

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I would like to congratulate the authors on their manuscript titled 'Biomarkers for gastrointestinal adverse events related to therapy with thiopurines'. The authors have done a commendable job consolidating evidence that currently exist on biomarkers implicated in GI toxicity. However, I do have a few comments:

1. In the manuscript, the mechanism via which different genes contribute to toxicity should be discussed in more detail. World Journal of Gastroenterology has a wide outreach within the medical community and the readers may not always be Hematology-oncology/Gastroenterology specialists. A detail description of the exact mechanism of toxicity will enhance reader experience.

We thank the reviewer for his comment, and reviewed the manuscript accordingly. We better explained that increased TGN levels due to TPMT and NUDT15 defects stand at the basis of enhanced thiopurine-induced hematological toxicity. We highlighted that PACSIN2, besides modulation of TPMT activity, could act as regulator of intestinal mucosal homeostasis and could contribute to maintain GI epithelium integrity, although we emphasized that this is still an unproven hypothesis and dedicated studies to clarify this issue are needed. For ITPA, we reported different results about the possible role of its genetic variants on thiopurine toxicity in the intestine to underline that further investigations are needed.

2. In the clinical implementation section of the manuscript, any current ongoing clinical trials should also be mentioned and referenced.

We thank the reviewer for his comment, and reviewed the manuscript accordingly. We referred to the "Clinical trial. Gov" and the "EU clinical trial register" websites (2021 April, 21th), looking for clinical trials with following criteria: 1) regarding ALL or IBD thiopurine treated patients; 2) in a currently ongoing, completed or unknown recruiting status; 3) retrieved by keywords "TPMT", "NUDT15", "PACSIN2", "RAC-1", "ITPA" and "GASTROINTESTINAL TOXICITY". While there are some studies on TPMT and NUDT15 investigating thiopurine induced hematological toxicity, no clinical trial about GI toxicity has been found. This detail has been added to the manuscript.

3. Although the molecular effects of these biomarkers are still relatively unknown, I believe that the readers would highly benefit from the authors take on the possibility of their use in clinical practice and how these agents may be used to guide therapy in the future

We thank the reviewer for his comment, and reviewed the manuscript accordingly in the clinical implementation part.

4. The manuscript would need additional language polishing before publication.

We thank the reviewer for his comment, and language polishing was conducted by a native speaker.

(1) *Science editor*: 1 Scientific quality: The manuscript describes an editorial of the biomarkers for gastrointestinal adverse events related to therapy with thiopurines. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: The authors have done a commendable job consolidating evidence that currently exist on biomarkers implicated in GI toxicity. However, the questions raised by the reviewer should be answered; and

(3) Format: There are no tables and figures.

A Figure describing the thiopurine pathways has been added to the manuscript.

(4) References: A total of 50 references are cited, including 8 references published in the last 3 years;

(5) Self-cited references: There are 6 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

In the revised manuscript, a total of 53 references, including 5 self-cited references are included, respecting the 10% self-referencing rate.

2 Language evaluation: Classification: Grade C.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG.

5 Issues raised: (1) The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend:
<https://www.wjgnet.com/bpg/gerinfo/240>;

(2) The "Author Contributions" section is missing. Please provide the author contributions; and

Author Contributions have been provided.

(3) The authors should add some figures or tables.

A Figure describing the thiopurine pathways has been added to the manuscript.

6 Recommendation: Conditional acceptance.

(3) *Company editor-in-chief*: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>. Language Quality: Grade C (A great deal of language polishing).

We thank the reviewer for his comment, and reviewed the manuscript accordingly.