

May 14th, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18128-review.clear.doc and 18128-review.highlighted.doc).

Title: Interaction between *Helicobacter pylori* infection and low-dose aspirin in gastroduodenal mucosal injury

Author: Katsunori Iijima & Tooru Shimosegawa

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18128

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Response to reviewer 03259423

Reviewer's Comment: Iijima and Shimosegawa reported that there was a difference between East Asia and Western countries in the interaction between LDA and H pylori infection on adverse gastroduodenal lesions. They explained this difference based on the fact that there was a geographic difference in the net effect of H pylori infection on gastric acid secretion. The type of manuscript is not clear enough (a review, a meta-analysis, an editorial,...).

Response: This is invited review article. I am sorry for not having informed you of it at first.

Reviewer's Comment: In the first two paragraphs there is an indirect comparison of different studies from which the authors concluded that there is a difference in the effect of H pylori on LDA induced gastroduodenal injury. However, this conclusion did not supported by any statistical analysis. On the other paragraphs the authors made many assumptions on the putative mechanisms that could explain the above difference. Although someone can argue that these assumptions are true, the data are not so robust to justify putative responsibility.

Response: As you indicated, in the table 1 & 2, we made indirect comparison between Japan and Western countries regarding prevalence of low-dose aspirin induced gastroduodenal adverse lesions. We recognized that such international comparison may be difficult especially for Table 1 due to the reason that we already mentioned in the paper (P4, L18-22) (although it may be difficult to make a direct comparison due to variations in the study subjects (inclusion and exclusion criteria, proportion of concomitant administration of proton pump inhibitors: PPI) and the study design (e.g. the definition of ulcer, retrospective or prospective sampling) among these studies). On the other hand, comparisons according to the presence or absence of H. pylori infection in table 2 would be more reliable because each comparison were made within the same study design as we already mentioned (P4, L2-4 from the bottom) (These comparisons according to the presence or absence of H. pylori infection within the same study design should be more reliable than those of prevalence of events among different studies.). In any case, we hesitated to circulate statistical significance because there is large methodological difference between the studies. Nonetheless, we believe that the fact that virtually all studies indicated the same trend as we shown in the Tables supports our current conclusion although we did not perform statistical comparison.

Reviewer's Comment: Moreover, it is difficult to find a clear message for the management of patients with H pylori infection and LDA in the Asian population.

Response: As you indicated, our manuscript did not provide a clear message for the management of patients with H pylori infection and LDA in the Asian population because we focus on the future trend of LDA-induced peptic ulcers in Asia in this review. However, we agree with you that management of patients is also important. We added the following comment on the management of patients in the last part of the manuscript.

"Currently, because H. pylori infection could have diverse effects on the LDA-induced adverse gastroduodenal lesions, especially in Eastern Asia, appropriate measures to extract high-risk groups among these patients and administer the concomitant gastro-protective drugs to the targeted subjects need to be established"

Reviewer's Comment: In any case a shortening of the manuscript could be helpful.

Response: As you suggested, we shortened the revised manuscript as in highlighted version.

Response to reviewer 01554907

Reviewer's Comment: The manuscript is a well written review discussing the potential difference of gastroduodenal mucosal injury between Asia and western countries in LDA user considering H.pylori infection. The topic is interesting and is valuable.

Response: I appreciate your evaluation to our paper.

Response to reviewer 00503405

Reviewer's Comment: Interesting meta-analysis about the relation of low-dose aspirin treatment/HP infection to GI adverse effects in Eastern Asian and Western populations. The topic is very interesting and of great clinical importance, however, one point is not included/discussed. Namely, what about the use of PPIs in case of LDA treatment? Were there any differences in GI adverse effects in case of HP pos. and HP neg. patients using LDA+/-PPI? This aspect must be discussed.

Response: I appreciate your thoughtful comments. In many studies, PPI takers were also included as study subjects, hence we agree with you that the influence of PPI intake on the prevalence of LDA-induced gastroduodenal mucosal injury need to be considered. In the third paragraph of the revised paper, we discussed the issue as follows.

"The potential diverse effect of PPI administration on the LDA-induced gastroduodenal mucosal injury between H. pylori-negative and -positive subjects need to be addressed when comparing the prevalence between the Japanese and Westerners because many of these studies comprised a portion of LDA users with co-treatment of PPI. However, thus far, there has been no consistent conclusion on this issue; that is, although a study reported that PPI treatment is more efficient to suppress LDA-induced adverse gastroduodenal lesions in H. pylori-negative subjects than in H. pylori-positive ones [27], another study reported the opposite result [28], and the remaining studies have indicated that the treatment is efficient to the same degree regardless of the infection status [29, 30]. In addition, the different association of H. pylori infection with LDA-induced adverse gastroduodenal lesions between Western and Japanese subjects seems to persist in the three studies in which patients with co-treatment of PPI were excluded [11, 22, 25]. Thus, the inclusion of PPI users could have a minimal impact on the geographic difference in LDA-induced adverse gastroduodenal lesions according to H. pylori infection status."

Reviewer's Comment: The format of the manuscript needs revision as well. It must be formatted according to the guidelines of WJG. After major revision I suggest the consideration of a possible publication in WJG.

Response: The format of the manuscript was revised according to the paper you attached.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, reading "Katsunori Iijima". The signature is written in a cursive style with a large initial 'K'.

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