1/8/2017

Dear Dr. Qi:

We thank the reviewers for their comments. We have replied to each reviewers comments in a point by point way, and we hope the manuscript now meets criteria for acceptance in the World Journal of Gastroenterology.

Reviewer 1:

The manuscript is well written and there are not need to major revisions. Only a some clarifications to add on the text:

1. in the background of the study, the Authors reported that PUCAI is not reliable in clinical practice or in clinical trials.

The authors feel that the PUCAI is in general, an excellent measure of disease activity, and we widely utilize it in our clinical practice. It is well validated, and high PUCAIs correlate well with the need to escalate therapy or hospitalize patients. However, regulators from the EMA and FDA have published an opinion paper that suggests the PUCAI may not be sensitive or accurate enough for use in clinical trials. This paper suggests that additional studies of UC disease activity, including patient reported outcomes and endoscopic activity indices need to be performed.

The EMA/FDA paper is here: Steps toward harmonization for clinical development of medicines in pediatric ulcerative colitis-a global scientific discussion, part 1: efficacy endpoints and disease outcome assessments. Sun H, Vesely R, Taminiau J, Szitanyi P, Papadopoulos EJ, Isaac M, Klein A, Uzu S, Griebel D, Mulberg AE; International Inflammatory Bowel Disease Working Group. J Pediatr Gastroenterol Nutr. 2014 Jun;58(6):679-83.

2. in the conclusions, the sigma's Mayo score is more reliable than rectum to correlate to PUCAI, can the authors to explain why ?

While this was a finding in our data, we doubt it is very significant, and we have modified the discussion to de-emphasize that point. We probably need much more data from photos or central reading to make that a significant claim.

Reviewer 2 points out the l major limitation of the manuscript, that PUCAI and Mayo scores were not done simultaneously. We discuss this limitation extensively, but do not feel it affects the conclusions in the manuscript. Specifically, if a colonoscopy is done, a patient's disease status doesn't change over a few days, and a PUCAI is done on a followup visit around a month later or sooner, we propose that the PUCAI and Mayo should still reflect the same clinical status even if done at different times.

1. Evaluation of the endoscopic Mayo score was done by the review of photographs obtained in a preview colonoscopy. This is very limitative because the most severe colon/rectum area affect may have not be recorded, some images may not have the best quality for assessment.

Response: Since ulcerative colitis is a diffuse continuous disease, there is usually little variability between photographs. Photographs were obtained utilizing a high quality Provation capture system and loaded in the medical record at the time of the patient's procedure. While this approach of looking at photos is probably inferior to central reading and video colonoscopy, we do feel that evaluating photographs is a reasonable approach of assessing Mayo score. In fact Mayo score training is often done on still photographs.

2. In some cases the PUCAI score was calculated based on data abstracted from the chart. This was done retrospectively, based on the chart data and accurate data can not be guarantied.

Response: Documentation and our charts is generally accurate to calculate a PUCAI retrospectively. Other studies that have been done have also calculated PUCAI scores retrospectively and our published in the literature.

3. Endoscopic and clinical assessments were not always performed on the same day. Median time was 14 days. So how can the authors assure that this data area accurate for comparison?

Response: As stated extensively in the discussion, this is the major limitation of the study. However, the patient's that came in for elective colonoscopies had clinically stable disease, and medications were not changed between the time the endoscopy was done and the time the PUCAI was scored. For example, a patient with stable ulcerative colitis might come in for a screening examination to rule out dysplasia or for minor symptoms, and his Mayo score would be 0. In this situation, we feel a PUCAI performed within a month after the colonoscopy would accurately reflect the disease, as long as there is no clinically significant.

4. PUCAI scores were obtained before colonoscopy in 30% of patients, and after colonoscopy in 70% of patients. How can the authors explain this? Clinical activity is a very good indication for colonoscopy and normally obtain before the procedure. In this study the main indication for colonoscopy was disease activity so should not the PUCAI score have been calculated and recorded before?

Response: In some patients, a clinic visit resulted in a clinician ordering a colonoscopy, and the colonoscopy be performed to see if a change in therapy was indicated. For other patients, particularly college students, the decision to perform colonoscopy would be decided after a phone call. In those situations, a colonoscopy would be scheduled electively, and the clinic visit would occur after the colonoscopy to discuss the results with the patient.