Subrata Ghosh,

Andrzej S Tarnawski,

Editor-in-Chief

World Journal of Gastroenterology

Dear Editors:

MS. ID: 46275

Title: Development of *Helicobacter pylori* treatment: How do we manage antimicrobial resistance?

We would like to thank the reviewer and editors for their careful review of our manuscript and for their thoughtful comments. Please find below a point-by-point response to these comments, and please find attached our revised manuscript. Changes made in response to the reviewers' comments are highlighted in red color in our manuscript. We believe that the reviewers' comments have enabled us to improve our manuscript significantly, and we hope that it is now suitable for publication in your journal.

Regarding to references, we would like to cite one reference not indexed on PubMed, that is reported by Furuta et al. reference number is 32, because this reference is very important and meaningful for our manuscript. Thus, we provide printed copy of this reference in Supplementary Material. We hope that this reference is acceptable to be cited in our manuscript.

Sincerely,

Sho Suzuki, MD, PhD

Division of Gastroenterology and Hepatology, Department of Medicine,

Nihon University School of Medicine

1-6 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8309, Japan

Tel; +81-3-3293-1711, Fax; +81-3-3292-2880

suzuki.sho@nihon-u.ac.jp

Reviewer comments

1. The main problem of this article is that vonoprazan is currently available only on Japanese market. This point must be underlined and discussed. Indeed, it is questionable whether vonoprazan is a lesson from Japan to apply worldwide or a limited geographic phenomenon.

Response

Thank you for valuable suggestion. We agree that vonoprazan is available in limited area and that is major limitation of vonoprazan-based regimens. Thus, we have added the description of this issue in the manuscript. In addition, vonoprazan is now available not only in Japan but also in other Asian countries such as Philippine, Singapore, and Thailand, and it has been approved in South American region such as Argentina and Peru. Thus, vonoprazan may become available worldwide in the near future. These descriptions have been also added in the manuscript.

See page 10 line 4: Although vonoprazan-based dual therapy potentially has these advantages, it also has several limitations for implementation in clinical setting. First, vonoprazan is available in a few countries. Vonoprazan was developed and launched in Japan in 2015. However, it is now available in several Asian countries including Philippine, Singapore, and Thailand, and has been approved in other regions, including South America (countries such as Argentina and Peru). Thus, vonoprazan may become available and can be used for H. pylori eradication therapy worldwide in the near future.

Reviewer comments

2. Page 6: please delete furazolidone from the list, since it is not recommended by any guideline and it may have harmful potential and not approved for use in humans in many countries.

Response

We have deleted “furazolidone” in the list as suggested.

See page 6 line18: Both BQT and CQT contain PPI and two to three kinds of antibiotic agents including AMPC, CAM, MNZ, nitroimidazole, and tetracycline with longer treatment durations of 10–14 days.

Reviewer comments

3. Dual therapy cannot be used in subjects with penicillin allergy. In this case, a tailored therapy could be an alternative. Indeed, the possibility of first-line personalization of antibiotic treatment based on a non invasive assessment of susceptibility should be discussed more in depth (see Ierardi E et al, World J Gastroenterol 2017).

Response

That is major limitation of dual therapy using amoxicillin. We agree with you about antimicrobial susceptibility test, especially non-invasive method, should be performed in the patients with penicillin allergy before eradication treatment. We have added the description of non-invasive antimicrobial susceptibility test for patients with penicillin allergy, and cited the reference reported by Ierardi E et al in World J Gastroenterol 2017.

See page 10 line 11: Second, this regimen cannot be used in patients with penicillin allergy and thus antimicrobial susceptibility testing should be performed in these patients to optimize H. pylori eradication therapy. Although the conventional antimicrobial susceptibility testing is invasive due to the need of endoscopy and biopsy as mentioned above, a non-invasive molecular test using fecal sample has also been recently developed[34]. This method involves the isolation of H. pylori DNA from stool and detection of point mutations conferring antimicrobial resistance by polymerase chain reaction. This method should be considered for testing antimicrobial susceptibility in patients with

penicillin allergy before H. pylori eradication therapy.

4. A table summarizing all the studies with vonoprazan-based dual therapy may make the paper more appealing for the readers. Additionally, specific meta-analyses must be cited, if available.

Response

We have revised the references in Table 1, and recent meta-analyses were cited for eradication rates of all regimens except vonoprazan-based dual therapy in Table 1. However, in our best knowledge, there is only one study about vonoprazan-based dual therapy, and there is no meta-analysis about it. Thus, only eradication rate of vonoprazan-based dual therapy is based on single study in Table 1.

See page 5 line 12 and Table1: The eradication rates for first-line H. pylori treatment regimens published in meta-analysis and in a study of eradication rates of vonoprazan-based dual therapy are shown in Table 1.

5. A minor linguistic revision is necessary due to some typos.

Response

This manuscript has been carefully reviewed and edited again by English editing service named “Editage”. Please refer the document of Non-Native Speakers of English Editing Certificate.