Author’s response to reviews

Title: Infliximab for pediatric patients with ulcerative colitis: a phase 3, open-label, uncontrolled, multicenter trial in Japan

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Pierluigi Marzuillo, MD
Associate Editor
BMC Pediatrics

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Dear Dr Marzuillo,

On behalf of my co-authors, I would like to resubmit our manuscript entitled “Infliximab for pediatric
patients with ulcerative colitis: a phase 3, open-label, uncontrolled, multicenter trial in Japan” for consideration for publication in BMC Pediatrics as a Research Article. I would like to thank you and the reviewers for providing insightful comments on our paper.

We have attached our responses to the reviewers’ comments below. Please note that the page and line numbers in our responses refer to those in the resubmitted manuscript.

We have revised the manuscript according to the reviewers’ comments. We hope that these revisions suitably respond to their concerns and hope that our manuscript is now acceptable for publication in BMC Pediatrics.

We look forward to hearing from you after the re-evaluation of our manuscript.

Thank you again.

Yours sincerely,

Hitoshi Tajiri

Response to Reviewers

Reviewer’s comments:

Reviewer 1:

Comment 1.

Background:

Line 58: UC is a “rare” inflammatory disease. UC is not considered a rare disease any more. Therefore, it should be mentioned that the disease is considered rare in Japan.

Response: We thank the reviewer for this comment. According to an annual nationwide survey, the number of patients with UC is increasing in Japan. Therefore, we have deleted “rare” from the background sentence (Background section, line 58, page 4) as follows:

“Ulcerative colitis (UC) is an inflammatory disease of unknown etiology that is characterized by repeating periods of relapse and remission.”

In addition, we have revised a relevant sentence in the Statistical analyses section as follows (Methods section, line 150, page 7):

“As pediatric UC is a rare and relatively intractable disease, the number of pediatric patients with moderate-to-severe disease is small, with an assumed indication of around 1200 patients in Japan when
this study was planned, and even fewer patients expected to meet this study’s eligibility criteria.”

Comment 2.
Patients:
Line 102: “≥6 episodes/day of bloody diarrhea”. Those patients with that much of bloody diarrhea were excluded from the study, why?? This might indicate moderate-sever UC, why were they excluded? Other exclusion factors were OK.

Response: Thank you for this comment. Eligible patients in this study included those with severe UC. However, to ensure the safety of the subjects, we excluded UC patients with very severe symptoms and systemic illness, defined as follows:

Patients who had total colitis and satisfied either (1) or (2) below:

(1) Patients who were found to need a colectomy at registration.

(2) Patients who satisfied ≥4 of the following criteria (a-e):
   a) ≥6 episodes/day of bloody diarrhea
   b) intense abdominal pain or rebound tenderness
   c) persistent pyrexia of >37.5°C
   d) pulse rate >90 beats/min
   e) hemoglobin <8.5 g/dL

Comment 3.

Table 1:
Aminosalicylates used in 19 patients (90.5%) and 5-aminosalicylates used in17 patients (81.0%). What is the difference between those 2 medications? The available aminosalicylates used in UC patients are usually 5-ASA.

Response: Thank you for this question. We included both 5-aminosalicylates and sulfasalazine among aminosalicylates. For clarity, we have changed the location of “5-aminosalicylates” and “Sulfasalazine” in Table 1 (Table 1, page 9).

Comment 4.

Discussion:

Line 286: "PUCA at 30 weeks (19%), which is lower than other reports". This might indicate that IFX
is not affective over time on Japanese patients. It will be interesting to know what was the management plan for those patients. Did they continue IFX maintenance further? Did they receive higher doses or discontinue therapy?

Response: Thank you for these insightful comments and questions. Dose intensification by dose escalation or shortening of infusion intervals may be useful for maintaining the efficacy of IFX in UC patients with loss of response. Unfortunately, we cannot recommend these strategies because dose intensification of IFX is not approved in Japan. However, based on the reviewer’s comment, we have added the maintenance regimens of the non-Japanese pediatric Phase 3 study, which had a higher PUCAI remission rate, to the text as follows (Discussion section, line 288-290, page 15):

“This difference may be attributed to the increase in dosage in the non-Japanese study from 5 mg/kg to 10 mg/kg at 8-week intervals in approximately 40% of patients before Week 54 due to decreased treatment efficacy, which was defined as “either (1) an increase from the week 8 partial Mayo score of \( \geq 2 \) points at 2 consecutive visits at least 7 days apart or (2) an increase from the week 8 partial Mayo score of \( \geq 3 \) points at any visit” [10].”

Unfortunately, we did not follow-up the patients after the end of our study. Therefore, we do not know if they continued IFX 5 mg/kg therapy, received higher doses, or switched to other drugs.

Reviewer 2:

Is there any evidence that Asian patients respond differently to biological treatments for other conditions compared with Western patients that further justifies this trial?

Response: Thank you for these questions. There is no evidence that the response to biologic therapy differs between Western and Asian patients, including for other conditions. Our results were similar to those of the non-Japanese pediatric Phase 3 study.

In the Methods, as a non-paediatric gastroenterologist, I would like you to describe why you chose the CAI, PUCAI and Mayo scores as your outcome measures. What is the benefit of using all 3 classification systems as outcome measures as compared with using just 1 classification system? Given that there are non clinical measures in these classification systems, is there an opportunity to introduce bias?

Response: Thank you for this comment. The CAI and Mayo were chosen to ascertain whether the results of our study were similar to those in the Japanese adult Phase 3 study, and the PUCAI was chosen to ascertain whether the results of our study were similar to those in the non-Japanese pediatric Phase 3 study.

Although we cannot determine whether there is any possibility of introducing bias by scoring clinical measures (e.g., stool frequency, blood per rectum, abdominal pain, fever, laboratory tests), the CAI, Mayo, and PUCAI scores are common outcome measures used to evaluate the efficacy of existing drugs and compounds under development in clinical trials.
Reviewer 3:

1) In table 2, the IFX concentration on week 14, 22, and 30 of 6 to 12 years seemed to me less than those of 12 to 17 years. Did the authors evaluate it statistically?

2) I would like to know the incidence of the secondary failure of the infliximab in these patients.

Response: Thank you for these insight comments.

1) We did not statistically evaluate differences in the IFX concentration between the two age groups because the sample size of the 6 to <12 years age group was very small (n=3).

2) Among the patients who achieved CAI remission at Week 8, the percentage of patients who did not achieve CAI remission at Week 30 (overall) was 33.3% (1/3) in the 6 to <12 years age group and 46.2% (6/13) in the 12 to 17 years age group. Because of the very small sample size of the former group, we did not add the incidence of secondary failure to the manuscript.