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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5064-review.doc).

Title: Long-term Pretreatment with Proton Pump Inhibitor and Helicobacter pylori Eradication Rate

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We provide a point-by-point response to all reviewers as outlined below. We have modified the manuscript, where appropriate, and have highlighted the changes. The manuscript has been improved according to the suggestions of reviewers:

Reviewer #1.

1) The reviewer considers that rapid urease test and histologic examination should not be used for the assessment of H. pylori eradication. ¹³C-urease breath test is the most adequate.

We agree with your point.

Guidelines recommends [1, 3] that ¹³C-urease breath test should be used for confirmation of eradication except in cases where repeat endoscopy is indicated, for example in patients of gastric ulcer. Also in our study, urease test and histologic

examination were performed only in limited cases which needed repeat endoscopy (14.4%, 157/1090). Previous study reported that rapid urease testing and Warthin-Starry stain as well as ¹³C-urease breath test showed above 90% of sensitivity and specificities in predicting *H. pylori* status after antibiotic treatment [36].

We revised the section of Assessment of *H. pylori* status in METHODS and discussed this point in the DISCUSSION (page 6), accordingly.

2) Generally, patients with gastric neoplasm have lower gastric acid secretory function, compared with peptic ulcers, in particular, duodenal ulcers. This possibly affects the similarity of eradication rates between the study groups.

We agree with your point. We added this point in the DISCUSSION (page 5). Furthermore, we newly commented this finding in RESULTS (page 5) and Study design in METHODS (page 4) to clarify the adjustment for potential associating factors, as follows:

There has been no study directly comparing the eradication rates between in gastric cancer and ulcer patients. We assumed that diagnostic factor might affect the eradication rate, so we included this in the various adjustment factors. PPI-pretreatment did not affect eradication rate even after adjustment for various factors including diagnosis. Actually, eradication rates were similar in iatrogenic ulcer (79.0%, 109/138) and peptic ulcer (79.8%, 665/833) patient. In addition, the eradication rates were also not different between Group A (non-pretreatment) and B (PPI-pretreatment) in any diagnostic subgroups; 87.1% (27/31) vs. 76.6% (82/107) in iatrogenic ulcer, 77.6% (340/438) vs. 82.3% (325/395) in peptic ulcer, and 83.7% (87/104) vs. 86.7% (13/15) in non-ulcer disease (all $P > 0.05$).

Reviewer #2.

PPIs cause few adverse effects with short-term use; however, recent literature reports of potential adverse effects of PPIs, especially during long-term treatments. Although PPIs are generally considered safe, the PPIs should be taken in the lowest effective dose and only for as long as clinically indicated. As with any therapy, therefore, it is advisable to prescribe PPIs only to patients for whom these drugs have been proven beneficial. I think that these problems should be embodied in the

Introduction and Discussion.

We added the comments about potential adverse effects of long-term PPI treatment in INTRODUCTION (page 3) and added the limitation of not assessing the adverse effects of PPI-treatment in DISCUSSION (page 6). However, PPI was not prescribed for more than 6 months in any patients (the longest, 168 days); the adverse effects of long-term PPI-treatment might be rare.

The authors stated in the Introduction "In this regard, pretreatment with a PPI can be considered beneficial to H. pylori eradication." However, in fact, there is conflicting evidence whether pretreatment influences the efficacy of H. pylori eradication, little evidence supporting this pretreatment has been reported so far.

We agree with your opinion. We deleted this sentence, and corrected the 1st and 2nd paragraphs in the INTRODUCTION (page 3).

Is long-term PPI-pretreatment urgently required by the 517 patients (Group B) selected in the study? Have the authors considered adverse effects as far as the patients who didn't need long-term PPI-pretreatment are concerned?

Among 517 patients (Group B), only 97 patients (Group B-3) were pretreated with long-term (56 days or more) PPI. The other patients in Group B were pretreated with PPI for less than 8 weeks; 146 patients in Group B-1 (3-14 days), and 274 in Group B-2 (15-55 days). Patients in Group B-3 mostly needed long-term PPI-pretreatment for ulcer healing, including iatrogenic ulcer, followed by gastroesophageal reflux disease. We could not control the duration of PPI use because of a limitation of retrospective study. Further prospective and controlled studies are needed to complement the limitations of the study. We revised the limitation section in DISCUSSION (page 6).

Reviewer #3.

The Influence of Long-term Pre-treatment with a Proton Pump Inhibitor on the Cure Rate of Helicobacter pylori Eradication is a well written study that asks a pertinent clinical question does adding PPI to an antibiotic regimen increase H. pylori eradication. It has a large cohort size. I would have excluded out the 138 patients with iatrogenic ulcers caused by endoscopic resection of gastric neoplasm. These

EMR patients were not randomized into a prior treatment with ppi or standard treatment cohorts and I wonder if this may have biased the results as the patients with gastric neoplasms may have more severe cases of h pylori. I would like to know what the outcome would be if this group were excluded.

We included 138 patients with iatrogenic ulcers caused by endoscopic resection of gastric neoplasm because these patients clinically often need both of long-term PPI-treatment and *H. pylori* eradication therapy. We also assumed that diagnostic factor might affect the eradication rate, so this was included in various adjustment factors. However, PPI-pretreatment did not affect eradication rate even after adjustment for various factors including diagnosis. In addition, eradication rates were not significantly different between Group A and B in any diagnostic subgroups; 87.1% (27/31) vs. 76.6% (82/107) in iatrogenic ulcer, 77.6% (340/438) vs. 82.3% (325/395) in peptic ulcer, and 83.7% (87/104) vs. 86.7% (13/15) in non-ulcer disease (all $p = NS$). We newly commented this finding in RESULTS. Consequently, the outcome that PPI-pretreatment did not affect eradication rate is not changed after excluding 138 patients with iatrogenic ulcers

2) The paper looked only at daily ppi therapy. Were there enough patients to analyze a bid ppi dose and its effect on h pylori eradication?

Our paper could not help looking only at daily PPI treatment, because PPI bid therapy was not covered by medical insurance in Korea, except using in *H. pylori* eradication regimen.

3) The fact that the patients were on three different ppi's was not listed as a weakness of the study and should be included in the limitations.

Because this study was a retrospective analysis, enrolled patients received different types of PPI in pretreatment and *H. pylori* eradication regimen. We used multivariate analysis to overcome this limitation. We mentioned this limitation in DISCUSSION.

4) How was treatment compliance assessed in the study? It should be included in the methods.

A good compliance is defined as consumption of more than 90% of the prescribed drugs. Only patients with a good compliance were accepted as completing the

treatment and enrolled in the study. We added the sentence in METHODS.

5) The test for cure was not consistent for all patients and this should be listed as a weakness of the study and explained in the discussion. It would also be good to have a figure outlining how this was analyzed between the 2 cohorts.

Different methods assessing the eradication as well as different types of PPI were the weak points of our study. We adjusted these factors using multivariate analysis. We mentioned this limitation in DISCUSSION.

We changed the Figure according to the reviewer's comment.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Sincerely,

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