BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

# ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 14405
**Title:** Variations of thiopurine metabolites during co treatment with aminosalicylates in young patients with inflammatory bowel disease: effect of N-acetyl transferase polymorphisms.
**Reviewer code:** 00036648
**Science editor:** Ya-Juan Ma
**Date sent for review:** 2014-10-03 21:21
**Date reviewed:** 2014-10-14 06:40

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [Y] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] Existing | [ ] High priority for publication |
| [ ] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] No records | |
| [ ] Grade D: Fair | | BPG Search: | [ ] Rejection |
| [ ] Grade E: Poor | [ ] Grade D: Rejected | [ ] Existing | [Y] Minor revision |
| | | [ ] No records | [ ] Major revision |

## COMMENTS TO AUTHORS

This is an interesting and clinically relevant paper. Obviously the study has a small sample size and thus it is best described as a pilot study. I have the following concerns for the authors to please address: 1. For the patients enrolled in this study, what was the clinical reason for ceasing the aminosalicylate and then restarting it – if no clinical reason, then are there not ethical concerns if the aminosalicylate was part of the medication regimen for these patients and then ceased (albeit relatively briefly) with any reason but for the purposes of this study? That is, were the participants put at clinical risk by participation in this study? 2. The study is premised on the hypothesis that NAT1 is inherent to 5ASA inactivation and this appears to be based on only one paper published 25 years ago! (Allgayer et al, Gastroenterol 1989) Can the authors please further enlighten the reader on why NAT1 is thought to be integral to 5ASA inactivation? 3. There are only 12 patients in this study providing an opportunity for more data transparency by inserting another table including each of the participants, their age, their disease, their thiopurine and 5ASA dose and their before/after 6TGN and percentage change in 6TGN. This would inform the reader about what happened in each case, according to NAT1 status. 4. Was there a dose-dependent effect of either the 5ASA or the thiopurine on the change in 6TGN? This is important given that if so, hypothetically a clinician may be able to dose-reduce the 5ASA (eg from 4g to 2g daily) maintaining theoretical chemopreventive benefits,

rather than cease it in someone with adverse NAT1 status and high 6TGN levels… 5. Using the linear mixed effects model for most analyses you have presented p values, but I think you should also present the coefficient for each analysis also (with p value following in brackets). I am a little surprised that you can derive such statistically significant results with such a small sample size? 6. Minor typographic/ grammatical errors: ? Short title "aminosalycilates" should read "aminosalicylates" – same error also in Results/ Conclusions sections of Abstract and multiple times in rest of manuscript – please correct ? Last sentence of 1st paragraph in Material and Methods "parents or tutors" – do you mean "parents or guardians"? ? Last sentence of 2nd paragraph in Materials and Methods "The ratio between TGN and the dose of azathioprine was calculated considering for each individual measurement the dose the patients was taking the day the blood sample for the metabolites assessment was collected," could instead read "The ratio between TGN and the dose of azathioprine was calculated to account for the respective dose each patient was taking on the day that the metabolite testing was performed." ? Last sentence of Statistical analysis paragraph "in order to adjust the normality of the distribution," could instead read "in order to achieve normality of the distribution." ? 2nd sentence of 2nd paragraph of Results section "MMPN concentration where not affected.." should read "MMPN concentration were not affected…" ? There may be others, please check carefully!

BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

# ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 14405
**Title:** Variations of thiopurine metabolites during co treatment with aminosalicylates in young patients with inflammatory bowel disease: effect of N-acetyl transferase polymorphisms.
**Reviewer code:** 01115220
**Science editor:** Ya-Juan Ma
**Date sent for review:** 2014-10-03 21:21
**Date reviewed:** 2014-10-13 23:30

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ Y] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [ ] Grade B: Minor language polishing | [ ] Existing | [ ] High priority for publication |
| [ Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] No records | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | BPG Search: | [ ] Minor revision |
| [ ] Grade E: Poor | | [ ] Existing | [ Y] Major revision |
| | | [ ] No records | |

## COMMENTS TO AUTHORS

The authors have attempted to explore the interactions of 5ASA drugs and thiopurines including the effect of enzymes thought to be important in metabolizing 5ASA drugs. The results of this small study are of interest in that there seems to be some pharmacokinectic interaction between 5ASA drugs and thiopurines, there also seems to be a potentially important and previously unexplored effect of N-acetyl transfersase polymorphisms. The main issue regarding this study is the small size and although several statistical analysis have been applied, there is lack of clarity over the precise aim and sample size required of this study. Major points. 1. There are 12 patients but 36 samples distributed across the 2 time points. This seems a very unusual design and I very much suspect this was not how the study was designed. There really should only be 2 samples used per subject, otherwise the risk of bias increases. The results do need to be recalculated with only 2 data points per subject. 2. The methods should be explicit in terms of what was the primary intended outcome for this study and how the sample size and power we calculated from this. 3. The potential effect of NAT1 genotype on thiopurine levels is very interesting but and although data figures are provided it would be very interesting to know the absolute mean values of fall of red cell 6TGNs over the study period and absolute 6TGN levels depending on NAT genotype. 4. Given the possible mechanisms of NAT1 interacting thiopurine metabolism, the authors really seem to have only performed half a

study now. The study would be greatly enhanced by the inclusion of a separate group taking thiopurines but no exposure to 5ASA drugs within a much longer period (say 3 months) and this would help determine if NAT1 does directly influence thiopurine metabolism or whether these effects reported in the current study are predominantly influenced by red cell TGN levels at the initial point in the study and the level of decrease is determined more by red cell life span.

BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

# ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 14405
**Title:** Variations of thiopurine metabolites during co treatment with aminosalicylates in young patients with inflammatory bowel disease: effect of N-acetyl transferase polymorphisms.
**Reviewer code:** 00186128
**Science editor:** Ya-Juan Ma
**Date sent for review:** 2014-10-03 21:21
**Date reviewed:** 2014-10-16 16:09

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] Existing | [ ] High priority for publication |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] No records | [Y] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | BPG Search: | [ ] Minor revision |
| [ ] Grade E: Poor | | [ ] Existing | [ ] Major revision |
| | | [ ] No records | |

## COMMENTS TO AUTHORS

The manuscript "Variations of thiopurine metabolites during co-treatment with aminosalicylates in young patients with inflammatory bowel disease: effect of N-acetyl transferase polymorphisms" report two results: the first is the concentration of 6-TGN before and after the interruption of the aminosalicylate and the second is the correlation between NAT1 genotypes and 6TGN concentration.

Comments: The first results is not original because various studies have reported elevated 6-TGN levels caused by co-administration of 5-ASA during thiopurine therapy (Szumlanski and Weinshilboum,1995; Lewis et al., 1997; Lowry et al., 2001; Dewit et al., 2002; Xin et al., 2005; Hande et al., 2006; De Boer et al., 2007b). The underlying pharmacological mechanism remains to be verified. Furthermore, a dose dependent effect was observed for two different 5-ASA doses (2 g followed by 4 g, both daily during 4 weeks) on total levels of 6-TGN and 6-MMPR metabolites. This effect is not mentioned in this manuscript. The second result concerned a few number of patients (12) and can't be considered to evaluate the role of genetic polymorphisms on the evolution of 6-TGN concentration. The results of previous studies concerning the frequency of NAT 1 and NAT2 polymorphisms in IBD is not mentioned in this manuscript (proportion of slow and rapid acetylators in the group of patients with IBD than in the group of healthy subjects.)