Author’s response to reviews

Title: Possible etiology of improvements in both quality of life and overlapping gastroesophageal reflux disease by proton pump inhibitor treatment in a prospective randomized controlled trial

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Author’s response to reviews: see over
Re: Manuscript: WG: 2144527681102780

Possible etiology of improvements in both quality of life and overlapping gastroesophageal reflux disease by proton pump inhibitor treatment in a prospective randomized controlled trial

Dear Dr Foote

On behalf of my fellow authors, I would like to re-submit the amended manuscript, Possible etiology of improvements in both quality of life and overlapping gastroesophageal reflux disease by proton pump inhibitor treatment in a prospective randomized controlled trial, to BMC Gastroenterology for further consideration.

We would like to thank the reviewers for their helpful comments. All amends have been made in the manuscript in track changes and our specific responses to the reviewers’ comments are outlined below.

Reviewer 1 comments:

Major compulsory revisions:

1. A section in methods should be created for data and statistical analysis. Descriptions of analysis and statistics mentioned in the assessment of GI symptoms and HRQOL are to be moved into this section. Please clarify whether the ReQuest™ scores in the results were reported in mean or median (mean mentioned in Figure 2).

A separate statistical analysis section has been created as requested by the review and the text relating to the statistical assessment of HRQoL and symptoms as assessed by ReQuest™ has been moved into this section.

2. Results; are there any differences in symptoms and HRQoL improvement between different grades of esophagitis?

We fully appreciate this clearly interesting question. However, because of the need to focus the evaluation of the clinical trial, this aspect was not included in the statistical analysis.
3. Discussion; the authors proposed the sustained improvement of functional symptoms with PPI over time could be immune-mediated but evidence were lacking and remain largely speculative. Likewise, current data on genetic polymorphisms being useful in such circumstances is also speculative and should be toned down in the conclusion in the abstract. The improvement seen is likely to be multifactorial.

We have reworded the final sentence in the abstract to tone down the forward-looking conclusion (page 4). “Since the improvement observed is likely to be multifactorial, the possibility for an immune-mediated etiology and identification of putative susceptibility factors by genome-wide association study may provide focus for future research.” We have also made a similar change in the conclusion.

4. Discussion; limitations of study were not mentioned. One would be a small number of patients in subgroups of FD and IBS. This study did not address patients with the more prevalent endoscopy-negative GERD, who are more resistant to PPI. Lack of a control group with purely functional symptoms.

We have now included an additional paragraph in the discussion (page 19), in which we present the limitations of the study that have been raised by the reviewer.

**Minor essential revisions**

1. Page 6, Methods, study design and patients, line 3 – need to rephrase the sentence “In brief, this randomized, multicenter…” and clarify treatment intensity comparison and diagnosis of GERD which was based on the presence of erosive esophagitis (LA classification) and symptoms.

This sentence and the ones following have been reworded to clarify the comparison between the two different treatment concepts and how each was assessed in terms of healing of erosive esophagitis and symptom resolution (page 7).

2. Page 6, Methods, study design and patients, line 7 – is it treatment “endpoints” or “concepts”?

We would like to explain that ‘classical healing’ and ‘complete remission’, as used in the context of the current manuscript, provide longitudinal treatment efforts rather
than short-term treatment endpoints. Therefore, we have chosen to use the term ‘treatment concepts’ instead of ‘treatment endpoints’ throughout the manuscript.

3. Page 7, Methods, study design and patients, line 18 – functional missing from “dyspepsia”, FD was used in quoted reference 16. Also maintain consistency of use for the term FD throughout the manuscript.

We have changed all wording throughout the manuscript to FD for consistency, as per the reviewer’s request.

4. Page 9, Results, therapy-associated change in GI symptoms, para 2, last sentence – there is no need to mention “highly” and it is appropriate to report p value for each comparison.

We have deleted the word “highly” as requested by the reviewer and have indicated that the p values are for all comparisons (page 11).

5. Page 12, Discussion, para 1, line 10 – remove “e” from the sentence.

This has been done according to reviewer’s request (page 13).

Reviewer 2 comments:

Major compulsory revisions:

1. Introduction. Please, cite more recent manuscript describing the frequent overlap between reflux disease and FD or IBS (Gut. 2012 Apr;61(4):501-6; Gut. 2009 Sep;58(9):1185-91). Indeed, since the main aim of the investigation is to study the effect of PPI on reflux symptoms and esophageal lesions, and then the effect of PPI on functional symptoms and quality of life, the Authors should “start” from GERD and then moving to FD or IBS and not the contrary.

The two references requested by the reviewer have been added into the introduction (page 5, paragraph 2) and listed in the reference list. The introduction has been reorganised so that the information about GERD is reported before the information
about FD and IBS, as suggested by the review. As a result of these two changes the order of the references throughout the manuscript has changed.

2. Introduction. It is well known that the large majority of patients with reflux disease are affected by Non-Erosive Reflux Disease (Nat Rev Gastroenterol Hepatol. 2013 Jun;10(6):371-80) and only a minority may present with erosive esophagitis. Thus, the sentence “…a patient population that closely resembles the general population,….” appears really misleading and this concept should be deleted from the introduction and from the discussion sections.

We very much appreciate the thorough medical insight kindly offered by the reviewer. In order to more succinctly describe this rather common scenario of patients that GI clinicians often encounter and to clarify the patient group within this study, we have taken the following actions. (1) We have included a section within the discussion making the limitations of our study more transparent. Here we have indicated that endoscopy-negative GERD patients have not been studied. (2) We have indicated more closely the focus of the current study by using the term ‘endoscopically-confirmed GERD’ throughout when referring to the study population, rather than citing the much broader term ‘GERD’. Thereby, in the sentence referred to by the reviewer, we have indicated that this study is more representative of a real-world endoscopically-confirmed GERD population.

3. Introduction. Third paragraph (from cumulative to IBD) is really difficult to understand. Please, try to simplify these concepts.

In accordance with the reviewer’s request, portions of this paragraph have been reworded and sentence structure altered to simplify the concepts communicated.

4. Results. Do you have endoscopic data on erosive esophagitis relapse after PPI suspension. No data are present in medical literature assessing this topic and this data would be very interesting for the readers.

We agree with the reviewer that these data would indeed be of interest to the readership of the journal. However, given the focus of this elaborate clinical trial, these data were not evaluated in the statistical analysis.
5. Discussion. It should be shortened and simplified.

We feel that the information within the discussion is important in order to attempt to explain why erosive esophagitis appears to be a ‘silent’ disease in many cases, and why symptoms suggestive of FD and IBS respond somewhat after healing of erosive esophagitis. As such, we have attempted to discuss the findings of this study by utilising information from different scientific fields in order to provide context and offer some possible avenues of future research. This is a complex topic. In order to simplify the communication of these concepts to the reader we have altered some of the language, grammar and sentence structure in this section.

Editorial Request:

Please state the full name of the ethics committees that approved this study in your revised manuscript.

This has been added to the manuscript (page 8).

Please also ensure that your revised manuscript conforms to the journal style.

We have done this according to the format in the mentioned documents.

We believe that these helpful comments by the reviewers have resulted in an improved manuscript and we look forward to hearing your response regarding its suitability for publication.

Sincerely

Hubert Mönnikes