April 6, 2021

Subrata Ghosh
Andrzej S Tarnawski
Editors-in-Chief
World Journal of Gastroenterology
Subject: Revised Manuscript (Manuscript NO.: 65391, Retrospective Study)

Dear Dr. Ghosh and Dr. Tarnawski:

Thank you for providing us with the opportunity to revise our manuscript (**Manuscript NO.: 65391, Retrospective Study**), titled "**Early serum albumin changes in patients with ulcerative colitis treated with tacrolimus will predict clinical outcome**". The reviewers' comments were very helpful for revising and improving our manuscript, as well as for offering important guidance for our research.

We have carefully addressed the concerns, comments, and questions raised by reviewers 1 and 2. We have also verified that none of the referenced papers have been retracted. The main corrections and point-by-point responses to the reviewers' comments are provided below, with all corresponding changes marked in red font in the manuscript.

We hope that our responses and revisions have adequately addressed the reviewers' concerns, and that the revised manuscript will now meet the high standards required for publication in your esteemed journal. We have uploaded the marked and unmarked copies of our manuscript, as requested. We look forward to hearing from you.

Sincerely,

Ken Sugimoto, MD PhD
The First Department of Medicine
Hamamatsu University School of Medicine
1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan
Tel: +81-53-435-2261
Fax: +81-53-434-9447
Email: sugimken@hama-med.ac.jp

Manuscript ID: Manuscript NO.: 65391, Retrospective Study

Title: Early serum albumin changes in patients with ulcerative colitis treated with tacrolimus will predict clinical outcome

Point-by-Point Response

We are very grateful to the reviewers for their comments on this study. Responses the reviewers' questions are described below. Please note that the changes made do not influence the content, conclusions, or framework of the paper. We have not listed below all minor changes made; however, these are highlighted in red font in the revised manuscript.

Reviewer #1:

This is an interesting retrospective study, analyzing serum albumin levels among a group of patients with UC on tacrolimus. Authors found that week 2/week 0 Alb ratio ≤ 1 predicts failure within 3 months of tacrolimus administration, and high failure risk exists with week 2 Alb values ≤ 1 on admission. It will be helpful for doctors in their practice. There are some questions.

1. This article did not discuss why serum albumin level or ratio is related to therapeutic effect of tacrolimus, please turn to its pharmacokinetics

Response: In the treatment of ulcerative colitis with tacrolimus, a sufficient therapeutic effect is exhibited, and mucosal healing, is induced by promptly reaching the effective range of blood concentration after the start of tacrolimus treatment. Therefore, in cases in which tacrolimus is effective, albumin is elevated because leakage of albumin from the intestinal tract is limited by mucosal healing. However, mucosal healing is not achieved in patients in whom tacrolimus is ineffective; therefore, it is thought that albumin loss from the intestinal tract persists and hypoalbuminemia does not improve. We have described these reasons in the text (Page 12, Line 281–290).

2. Albumin ratio is important, concrete concentration is also very important. A vey lower level of serum albumin, even if with a higher ratio, could not predict an effective remission.

Response: In this study, even if the serum albumin level at Week 0 was low, we could predict an effective remission if the albumin ratio was high in our study. Specifically, in the sub-group of Alb <3 (n = 25), the Week 2/Week 0 Alb ratio of the failure group was significantly higher than that of the remission group (P = 0.003). In addition, a ROC analysis of the Alb <3 sub-group showed a cut-off value of 1.235 and AUC of 0.853 with a 95% CI of 0.705 – 1.000. We considered that the AUC of Alb <3 was higher than the AUC of all cases because low serum albumin level at Week 0 could be slightly increased after treatment improved the condition of UC. We have described these points in the text (Page 14, Line 331–338).
According to the advice of the reviewers, we have added more details to the analysis.

3. Bloody stools will not contribute to a higher level of albumin, on the other hand, it will lead to a lower level due to loss of albumin from GI tract.

Response: As reviewers have noted, hypoalbuminemia is caused by the loss of albumin associated with bloody stools in ulcerative colitis. The essence of this study is that in patients that respond to tacrolimus therapy, intestinal inflammation improves and the loss of albumin from the intestinal tract due to bloody stools is prevented. As a result, albumin levels improved after two weeks. This mechanism was added to the Discussion along with the response to question 1 (Page 12, Line 284–290).

Reviewer #2:
It would be interesting to know how the valley levels are in relation to the albumin levels and whether this correlates with the clinical response.

Response: The CAI of the failure group and the non-failure group were compared. The CAI of both groups showed significant improvement from Week 0 to Week 2, but the non-failure group showed greater improvement ($P < 0.001$ and $P = 0.007$, respectively). In ulcerative colitis, the factors that influence serum albumin concentration are the loss of albumin due to diarrhea and bloody stools. The change in CAI that assessed diarrhea and bloody stools may be associated with changes in albumin in the non-failure group and failure group at the week 2.
The relationship between CAI and albumin levels was added to the Discussion (Page 12, Line 288–290).