

December 24, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6523-review).

**Title:**

**Use of thiopurines in inflammatory bowel disease: safety issues**

**Authors: Anastasia Konidari, Wael El Matary**

*Name of Journal: World Journal of Gastrointestinal Pharmacology and Therapeutics*

ESPS Manuscript NO: 6523

The manuscript has been improved according to the suggestions of reviewers:

a) Format has been updated as required

b) Revision has been made according to the suggestions of the first reviewer:

1. Figure of thiopurine metabolism and table of adverse drug reactions with absolute frequencies have been added to the manuscript.
2. We would like to clarify the meaning of thiopurine therapeutic drug monitoring for the purpose of this manuscript; we refer to implementation of clinical and biochemical surveillance for enhanced drug safety in patients on thiopurine treatment (page 7).
3. Our statement about greater efficacy of azathioprine in comparison to mercaptopurine has been removed.
4. We have added the likely mechanism of immunosuppression by thiopurines in IBD - inhibition of Rac1 signalling and resultant T cell apoptosis (J Clin Invest 2003 111: 1133) in the end of the section on 'Metabolism of action of thiopurines' (page 4).
5. The section of liver adverse effects has been revisited (page 4). Association with intermediate methylated metabolites is clearly indicated in page 3.
6. The section on malignancies has been expanded (pages 5-7).
7. The section on TPMT bone marrow suppression and re-challenge with thiopurines has been revisited in pages 12-13.
8. Section on allopurinol has been rewritten as suggested (page 8).
9. Absolute safety is described in pages 4-5 and relative safety in different patient groups (including elderly patients, children and pregnant women) has been clearly identified in the centre of the manuscript with the use of relevant subheadings and paragraphs (pages 6-7).

10. The section on pharmacogenetics has been shortened and focusses mainly on TPMT which is of clinical relevance (page 13-14).

11. Section on thiopurine drug interactions with biologics has been expanded (page 11-12).

c) Revision has been made according to the suggestions of the second reviewer's

The title of this review has been modified so as to reflect focus on safety rather than efficacy. Sections about the relative safety of thiopurines in different patient groups have been clearly highlighted. We have re-arranged the order of different parts of the manuscript and changed the subheadings so as to highlight and focus on different ways of enhancing drug safety through clinical, surveillance biochemical and genetic indices. The language has been corrected.

The pharmacology and efficacy sections have been shortened and a schematic figure of thiopurine metabolism has been added; if required they could be completely omitted if both reviewers and editor are in agreement on this and if manuscript is still considered too long.

The pharmacogenetics section has been rewritten so as to avoid too much unnecessary detail, currently irrelevant to patient management. The focus is again on TPMT monitoring and recommendations are made so as to use this biomarker for enhanced drug safety; we clearly state that this biomarker cannot fully predict or explain toxicity.

Thank you for the further two suggested references which have now been included in this review (153, 157). The large number of references included reflects the exhaustive review of the literature that has been conducted for the purpose of this manuscript. According to the instructions for authors the references for reviews should exceed 100; however no upper limit is set by the editors to our knowledge. References from adult and not mainly paediatric studies for therapeutic drug monitoring purpose have been added as recommended.

d) References and typesetting were corrected as required.

Thank you again for considering our manuscript for publication in the World Journal of Gastrointestinal Pharmacology and Therapeutics.

Sincerely yours,

Dr Wael El-Matary MBBCh, MSc, MD, FRCPCH

Head, Section of Pediatric Gastroenterology

Associate Professor, Faculty of Medicine, University of Manitoba.

Scientist, the Manitoba Institute of Child Health.

AE-408, Children's Hospital, Health Sciences Centre,

840 Sherbrook St. Winnipeg, Manitoba R3A 1S1, Canada.

Tel: 204-787-1039/ Fax: 204-787-1450