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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43438

Title: Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients

Reviewer's code: 03017551

Reviewer's country: Poland

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-12

Date reviewed: 2018-12-21

Review time: 6 Hours, 9 Days

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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced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

SPECIFIC COMMENTS TO AUTHORS

Summary- First - current research topics, Second - interesting research results, Third - continuous search for new IBD markers.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43438

Title: Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients

Reviewer's code: 02822066

Reviewer's country: France

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-12

Date reviewed: 2018-12-24

Review time: 12 Hours, 12 Days

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[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High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

SPECIFIC COMMENTS TO AUTHORS

The manuscript number NO: 43438 « Consecutive Fecal Calprotectin Measurements for Predicting Relapse in Pediatric Crohn's Disease Patients» presents the results of a protective cohort study which aims at evaluating the accuracy of serial measurement of

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fecal calprotectin to predict clinical flares in pediatric population with Crohn's disease in remission on maintenance with anti-TNF therapy. They suggest a FC level > 250 µg/g to be a good predictor of clinical relapse in the subsequent 3 months Major comments This is an important topic as development of markers predictive of relapse in IBD in clinical remission would have important implications for clinical practice. Indeed, studies in adult population have shown that level of calprotectin may help to identify patients with higher risk of relapse in IBD in clinical remission, although reported cut-off varied greatly, ranging from 130 µg/g to 340 µg/g. In pediatric population, data are scarce and mostly obtained through retrospective studies. A cohort prospective study with prolonged follow-up is thus of importance to address this question. Population: - Patients were in remission at enrolment: what was the duration of disease ? was this remission recently obtained or considered as maintained ? What is the duration between each visit ? A clear flow chart should be presented as figure 1 - The primary endpoint was "symptomatic disease relapse defined as a PCDAI score of ≥ 10 with a change of at least 10 points from the prior visit". Does it means that it lead to a systematical change in medical care i.e., addition or switch for new drug or dose escalation? Statistics: - Statistical analyses performed to identify and validate the cut-off values should be clarified. This point is of major importance as the value of 250 µg/g as a threshold appears debatable Results - A population of healthy children has been added to this study. Results are surprising as 8/25 (32%) had FC levels > 50 µg/g which is considered to be over the normal range. The authors suggested that normal FC reference range in pediatrics may be higher than in adults. Such an increase of FC levels have been previously reported in infants and young children below 4-years-old (Fagerberg et al., 2003; Davidson and Lock, 2017…) but no significant difference was observed between the age groups 4-17.9 years and 18 years plus. The use of unique threshold is this cohort population is thus questionable - The authors have developed a

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correlation study between results obtained in their lab, a comparison lab and the Buhlmann Diagnostic samples. Does it mean that the method was not previously validated? Do they use an EEQ for FC assay? These data, together with results of EEQ, are not helpfull for this article but may be given as supplementary data - Baseline FC levels are surprisingly high in patients with clinical remission even in the non-relapsing group - The median FC level prior to relapse was similar to the median FC levels at baseline. It is surprising that no increase in FC levels was observed in-between, from baseline to time of relapse. - To illustrate, the threshold, results of sensitivity, specificity, PPV and NPV should be given. In this study, patient who did not relapse (53-18, i.e. 35 (66%) had a median FC levels of 244 μg/g. Moreover, 25 (64% ? 25/53) patients with FC levels > 250 μg/g did not have a clinical flare, and even 4 of them had their therapy de-escalated. Lastly, in the 14 patients with clinical flare and raised FC, 8 (57%) has no medication change. These results challenge the value of the level of 250 μg/g as threshold. Figure 6 and 7 should be given as supplementary data - This study allowed a follow-up for 1.5 years which is very interesting. The authors suggest a cut-off level of 500 μg/g for predicting relapse over 3 months from baseline. The statistical analyze use to define this cut-off should be clarified Discussion - How can the serial FC levels predict clinical disease relapse as 25 patients from the cohort (of 53 patients) did not relapse although they have a FC levels > 250 μg/g Minor comments Legends of the figure should be clarified to allow the complete understanding

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43438

Title: Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients

Reviewer's code: 02719834

Reviewer's country: Portugal

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-25

Date reviewed: 2018-12-28

Review time: 10 Hours, 3 Days

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

SPECIFIC COMMENTS TO AUTHORS

In this study, authors aimed to assess the utility of serial fecal calprotectin measurements to detect intestinal inflammatory activity and predict disease relapse in a cohort of pediatric Crohn's disease patients. They have done this by measuting fecal calprotectin

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levels at baseline and at subsequent 2-5 visits, and also by assessing clinical and biochemical disease activity using the Pediatric Crohn's Disease Activity Index, C-reactive protein and erythrocyte sedimentation rate at baseline and at visits over the following 18 months. Authors came to the conclusion that fecal calprotectin levels >250 μg/g are a good predictor of relapse in the following 3 months. I see value in publishing these results as they will add a piece to the puzzle of the early diagnose of Crohn´s exacerbation. The study is well written (good use of English language) and uses a robust methodological approach, hence I advise publication after a couple of changes/suggestions and clarifications. Please provide reference numbers for the ethics permission by the University of British Columbia Clinical Research Ethics Board and the British Columbia Children's and Women's Research Review Committee and state it in the "study design and methodology" section I find hard to understand why have authors calculated a sample size if they performed a prospective study, with a "pragmatic" approach using their database for the past 4 years. Did authors sample until reaching the 58-66 patients? Or did authors sample all cases (within their inclusion criteria) between june 2013 and may 2015? Please clarify

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43438

Title: Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients

Reviewer's code: 03699937

Reviewer's country: Iran

Science editor: Jia-Ping Yan

Date sent for review: 2018-12-25

Date reviewed: 2018-12-29

Review time: 4 Days

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

SPECIFIC COMMENTS TO AUTHORS

nice job

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