Reviewer’s report

Title: Symptom profile in partial responders to a proton pump inhibitor compared with treatment-naive patients with gastroesophageal reflux disease: a post hoc analysis of two study populations

Version: 1 Date: 10 June 2014

Reviewer: Walter W Chan

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Vakil et al. aimed to study the symptom profile of GERD patients who are partial responders to PPI, compared to those who are PPI treatment-naïve, utilizing a validated patient symptom questionnaire. The data were generated from post-hoc analyses of 2 independent clinical trials (PRO Validation Study and Diamond Study). The authors found that partial PPI responders have higher symptom scores in the reflux, abdominal pain, and constipation domains than PPI treatment-naïve patients. In addition, reflux, indigestion, and abdominal pain scores were highest in both groups, compared to other symptom domains. In the treatment naïve group, the authors found that post-PPI scores were significantly lower compared to pre-PPI results. The use of a standardized, validated outcome measurement and the prospective recruitment of patients with established inclusion/exclusion criteria were particular strengths of this study. However, there are several weaknesses with the study design and analyses that would affect interpretation and applicability of the results, including comparing 2 patient cohorts with different inclusion criteria, varying definition of GERD, and the selection of comparison groups, as outlined below.

Major Compulsory Revision:

1. The authors stated that the duration of symptoms were different between the 2 groups, with the partial responders having a higher mean symptom duration compared to treatment-naïve patients. However, the inclusion criteria of the 2 studies were different with regards to length of symptoms prior to study entry, with the PRO Validation study requiring patients to be symptomatic for at least 6 months and the Diamond study requiring only 4 weeks. This may explain the difference in mean symptom duration between the 2 groups. Although the means for both groups are higher than 6 months, such bias in patient enrollment may still account for the difference in mean symptom duration observed, especially if the distribution within each group is non-normal. What are the medians for symptom duration between the 2 groups? Are both medians still significantly higher than 6 months and different from each other statistically?

2. As indicated by the authors, the definition of the 2 patient populations represents a significant limitation and cannot be understated. The partial responder group included all patients with reflux symptoms who did not achieve complete relief with PPI, regardless of endoscopic or reflux testing findings. Therefore, this group likely represents a mixture of patients ranging from those


with severe reflux requiring higher doses of PPI or surgical therapy, non-acidic/weakly acidic reflux, visceral hypersensitivity, or functional heartburn/dyspepsia. On the other hand, the treatment naïve group included only patients with either esophagitis on endoscopy or a positive pH monitoring (increased acid exposure OR positive symptom-association). Patients with functional causes for their symptoms were likely excluded from this study as a result. Therefore, a selection bias was likely introduced, affecting the analysis. While it is true that both clinical diagnoses and objective data are used in clinical practice for GERD as stated by the authors, the fact that the 2 comparison groups employed distinct methods for diagnosis remains problematic.

3. What were the treatment responses of the subjects in the treatment naïve group after 2 weeks of PPI? In other words, what proportion of them achieved complete vs partial vs no response? If the treatment naïve group also included patients who partially responded to PPI, the results may have been biased (but likely towards the null). A more robust analysis may involve comparing the subgroup of partial responders to the subgroup of complete responders or the whole population within the Diamond study.

4. In the conclusion, the authors stated that “while visceral sensitivity in the esophagus remains a possible explanation for persistent symptoms while receiving PPI therapy, the absence of meaningful differences in Indigestion or Diarrhea domain scores between PPI partial responders and treatment-naïve patients suggests that a generalized disorder of gastrointestinal visceral hypersensitivity is unlikely.” This statement may be problematic because, as stated in comment #3 above, the lack of significant difference in indigestion and diarrhea observed may have resulted from a selection bias due to the treatment naïve group potentially including patients who were later partial responders.

5. In the introduction, the authors stated that “a better understanding of symptom patterns in partial PPI responders with GERD is needed to understand the genesis of symptoms and to improve medical management in this patient group.” How did the results and conclusions from this study contribute to these goals? It is not completely clear that comparing the symptoms of a group of clinically diagnosed GERD patients on PPI with partial response to those from a group of objectively-defined GERD patients pre-PPI therapy would yield much relevant information regarding the pathophysiology or clinical management of partial PPI responders. A more detailed discussion of why the comparison group (treatment naïve group) was selected and the clinical or pathophysiological implications of the results observed would be helpful.

6. In the Discussion, there was a paragraph regarding the prior evidence of reflux inhibitors’ effects on symptoms: “Treatment with reflux inhibitors has been explored as a possible alternative to PPI therapy when remaining symptoms are clearly reflux related [19, 20]. Studies of drugs designed to decrease transient lower esophageal sphincter relaxations have, however, shown disappointing results so far [21-23]. A few insights have emerged from these trials, such as that mild reflux symptoms in patients on PPI therapy do not appear to respond well to reflux inhibitors [23], whereas moderate or severe symptoms might be more responsive [22, 23].” What is the purpose of this paragraph, especially in the
context of the results of this study? The relevance of this paragraph to the current study should be better explained and expanded, or it should be removed.

7. As stated in the Discussion, the interpretation of the data should be taken with caution, since the GSRS and the clinically significant difference established were mainly validated and used for within group comparison, rather than inter-group differences. Therefore, the true clinical significance and implication of the small differences in domain scores observed between the two patient groups in this study are not clear. The authors should be careful to state their results and conclusions in this context.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.