

Dear Dr. Ke Chen,

I am attaching a revised version of our paper entitled, "Influence of *NUDT15* Variants on Hematological Pictures of Patients with Inflammatory Bowel Disease Treated with Thiopurines", which was originally submitted on October 16, 2017. The manuscript ID is 36607.

We greatly appreciate the suggestions and comments by three reviewers.

We made the changes according to the suggestions and comments as follows.

Regarding the comments made by a reviewer (00070280)

Regarding the measurement of folate and B12;

Thank you for the indication of the measurement of folate and vitamin B12. It is reported that salazosulfapyridine, one of 5ASAs, decreased the absorption of folate and, hence, increase MCV. In our study, there were 9 patients who had salazosulphapyridine, but the average MCV was not different from those 89 who did not take the drug.

Accordingly, we have revised the manuscript as follows;

Page 14, line 16 in Discussion

We didn't measure the concentrations of folate and vitamin B12, which affect MCV. Before starting thiopurines, MCV was in normal range. Previously it was reported that salazosulfapyridine, one of 5ASAs, decreased the absorption of folate, but in our study, only nine patients were taking salazosulphapyridine and the MCV was also in normal range at the initiation of 6MP.

Regarding TPMT;

Thank you for the suggestions that to add the results of the TPMT which we tested in all 96 cases. We have added the results of TPMT in Discussion as follows;

Page 15, line 10 in Discussion

We also tested three SNPs of *TPMT*, and as previously reported, no *TPMT* variant was found. So it is not necessarily performed in Asian patients. Our results support previous data that *TPMT* variant is low in Asian patients.

Regarding the comments made by a reviewer (00038617)

Regarding the WBC count with and without prednisolone;

Prednisolone induced dynamic changes of WBC counts, thus the counts varied in each case. It was very important to stratify the group into two, namely, one with and without prednisolone. WBC count in patients with prednisolone treatment was not significant at time points other than 8 and 10 weeks. When we look back the literature, there is no report on leukopenia by stratifying two groups by prednisolone treatment. We revised the sentences as follows in this regards;

Page 12, Line 11 in Results

Prednisolone induced dynamic change of WBC counts which varied in each case. Statistical difference was only obtained at 8 and 10 weeks.

Regarding severe hair loss and agranulocytosis;

Thank you for the variable suggestions. We did not encounter any patients with agranulocytosis and severe hair loss. According to the suggestions, we have revised our manuscript as follows;

Page 15, Line 16, in Discussion

Our study has several limitations. Firstly, the number of patients was too small to have definite conclusions. For example, the WBC count in patients with prednisolone treatment was not significant at time points other than 8 and 10 weeks. We have not encountered any patients with agranulocytosis and severe hair loss. If we are able to recruit more patients we may obtain definite conclusions. Secondly, our study was a retrospective in nature, and therefore clinical utility of SNP analysis is not assured to avoid complications related to use of 6MP. Thirdly, we only observed the patients for 16 weeks after initiation of thiopurine treatment, the long-term effects of thiopurines remain unclear. We are planning further studies to clarify these limitations.

Regarding adding the limitations of our study:

We have added the limitations in Discussion as was suggested by the reviewer

Page 15, Line 10

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patients with prednisolone treatment was not significant at time points other than 8 and 10 weeks. We have not encountered any patients with agranulocytosis and severe hair loss. If we are able to recruit more patients we may obtain definite conclusions. Secondly, our study was a retrospective in nature, and therefore clinical utility of SNP analysis is not assured to avoid complications related to use of 6MP. Thirdly, we only observed the patients for 16 weeks after initiation of thiopurine treatment. the long-term effects of thiopurines remain unclear. We are planning further studies to clarify these limitations.

Regarding the comments made by a reviewer (1467363)

Regarding typographical errors:

After you kindly pointed out, our manuscript has been checked by Allison Sherwin (Ph.D Biochemistry, University of Kent) and certificated by Edanz Group Japan, which was attached with PDF file.

Regarding the suggestions to add limitations of our study:

AS was indicated by a previous reviewer (00038617), we have already changed and included the limitations of our studies.

Finally, we appreciate the very constructive suggestions made by three reviewers. We trust that the revised manuscript will meet the questions and comments by the reviewers and also approval of the editor.

Sincerely yours,
Yuichiro Kojima, M.D,

Ph.D.