

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 50351

Title: Nucleoside diphosphate-linked moiety X-type motif 15 R139C genotypes impact the 6-thioguanine nucleotide cut-off levels to predict thiopurine-induced leukopenia in Crohn's disease patients

Reviewer's code: 03254999

Reviewer's country: United States

Science editor: Jin-Zhou Tang

Reviewer accepted review: 2019-07-24 12:04

Reviewer performed review: 2019-07-24 13:26

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I think this topic is of utmost importance and relevance for the utilization of thiopurines in IBD care. We are always searching for biomarkers we can use to assist us with the



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appropriate dosing. Having two markers work hand in hand to attain a great positive and negative predictive value is very beneficial. The authors did a great job demonstrating this in their study design and methods. The methods can be slightly more clear and maybe add something about the practicality of utilizing these tests in real world practices.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 50351

Title: Nucleoside diphosphate-linked moiety X-type motif 15 R139C genotypes impact the 6-thioguanine nucleotide cut-off levels to predict thiopurine-induced leukopenia in Crohn's disease patients

Reviewer's code: 03662987

Reviewer's country: Malaysia

Science editor: Jin-Zhou Tang

Reviewer accepted review: 2019-07-26 16:24

Reviewer performed review: 2019-08-02 15:13

Review time: 6 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Reviewer ID: 03662987 Manuscript ID: 50351; World Journal of
Gastroenterology_____ In this research

manuscript, the authors explored the possibility of incorporating the levels of 6TGN and NUDT15 R139C polymorphisms to predict the occurrence of leukopenia in Crohn's disease patients. The study poses substantial novelty and the finding is helpful to delineate practical cut-off 6TGN levels of CD patients with different NUDT15 R139C polymorphisms. The manuscript title is concise to reflect the finding of the study. The research objectives are realistic and measurable. The study is soundly designed. Research data is analyzed sufficiently with appropriate statistical methods. The conclusion is suitable to summarize the study findings, with reasonable study limitations. Below are some comments for consideration to the authors: 1. In context of leukopenia in this manuscript, it should be specified as thiopurine-induced leukopenia, instead of leukopenia in general. On the other hand, NUDT15 mutation should be stated specifically as NUDT15 R139C. 2. Methods: Elaborate on the details of the methods/assays used for the determination of 6TGN/6MMPR and NUDT15 genotyping. 3. Methods: TPMT*3C genotyping is not mentioned in method and abstract. 4. Results: Only CD patients were involved in this study, therefore the patients should be referred as CD patients, instead of IBD patients. 5. Results: Diplotype of NUDT15 R139C and TPMT*3C is mentioned in results, however diplotype analysis is not stated in methods. In addition, results on diplotype analysis is not shown. 6. Gene names should be in italic. 7. Some data was not stated clearly. Example: Pg11, "...leukopenia were found in the subgroups (P=0.55, P=0.30)." - the subgroups should be specified as CC and CT respectively. 8. Pg13, "...since half of patients who developed leukopenia (37/72) carried the T allele (CT/TT)." - May consider to rephrase or remove this statement as it seems vague. It could be stated the other way round as 'half of the leukopenia patients are C allele carriers' and the statement is still true. 9. There are some inconsistencies of terms used throughout of the manuscript. Eg, deoxy-TGTP or dTGTP; deoxy-TGMP or dTGMP; VS or vs; tiopurine or thiopurine. 10. Pg16, "...(<319.2 pmol/8×10⁸ RBC) or the



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TT genotype (>411.5 pmol/ 8×10^8 RBC)." - Please check, it should be "...(<319.2 pmol/ 8×10^8 RBC) and the CC genotype (>411.5 pmol/ 8×10^8 RBC)." 11. Supplement figure 1 is not cited in the manuscript. 12. Table 2 (odds ratios and 95% CI): Odds ratios and 95% CI are not correctly included in the table? The ranges given do not seem like a valid 95% CI neither. 13. Table 3 (categories 2 and 3): "...6TGN >301.1 " - the cut-off range should be 319.2 as stated in the manuscript instead.

INITIAL REVIEW OF THE MANUSCRIPT

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