Effect of Age on Effectiveness of Vonoprazan in Triple Therapy for *Helicobacter pylori* Eradication

Maho Kusunoki¹, Mika Yuki¹, Hitomi Ishitobi¹, Yoshiya Kobayashi¹, Makoto Nagaoka¹, Yoshiko Takahashi¹, Nobuhiko Fukuba¹, Yoshinori Komazawa¹, Toshihiro Shizuku¹ and Yoshikazu Kinoshita²

**Abstract:**

**Objective**  We evaluated the efficacy of vonoprazan-based eradication therapy for *Helicobacter pylori*, including the effects of age, gender, and grade of atrophy in comparison to proton pump inhibitor-based therapy.

**Method**  We retrospectively reviewed the records of 1172 patients who received first-line triple therapy with amoxicillin, clarithromycin, and a proton pump inhibitor or vonoprazan for *H. pylori* eradication, as well as 157 patients treated with second-line therapy consisting of amoxicillin, metronidazole, and vonoprazan or a PPI.

**Results**  The eradication rate of all cases treated with first-line triple therapy was 86.9% (1,019/1,172), while that in those treated with vonoprazan-based therapy was 92.5% (384/415). Our analysis showed that the use of vonoprazan resulted in a significantly improved success rate of first-line eradication therapy in comparison to proton pump inhibitor-based therapy (OR, 2.36; 95% CI 1.55 to 3.56). The superiority of vonoprazan was remarkable in non-elderly patients, while its effect was unclear in elderly patients. When used as second-line eradication therapy, the advantage of vonoprazan over proton pump inhibitor administration was not clear.

**Conclusion**  The inclusion of vonoprazan increased the success rate of first-line eradication therapy; however, the advantage was reduced with aging and remained unclear in elderly patients.

**Key words:** *Helicobacter pylori*, eradication, potassium-competitive acid blockers, elderly, atrophic gastritis, second-line therapy

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**Introduction**

There have been dramatic changes in the options for the eradication of *Helicobacter pylori* (*H. pylori*). In 2013, eradication therapy for gastritis caused by *H. pylori* infection was approved by the national health insurance system of Japan, resulting in an increased number of cases. Subsequently, in 2015, vonoprazan, a novel potassium-competitive acid blocker, was released and approved for the eradication of *H. pylori* infection.

A phase III randomized double-blind study showed that vonoprazan was not inferior to lansoprazole in first-line eradication therapy when either was used in combination with amoxicillin and clarithromycin, while a high rate of eradication was also shown in subjects who underwent vonoprazan-based second-line therapy with amoxicillin and metronidazole (1). Subsequently, a higher rate of *H. pylori* eradication was reported with vonoprazan-based therapy in comparison to proton pump inhibitor-based therapy (2). On the other hand, when used in second-line eradication therapy, the effectiveness of vonoprazan over the administration of...
of a proton pump inhibitor (PPI) has not been demonstrated (3-5). In addition, it remains unclear whether elderly patients require strong acid suppression drugs such as vonoprazan for the eradication of H. pylori, because gastric acid secretion decreases with age (6), which is a major issue throughout the world because of aging populations (7).

In the present study, we evaluated the rates of successful eradication in patients receiving first- and second-line therapy in order to compare the efficacy of vonoprazan to PPI administration, and also examined the effects of age.

**Methods**

**Study design**

In this retrospective open-label single-center study we reviewed the findings from patients who underwent H. pylori eradication therapy in a standard 7-day protocol. The eradication rates according to age, gender, grade of gastric mucosal atrophy, and acid suppression drugs were determined. The gastric mucosal atrophy grade was included in the analysis, as it is an indicator of acid secretion, which decreases with the progression of atrophic gastritis (6). The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Izumo-City General Medical Center (approval number 26-17).

**Patients**

Patients who underwent H. pylori eradication therapy at Izumo-City General Medical Center from January 2013 to April 2017 were enrolled in this retrospective study. We confirmed the success or failure of eradication in all cases during the study period. Second-line eradication therapy was only performed in cases in which first-line therapy failed.

**The diagnosis and eradication of H. pylori**

H. pylori infection was diagnosed based on the H. pylori IgG Ab titer (≥10 U/mL [plate E ‘Eiken’ H. pylori Ab]). H. pylori eradication was evaluated using a 13C-urea breath test at least 4 weeks after the end of therapy.

For treatment, each patient received the standard eradication therapy protocol used in Japan. PPI-based first-line therapy contained amoxicillin (750 mg) and clarithromycin (200 or 400 mg) with a PPI (PAC) twice daily for 1 week. Vonoprazan-based first-line therapy, which we began to prescribe in March 2015, contained amoxicillin (750 mg) and clarithromycin (200 or 400 mg), with vonoprazan (VAC; 20 mg). For second-line therapy we prescribed metronidazole (250 mg) instead of clarithromycin. PPI-based second-line therapy contained a PPI, amoxicillin, and metronidazole (PAM), and vonoprazan-based second-line therapy contained vonoprazan, amoxicillin and metronidazole (VAM). The PPIs administered to the present patients included esomeprazole (20 mg), lansoprazole (30 mg), and rabeprazole (10 mg). From January 2013 to February 2015, PPI-based therapy was exclusively prescribed, then from March 2015 to April 2017 the attending physician chose between vonoprazan- and PPI-based therapy depending on their individual treatment policy.

**Assessment of gastric mucosal atrophy**

Gastric mucosal atrophy was diagnosed based on the Kimura-Takemoto classification using esophagastroduodenoscopy findings (8). We classified patients into mild and severe atrophy groups. Mild atrophy was defined by the absence of atrophy or the presence of an atrophic border on the lesser curve, the same as the closed type in the Kimura-Takemoto classification. Severe atrophy was defined by a greater spread, the same as the open type in the Kimura-Takemoto classification.

**Statistical analysis**

Continuous variables were analyzed using the Mann-Whitney test. Binary variables were analyzed using a chi-squared test or Fisher’s exact test. A Steel-Dwass test was performed to compare multiple groups. A multivariate logistic regression analysis was performed to determine odds ratios (ORs) and 95% confidence intervals (95% CIs). P values of <0.05 were considered to indicate statistical significance. Statistical analyses were conducted using the IBM SPSS (version 22.0) or Bellcurve for Excel (version 2.14) software programs.

**Results**

**H. pylori eradication**

A total of 1201 patients completed H. pylori eradication treatment, with first-line therapy administered to 1172 and second-line therapy administered to 157. The baseline characteristics of the patients are shown in Table 1.

The eradication rate for all patients was 96.8% (1,162/1,201), while the rates for first-line therapy and second-line therapy cases were 86.9% (1,019/1,172) and 91.1% (143/157), respectively (Table 1). When the patients were divided by age, the success rate of first-line eradication therapy in patients of ≤39 years of age was significantly lower in comparison to that in patients of 40-49 (p=0.012), 50-59 (p=0.003), and 60-69 (p=0.009) years of age. When the patients were divided according to use of acid suppression drugs, the rate of eradication with vonoprazan was significantly higher than that with lansoprazole (p=0.001) or rabeprazole (p<0.001). When the patients were divided according to gender and grade of gastric mucosal atrophy, there were no significant differences in the success rate of first-line eradication.

In the multivariate logistic regression analysis, with age, gender, gastric mucosal atrophy grade, and acid suppression drugs employed as variables, only vonoprazan had a significant impact on first-line eradication success (OR, 2.36; 95% CI 1.55 to 3.56) (Table 2). None of those variables had a significant effect on the success of second-line therapy.
Comparison between vonoprazan and PPI

The baseline characteristics of the patients who received vonoprazan and those who received a PPI are shown in Table 3. Regardless of gender and grade of atrophy, the VAC regimen was superior to the PAC regimen when used as first-line therapy (Table 3). On the other hand, neither regimen was superior in the older age groups (60-69, ≥70 years), while the VAC regimen was superior in non-elderly patients.

In the univariate analysis, age, gender, and grade of atrophy had no significant effect on eradication success with the VAC regimen, while the eradication rate in patients of ≤39 years of age was significantly lower in comparison to the rates in older age groups that received the PAC regimen (Table 3). A multiple logistic regression analysis that included age, gender, and grade of atrophy as independent variables showed that age had a slightly negative effect in patients that received the VAC regimen (OR, 0.95; 95%CI 0.92 to 0.98) and a slightly positive effect in those that received the PAC regimen (OR, 1.02; 95%CI 1.00 to 1.04) (Table 2). As for second-line eradication therapy, analyses performed according to the above-mentioned methods revealed no significant differences.

Discussion

In the present study population, the success rate of first-line eradication therapy with the VAC regimen was significantly greater than that with the PAC regimen. However, there were no significant differences between those regimens when they were administered to elderly patients. In addition, there was no clear advantage of the VAM regimen when used as second-line therapy.

Seven-day PPI-based amoxicillin clarithromycin triple therapy was the standard first-line therapy for H. pylori eradication in Japan prior to the approval of vonoprazan. Both amoxicillin and clarithromycin require organism growth for their effectiveness. H. pylori organisms can grow in the periplasm at pH range of 6.0 to 8.0. The administration of a PPI increases the population of dividing organisms by elevating the gastric pH, and thus synergizes with antibiotics (9). Insufficient acid suppression can cause eradication failure (10). Another serious problem with this regimen is a decreasing trend in the rate of eradication, which is related to increasing clarithromycin resistance (11, 12). It seems that the frequent administration of clarithromycin to patients with respiratory infections has contributed to a remarkable increase in the rate of resistance in Japan (13).

Vonoprazan, a novel potassium-competitive acid blocker, inhibits gastric H+ and K+-ATPase like PPIs, but in a K+-competitive and reversible manner, unlike PPIs. Acid activation is not required for vonoprazan to exert its acid secretion inhibiting effect and this drug exerts a more potent inhibitory effect on gastric acid secretion, and also has a stronger and longer lasting effect on elevated pH in gastric perfusate in comparison to lansoprazole (14). A randomized open-
Table 2. Multivariate Logistic Regression Analysis of Independent Factors Related to Successful H. Pylori Eradication.

<table>
<thead>
<tr>
<th></th>
<th>First-line therapy</th>
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<th>Second-line therapy</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p value</td>
<td>Odds ratio (95% CI)</td>
<td>p value</td>
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<tr>
<td></td>
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<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>1.01 (0.99-1.02)</td>
<td>0.466</td>
<td>0.95 (0.92-0.98)</td>
<td>0.004</td>
</tr>
<tr>
<td>Gender</td>
<td>0.82 (0.58-1.18)</td>
<td>0.258</td>
<td>0.84 (0.39-1.78)</td>
<td>0.640</td>
</tr>
<tr>
<td>Atrophy</td>
<td>0.85 (0.59-1.24)</td>
<td>0.410</td>
<td>0.97 (0.43-2.18)</td>
<td>0.938</td>
</tr>
<tr>
<td>Vonoprazan (vs. PPI)</td>
<td>2.36 (1.55-3.56)</td>
<td>&lt;0.001</td>
<td>2.51 (0.58-10.87)</td>
<td>0.218</td>
</tr>
</tbody>
</table>

PPI: proton-pump inhibitor, VAC: vonoprazan, amoxicillin, and clarithromycin, PAC: proton-pump inhibitor, amoxicillin, and clarithromycin, VAM: vonoprazan, amoxicillin, and metronidazole, PAM: proton-pump inhibitor, amoxicillin, and metronidazole.
### Table 3. Patient Baseline Characteristics for Comparison between Vonoprazan and PPI, and Rates of Eradication.

<table>
<thead>
<tr>
<th></th>
<th>First-line therapy</th>
<th>Eradication rate</th>
<th>Second-line therapy</th>
<th>Eradication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline characteristics</td>
<td>VAC</td>
<td>PAC</td>
<td>p values</td>
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<tr>
<td></td>
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<tr>
<td>All</td>
<td>415</td>
<td>757</td>
<td></td>
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<tr>
<td>Age ≤39</td>
<td>39 (9.40)</td>
<td>74 (9.80)</td>
<td></td>
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<tr>
<td>40-49</td>
<td>60 (14.5)</td>
<td>81 (10.7)</td>
<td></td>
<td></td>
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<tr>
<td>50-59</td>
<td>93 (22.4)</td>
<td>194 (25.6)</td>
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<tr>
<td>60-69</td>
<td>136 (32.8)</td>
<td>227 (30.0)</td>
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<tr>
<td>≥70</td>
<td>87 (21.0)</td>
<td>181 (23.9)</td>
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<tr>
<td>Gender</td>
<td>0.316</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>male</td>
<td>196 (47.2)</td>
<td>370 (48.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>219 (52.8)</td>
<td>387 (51.1)</td>
<td></td>
<td></td>
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<tr>
<td>Atrophy</td>
<td>0.202</td>
<td></td>
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</tr>
<tr>
<td>mild</td>
<td>202 (48.7)</td>
<td>351 (34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>204 (49.2)</td>
<td>396 (52.3)</td>
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</tbody>
</table>

Values are shown as n (%) or median [IQR]. P values were calculated using a chi-square test and Mann-Whitney’s test.

Values for success of eradication therapy are shown as a percentage. P values for first- and second-line therapy were calculated using a chi-square test and Fisher’s exact test, respectively.

*p<0.05, vs. ≤39 years; **p<0.01, vs. ≤39 years (Steel-Dwass test).

VAC: vonoprazan, amoxicillin, and clarithromycin, PAC: proton-pump inhibitor, amoxicillin, and clarithromycin, VAM: vonoprazan, amoxicillin, and metronidazole, PAM: proton-pump inhibitor, amoxicillin, and metronidazole.

On the other hand, vonoprazan, which is not available in an enteric-coated tablet form, may potently inhibit acid suppression regardless of the severity of gastric mucosal atrophy. In the present study, the patients with severe gastric mucosal atrophy...
cosal atrophy treated with first-line therapy were older than those with mild atrophy (median 65.0 years [interquartile range 58.0-72.0] vs. 55.0 years [44.0 to 64.0], p < 0.001). Indeed, gastric mucosal atrophy extends with aging, resulting in decreased gastric acid secretion in H. pylori-positive patients (6). Furthermore, gastric acid secretion in elderly patients is often reduced by factors other than atrophic gastritis caused by H. pylori (21). Aging, which can be directly evaluated, seems to be an important factor in relation to gastric acid secretion. Our results suggest that patient age may be more useful for choosing an acid suppressing drug for H. pylori eradication than endoscopic atrophy.

In the present study, the VAM regimen was not superior to the PAM regimen for second-line eradication therapy regardless of age. The main reason seems to be that the efficacy of metronidazole, which targets DNA, is independent of the stationary or growth phase distribution, as it does not require acid suppression (22). In addition, it may have had effects on equality, as metronidazole has a lower rate of resistance than clarithromycin due to its limited use in the treatment of anaerobic and protozoan infections in Japan, despite the fact that increasing rates of metronidazole resistance have been reported in various regions of the world (12, 23, 24). It seems that the role of acid suppression in second-line therapy is reduced in comparison to first-line therapy.

This study was associated with some limitations, including its retrospective single center design. We did not evaluate antibiotic resistance or the expression of CYP2C19, which are known to be major causes of eradication failure. Notably, it is recommended that clarithromycin resistance, which greatly affects eradication, be evaluated before starting eradication therapy. We diagnosed H. pylori infection based on the H. pylori IgG Ab titer. This method is commonly used and is suitable for clinical practice even in our hospital where many patients come for medical checkups, as the procedure is only minimally invasive and the results can be obtained within 1 day. Furthermore, the registration periods of patients who received vonoprazan- and PPI-based therapy were different. Vonoprazan has been prescribed since March 2015, following its release in the previous month. This resulted in a decrease in the number of PPI prescriptions. In this study, clarithromycin (200 or 400 mg) was administered in the first-line therapy regimen, although its impact on the present results was likely not significant (25). Based on these limitations, our results must be interpreted with care.

The present findings demonstrate that the efficacy of vonoprazan is superior to that of PPI treatment for first-line therapy, while there were no significant differences seen between them when used for second-line therapy. Furthermore, the superiority of vonoprazan in first-line therapy for elderly patients was not clear.

The authors state that they have no Conflict of Interest (COI).

References


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