted, topics related to irAEs are frequently discussed, e.g., collective analysis of the incidence of irAE-related diarrhea or colitis, as in other meta-analyses. Therefore, we have highlighted the endoscopic and pathologic findings of immune checkpoint inhibitor-induced diarrhea/colitis in this mini-review. However, we agree that it is unclear what this review addresses, and we felt that the pathology section focused on the pathological findings of ICPI-induced colitis was weak. To highlight this topic, we have invited a GI pathologist, Dr. Shiro Adachi, to rewrite the pathology section on pages 10-12 in the revised manuscript.

Comments #2. Details of therapeutic regimen of choice are very lacking in the provided table.

Response to comment: As we mentioned above in reply #1, we have highlighted the endoscopic and pathologic findings of immune checkpoint inhibitor-induced diarrhea/colitis in this mini-review, so we have manually selected mainly immune checkpoint inhibitor monotherapy regimens. However, we have added some therapeutic regimens in the tables.

Comments #3. More details on provided figure and more illustrating figures are needed (provided data on figure are very few and not informative).

Response to comment: We have provided pathological images in Figure 2.

Comments #4. Please concise introduction and discussion.

Response to comment: Thank you for your suggestion. We have shortened and simplified these sections, particularly the introduction section (467→275 words).

Comments #5. Update references, many reviews regarding this topic are added recently.

Response to comment: Thank you for your comments. We have updated and added some recent references in Table 1.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in ***the World Journal of Gastrointestinal Pathophysiology***.

Reviewer #3's comments (Reviewer's code: 03388124)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. In the revised manuscript, we asked an editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the grammatical errors.

Our responses to your comments are as follows.

Comments #1. The "Pathology" section is very weak, which may reflect the fact that the authors are not pathology expert. Thus the paper will be improved by including a gastrointestinal pathologist as a co-author and rewriting the pathology section. It should also include any features that may alert the pathologist of unsuspected ICPI-induced colitis such as autoimmune-type change, and stress the importance of sharing relevant clinical information with the pathologist.

Response to comments: Thank you for your comments. We agree about the pathology section. As you recommend, we have added the GI pathologist Dr. Shiro Adachi as a coauthor and asked him to rewrite the pathology section on pages 10-12 in the revised manuscript.

Comments #2. Representative pathology images of ICPI-induced colitis should be provided.

Response to comments: We have provided pathology images of ICPI-induced colitis, as shown in Figure 2.

Comments #3. A table to summarize clinical and pathological findings will further improve the paper.

Response to comments: Thank you for your helpful comment. We have added a table to summarize the endoscopic and pathological findings in Table 1.

Comments #4. The authors may consider to move the first section "Associated morbidity ..." to the end, after "Pathology".

Response to comments: As you pointed out, we have moved the first section "Associated morbidity ..." to the end, after "Pathology".

Comments #5. Some of the statements are difficult to understand and need to be re-worded or clarified, such as "Pathological findings of ICPI-induced colitis may not be associated with a different type of ICPI".

Response to comments: We have revised this statement as follows in the core tip and abstract.

The pathological findings of ICPI-induced colitis may vary among drug classes.

Comments #6. Minor grammar edits are recommended.

Response to comments: We have asked an editing company (American Journal Experts; <http://www.aje.com/jp/>) to correct the grammatical errors again. Thank you.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in the ***World Journal of Gastrointestinal Pathophysiology***.