Dr Xue-Jiao Wang
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7th July, 2018

Dear Dr. Wang,

Re: Response to reviewers

We thank the reviewers for their comments. Please find attached our response to the reviewer's comments and suggestions.

Reviewer 1:

- I strongly discourage using terminologies like villous atrophy or Oberhuber's subdivision of Marsh III to 3a, 3b and 3c. Villous atrophy is an incorrect and out of date terminology as atrophic organs do not regenerate. I suggest using the term like villous flattening or villous blunting instead.
    - *Thank you for this suggestion. We have amended the text.*

- Recent international consensus study has demonstrated no differences between Marsh III a, b and c, indicating that the subdivision of Marsh III has no practical value. I suggest analyzing the data based on Marsh III only and avoid the confusion. Alternatively the authors may compare the Marsh III to 3a, b and c as well and see if there is any difference between them. Please see: Rostami K, Marsh Mn, Johnson MW, et al. ROC-king onwards: intraepithelial lymphocyte counts, distribution & role in coeliac disease mucosal interpretation. GUT 2017 and Marsh Mn, Johnson MW, rostami K. Mucosal histopathology in

celiac disease: a rebuttal of Oberhuber's sub-division of Marsh iii. Gastroenterol Hepatol Bed Bench 2015;8:99–109.

- *Thank you for your feedback. We agree that the division of Marsh IIIa, IIIb and IIIc is not relevant in clinical practice, and does not assist in prognostication. However these sub-divisions have allowed us to better characterize and assess the degree of villous blunting as a continuum. Assessing villous blunting as a spectrum has allowed us to better determine the association with symptoms and serology.*

Results section:

- Table one need revision and correction of misspellings.
  - *Thank you. These have been corrected.*

- Over half of the patients (n=51, 52%) were asymptomatic at presentation. Please explain how the asymptomatic cases presented themselves for investigation for CD?
  - *Thank you. We did not make this clear in the text. Asymptomatic patients were often referred by their General Practitioner with positive serology for further investigation. CD serology was sometimes tested for reasons such as a patient with a strong family history if CD or incidental abnormalities on blood tests such as iron deficiency. We have clarified this in the manuscript.*
  - *"Over half of the patients (n=51, 52%) were asymptomatic at presentation, some of whom for example had been referred by their General Practitioner after having positive CD serology as part of a work-up to investigate iron deficiency."*
- It is unclear which 9 (9%) patients had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis? That would bring the total number of patients to 99.
  - *Thank you. We have clarified this in the results section.*

- *"Of the 9 patients who had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis, 2 (22%) patients had presented with fatigue, 4 (44%) patients had been detected on screening by a General Practiotioner, 2 (22%) had been investigated for iron deficiency and 1 (11%) patient had been investigated for dyspepsia."*

- Since atypical presentation are dominant, please clarify and discuss the clinical presentation of this group using Microscopic enteritis; Rostami K, aldulaimi D, Holmes g, et al. Microscopic enteritis: Bucharest consensus. World J Gastroenterol 2015;21:2593–604
  - *Thank you for these comments. We now included this paper in our discussion.*
  - *"Microscopic enteritis is a histopathological inflammatory condition (Marsh 0-II) which clinically may present as malabsorption or more subtle micronutrient deficiencies but with a relatively intact villous structure. 9 (9%) patients in this cohort could be classified at initial biopsy with microscopic enteritis secondary to CD. Microscopic enteritis is an important, novel diagnostic category of patients whom were previously diagnosed with a functional enteropathy."*

- Please mention how many patients in the whole group had negative serology at diagnosing? This is not clearly reported in results section.
  - *Thank you. We have added this to the results section.*
  - *"88 (89%) patients had positive CD serology at the time of diagnosis."*

- Bearing in mind negative serology is very rare and mostly don't have CD: Aziz I, Sanders D et al. Gut. 2017 Sep;66(9):1563-1572. The authors discus the literature on follow up biopsy in their discussion. It would be great if they come up with their own suggestion. For instance Does this study suggest that a routine biopsy follow up is lacking a clear prognostic value? (taking in consideration the limitation of the short follow up)

- *Thank you for this comment. We have added your suggestion to the text*
- *"Early repeat duodenal biopsy may have limited diagnostic and prognostic value due to delayed mucosal healing. Repeat biopsy after at least 1 year may provide more valuable results rather than an earlier biopsy as was done in this cohort."*

- Discussion can be shorter and more focused. A good part of discussion is introduction like information and not focused on this study
  - *Amended with thanks.*

Reviewer 2

SPECIFIC COMMENTS TO AUTHORS

The original findings of this manuscript are to include Australian patients with villous atrophy of different degrees and to make comparisons with the symptoms and the response to a GFD 2/ The quality and importance of the manuscript is great. There are no new or unknown findings, but the conclusions summarize clearly the data provided by the authors. 3/ I don´t find any limitations on this study

Reviewer 3

SPECIFIC COMMENTS TO AUTHORS

This is an interesting, well written manuscript which is worth of publication in the Journal.

Yours Sincerely,

Dr Oliver Cronin