

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 14876

**Title:** Clinical predictors of thiopurine-related adverse events in Crohn's disease

**Reviewer's code:** 00058695

**Reviewer's country:** Denmark

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-10-29 19:24

**Date reviewed:** 2014-11-14 21:57

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

This is a well-written and interesting retrospective study on chart review dealing with adverse events among patients with Crohn's disease followed in the Alberta IBD Consortium patient database. The paper reveals frequencies of a number of side effects observed in a referral centre cohort including that women older than 40 years have an increased risk for adverse events and discontinuation of thiopurines. In my opinion the paper is suitable for publication, and I only have some minor comments. 1. When mentioning refs 7 + 8 (Introduction p. 6) the authors should be aware, that these results solely indicate it is not a good idea to administer azathioprine to all newly diagnosed patients without evaluation of a need for this therapy, and that selection of patients with a potential benefit still is standard of care. 2. Is 5-aminosalicylic acid still prescribed for Crohn's disease in Calgary and Nottingham (Variables p. 9)? 3. The authors should consider modify "older women" (Abstract's conclusion), as it is questionable if a women of 41 y belongs to that group?

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 14876

**Title:** Clinical predictors of thiopurine-related adverse events in Crohn's disease

**Reviewer's code:** 00503513

**Reviewer's country:** Italy

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-10-29 19:24

**Date reviewed:** 2014-12-02 02:28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> [ Y] Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

## COMMENTS TO AUTHORS

The authors investigated the reason for thiopurine discontinuation in a retrospective cohort of 351 CD patients. The main findings are that older patients (>age 40 years), especially woman are more likely to discontinue therapy due to adverse events. The paper is well written. Minor points Fig. 1 give percentages in the old fashioned way 100% not 1.0, 67% not 0.67 Tab 1 alignment of rows Tab 2 age at thiopurine (years), you mean: age at first prescription? Are these mean values (what is indicated in the parentheses below? range? IQR?, or what?) the same for the following rows Page 7, line 2 what means ENREF? Page 11, 2nd para 2 .... occurred and in 110 patients Page 13, last two lines: This is novel finding

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 14876

**Title:** Clinical predictors of thiopurine-related adverse events in Crohn's disease

**Reviewer's code:** 02979036

**Reviewer's country:** United States

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-10-29 19:24

**Date reviewed:** 2014-11-25 00:21

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	[Y] No	<input type="checkbox"/> Minor revision
		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

## COMMENTS TO AUTHORS

1. Unfortunately, for me this paper does not add significantly to the existing literature on this topic.  
2. Significant factors leading to potential adverse events among patients on thiopurine therapy are not addressed or included in the multivariate (things that we see in clinical practice)--fatigue, lymphoma, skin cancers, etc. 3. Does metabolite levels 6TG and 6MMP affect rate of discontinuation? We have ways of shifting these metabolites (ie, split dosing, add allonpurinol). 4. Does initial thiopurine methyltransferase enzyme activity level predict discontinuation?

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 14876

**Title:** Clinical predictors of thiopurine-related adverse events in Crohn's disease

**Reviewer's code:** 00037018

**Reviewer's country:** Italy

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-10-29 19:24

**Date reviewed:** 2014-11-27 15:11

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

## COMMENTS TO AUTHORS

This is an interesting and well written report on clinical determinants for thiopurine safety in Crohn's disease. Results indicate that older patients, particularly women with age more than 40 are at increased risk of adverse events. In the introduction the authors write that age has no effect on TPMT activity: this is not perfectly accurate since in newborns TPMT is very high and it is high in children than adults (Serpe et al.). The authors should give more details on the effect of age on TPMT activity in the introduction and discussion. In the introduction the mention also that 5Asa has no effect on TPMT activity: this also may need more details since several reports have shown that 5asa increases TGN concentration during co-administration with thiopurines, with clinically relevant effects (more efficacy, perhaps toxicity) that should be mentioned in the paper. Was age different between female and male patients in this study?