

Reviewers' comments/suggestions

Reviewer 1

This manuscript is the retrospective study of *Helicobacter pylori* eradication using vonoprazan and conventional PPIs. I have several comments as follows. 1. Were there any patients who were excluded by adverse events? Authors should mention the data of both Intention to treat analysis and Per protocol analysis in the first-line treatment and the second-line treatment. 2. Authors should mention the clinical characteristics of patients in VPZ group and PPIs group. 3. Authors should mention the number of patients who underwent the second-line treatment. 4. Authors mention that smoking habit alone showed a significant difference among the four groups. Authors should mention the multivariable analysis of smoking habit.

Reviewer 2

A Comparative Study of Vonoprazan and Proton Pump Inhibitors in *Helicobacter pylori* Eradication Therapy: Comments. 1. The study is well performed and nice reported. 2. It shows the efficacy problems regarding HPs regimes typical used the last decade. The regimes used in Japan somewhat differ from typical regimes used in Europe and US in dosage (PPIs/antibiotics) and duration. 3. I believe that it would have been of even greater interest to gain knowledge about Vonoprazan 20 mg twice daily regarding regimes used the last 5 years – because there are substantial differences regarding dosage/duration in the regimes reported used in this study (*older regimes*) compared to those used in clinical practices in the western world. This consideration should at least be discussed as a limitation regarding results and conclusion. 4. Yes the eradication rate is higher for Vonoprazan, but even that is lower than 90% which is not a satisfactory results regarding efficacy of HP eradication. Bear this in mind when reporting results. 5. CYP – polymorphism, what is the prevalence in the Japanese population, is it so large that it will explain results – or is it only a theoretical possibility? Elucidate on that matter – it would be of interest.

Reviewer 1

Comment 1.1: The reviewer comments that authors should mention the data of both Intention to treat analysis and Per protocol analysis in the first-line treatment and the second-line treatment. The reviewer asks us whether there were any patients who were excluded by adverse events.

Response 1.1: The primary endpoint of the study was the eradication rate of *H. pylori* in clinical practice. This study was a retrospective study, and no patients discontinued *H. pylori* eradication treatment because of adverse events.

Therefore, we concluded there were no problems using FAS analysis as a statistical method.

Comment 1.2: The reviewer comments that authors should mention the clinical characteristics of patients in VPZ group and PPIs group.

Response 1.2:

The baseline clinical characteristics and demographics of patients in the PPI groups have been added to the Table 1.

Comment 1.3: The reviewer comments that authors should mention the number of patients who underwent the second-line treatment.

Response 1.3:

The details of the patient characteristics in the second-line treatment groups were also shown in Table 1.

The following sentence has been added to the Results section (*Patient characteristics*): "In total, 261 patients completed the second-line treatment protocol. Demographic and other baseline characteristics in the second-line treatment were also shown in Table 1 and there were not significant differences in all of them. "

Comment 1.4: The reviewer comments that authors should mention the multivariable analysis of smoking habit.

Response 1.4:

For both the first-line treatment and the second-line treatment patients, there

were no predictive factors found by multivariate analyses.

The following sentence has been added to the Results section (*Eradication rates*).

“There were no predictive factors observed for second-line treatment and there were no predictive factors demonstrated in both the first-line treatment and the second-line treatment by multivariate analyses (data not shown).”

The following sentence has been added to the Discussion section.

“Although smoking alone showed a significant difference between the four groups by univariate analyses, it was not a significant factor by multivariate analyses. We believe that this result might have arisen because we did not investigate drug sensitivity, and *H. pylori* resistance to CAM might be a major reason for treatment failure. It is necessary to investigate factors contributing to the success of *H. pylori* eradication treatment, including drug sensitivity, in the future.”

Reviewer 2

Comment 2.1: The reviewer comments that there are substantial differences regarding dosage/duration in the regimes reported used in this study (*older regimes*) compared to those used in clinical practices in the western world and this consideration should at least be discussed as a limitation regarding results and conclusion.

Comment 2.2: The reviewer comments that the eradication rate is higher for Vonoprazan, but even that is lower than 90% which is not a satisfactory results regarding efficacy of HP eradication.

Response 2.1: Response 2.2:

The following sentence has been added to the Discussion section(limitations) :

“Triple therapy combining a PPI with AMPC and CAM generates an unacceptably low eradication rate in most of the world. Sequential therapy, quadruple therapy, concomitant therapy and high dose dual therapy are recommended in the era of increased CAM resistance^[13]. However, although the resistance of *H. pylori* to CAM is increasing in Japan, only triple therapy with PPI, AMPC and CAM has been recognized under Japan’s national health insurance. Vonoprazan-based triple therapy has been available in Japan dating from February 2015. In our results, the vonoprazan eradication rate was high (87.9%), but it is not a satisfactory result regarding the efficacy of *H. pylori* eradication throughout the world. If vonoprazan-based triple therapy was

provided to CAM -sensitive patients, the eradication rate might increase to over 90 %. Therefore, it is necessary to investigate drug sensitivity before treatment in Japan. If the patients have CAM-resistant strains of *H. pylori*, they will require regimens of vonoprazan and different types and doses of antibiotics as well as different periods instead of CAM. “

Comment 2.3: The reviewer asks us about the prevalence of CYP-polymorphism in the Japanese population and comments whether it is so large that it will explain results – or it is only a theoretical possibility.

Response 2.3:

The population frequency of poor metabolizer, intermediate metabolizer, extensive metabolizers in Japan is 18.8%, 43.8% and 35.5% respectively^[16].

The following sentence has been added to the Discussion section: “The population frequency of poor, intermediate, extensive metabolizers in Japan is 18.8%, 43.8% and 35.5%, respectively^[16]. “and “We suggest that the eradication rates observed in our results correspond to the population frequency of genetic polymorphisms affecting the metabolism of the PPI. “

Reference:

16. Sugimoto K, Uno T, Yamazaki H, Tateishi T. Limited frequency of the CYP2C19*17 allele and its minor role in a Japanese population. *Br J Clin Pharmacol* 2008; 65: 437-439 [PMID: 18241287 DOI: 10.1111/j.1365-2125.2007.03057.x]