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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6523

**Title:** Safety of thiopurines in patients with inflammatory bowel disease

**Reviewer code:** 01115220

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-10-23 16:47

**Date reviewed:** 2013-11-06 18:49

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

The authors have reviewed a wide area of thioprine pharmacology. This is an important and topical area but in doing so the review has rather lost its focus. Is this review about safety of thiopurines and how to minimise risk or do the authors really want to concentrate on the more research-based elements of the interesting but not yet clinically relevant pharmacogenetics? major points 1. This review would really benefit from some figures and tables to support and break up the text. In particular it would seem very desirable for a paper discussing the safety of thiopurine to include a table listing the adverse effects and also the approximate absolute frequency of these. The section on thiopurine metabolism really does need a metabolic diagram to help explain this. I am a molecular pharmacologist with an interest in thiourines and I found the explanation of metabolic pathways confusing: many readers would be aided by a biochemical map of the different pathways. 2. The authors discuss therapeutic drug monitoring a lot without really explaining what they mean by this in relation to thiopurines. Do they mean metabolite monitoring (which is far from mandatory and not widely available), although it would be prudent to discuss the role of this or do they mean safety monitoring of patients whilst on thiopurines? This needs clarification. 3. The authors make a bold statement about the greater efficacy of azathioprine compared to mercaptopurine without any original research to support this (page 3). This does not seem to be the case in clinical practice and could the authors revisit this statement. 4. The authors have failed to discuss the likely mechanism of immunosuppression by thiopurines in IBD - inhibition of Rac1 signalling and resultant T cell apoptosis (J Clin Invest 2003 111: 1133). 5. The section on liver adverse effects is poorly explained. Some of the liver effects are clearly related to methylated intermediates. 6. The authors do discuss HSTCL, which whilst important is very rare but do not mention other much more common cancers



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that can be associated with thiopurine immunosuppression (cervix etc). 7. I would entirely agree with the authors that TPMT activity does not predict late bone marrow toxicity, but what is the mechanism of this and does this preclude rechallenge with the drugs? 8. I would suggest the section on allopurinol be rewritten. The use of allopurinol boosting to avoid certain adverse effects and maximise efficacy is not universally accepted but increasing data do point to the effectiveness and safety of this approach. 9. Throughout the manuscript, there is a disappointing amount of detail. A review like this really needs to place the relative and absolute safety of the drugs in very obviously in the centre of the paper. It would be very helpful to readers if the paper gave some idea as to how common the various side effects were, not just "low" etc. 10. The section on pharmacogenetics seems rather at odds with the rest of the paper about clinical safety. Apart from TPMT none of these pathways are near to any clinical utility, again a table would help illustrate this further. 11. I would recommend adding extra sections to the manuscript about the relative safety of thiopurines in children and the elderly and also the effects and risk of adverse effects when combined with biologics. The latter is mentioned rather in passing but as this is major focus of current treatment protocols and a common issue that requires discussion in the clinic, it probably deserves more specific attention.



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**Reviewer code:** 00050109

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

Comments to author In this review on "Safety of thiopurines in patients with inflammatory bowel disease" the authors aspire to highlight the latest evidence on efficacy, safety and toxicity of thiopurines and to emphasize the significance of drug interactions, current experience on their use during pregnancy and up to date information of their pharmacogenetics. The authors do not succeed in doing so for the following reasons: The length of the manuscript is 28 pages out of which 12 pages are in manuscript and 16 pages are for references. The numbers of references are too many (117). Many of the references are on the pediatric patient. The references are not being well discussed in the manuscript. The two important latest references related to the manuscript (1. Florian B?r, Christian Sina, and Klaus Fellermann. Thiopurines in inflammatory bowel disease revisited. World J Gastroenterol. 2013 March 21; 19 (11): 1699-1706. Published online 2013 March 21. doi: 10.3748/wjg.v19.i11.1699 and 2. Chaparro M, Ordás I, Cabré E, Garcia-Sanchez V, Bastida G, Pe?alva M et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflamm Bowel Dis. 2013 Jun; 19 (7): 1404-10. doi: 10.1097/MIB.0b013e318281f28f) have not been mentioned and discussed. The authors emphasize on strategy of therapeutic drug monitoring for prevention of ADRs and efficacy assessment but the references are given for pediatrics patients. Can we extrapolate the levels in child to adults? The title is misleading because the authors not only discussed the safety but efficacy and thiopurines's pharmacology also in the paper. Each section of the manuscript is not well organized and written. The authors should more elaborately discuss the efficacy and safety of thiopurines in adult IBD patients in the appropriate section. In its current state, the level of English throughout your manuscript does not meet the desired standard. There are a number of grammatical errors and



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instances of badly words/constructed sentences. Please check the manuscript and refine the language carefully. Further I would recommend rewriting the manuscript if editor allowed.