7/28/15

Lian-Sheng Ma, Editor-in-Chief

World Journal of Gastroenterology

8226 Regency Drive

Pleasanton, CA 94588

Dear Editor Ma,

We are pleased to submit our revised manuscript to the *World Journal of Gastroenterology* as a Topic Highlight.

The manuscript focuses on the use of biomarkers in the monitoring of disease activity in clinically silent Crohn's disease and ulcerative colitis. As there are many biomarkers available but too many to discuss within one review, we chose to focus mainly on the two most clinically utilized biomarkers - C-reactive protein and fecal calprotectin.

We appreciate the reviewers' comments. We have carefully considered each one and addressed their comments on the following page. Within the revised manuscript, the highlighted text was added based on reviewers' comments.

Several other changes were made as requested by the editor:

- Conflict of interest statement added
- Audio tip recorded and uploaded in MP3 format.
- Table 1 was divided into Tables 1a and 1b

Thank you for this wonderful opportunity.

Sincerely,

Drs. David Hudesman, Shannon Chang, and Lisa Malter

Reviewer 1:

"Congratulations on this very well written and topical review article. Much appreciated."

[Response: No changes requested.]

Reviewer 2:

"The authors have reviewed biomarkers in IBD, focusing on CRP and fecal calprotectin. The literature search is exhaustive. However the review could be made more useful for readers if the authors could give a table of all biomarkers including the proteomics and like CRP and fecal calprotectin also discuss fecal lactoferrin. They could summarise or give their comments about each biomarker in the context of ulcerative colitis and Crohn's disease separately (they have done this to quite an extent though)."

[Response: As noted by Reviewer #2, the paper would benefit from noting other previously studied biomarkers used for disease monitoring. To this end, we added to the introduction of the manuscript a list of the other biomarkers that have been studied by categories.

We chose to focus our review on the two most clinically used biomarkers: CRP and fecal calprotectin. Levels of fecal calprotectin and fecal lactoferrin almost consistently correlate in clinical studies. Fecal calprotectin tends to be somewhat superior in terms of sensitivity and specificity. We added mention of lactoferrin within the calprotectin portion of the manuscript ("Introduction" and "FC correlation with endoscopy").

We tried to further drive home fine points regarding both biomarkers in the context of UC and Crohn's disease separately. We paid particular attention to ileal disease in Crohn's and postoperative recurrence in Crohn's disease.]

Reviewer 3:

"A useful and well written review with many useful tables. A more detailed consideration of the studies exploring the use of faecal calprotectin and CRP in predicting clinical relapse is warranted particularly as this is one the main stated aims

of the review and the studies are relatively small in number and differing cut-offs are suggested. Likewise for postoperative recurrence. Perhaps useful points can be drawn out from this more detailed analysis. For instance perhaps lower cut-offs are useful for isolated ileal disease or in younger patients as FC levels do rise with age in normal subjects. There are some suggestions that CRP may be a better marker than FC for isolated small bowel disease. It may also be that nothing further can be drawn out by a more detailed consideration of these studies, but a least a consideration as to why they differ should be given in particular the widely differing cut-off points in table 4."

[More analysis was added to the manuscript considering reasons for the widely varying cutoffs published for FC and CRP. In the calprotectin "introduction," we added data on variation of FC with age. In the calprotectin "correlation with endoscopy section," we expanded the discussion on isolated ileal disease. In the calprotectin "postoperative recurrence section," we added more comparison of FC versus CRP performance. We considerably expanded the discussion regarding reasons for differing cutoffs in predicting relapse as well as in postoperative recurrence. Specifically, we considered the type of assay used, heterogeneity in study design, age, and distribution of disease.]