Seven-Day Triple Therapy with Amoxicillin and Clarithromycin Plus a Potassium-Competitive Acid Blocker Rather than a Proton Pump Inhibitor, as First-line *Helicobacter pylori* Eradication in Japan: A Single Clinic Retrospective Study

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Abstract

Objective: This study was conducted to evaluate the effectiveness and safety of vonoprazan, a potassium-competitive acid blocker (P-CAB) compared with proton pump inhibitors (PPIs) for a first-line *Helicobacter pylori* (*H. pylori*) eradication.

Materials and Methods: Data of patients who received first-line *H. pylori* eradication treatment (vonoprazan or PPIs with 400mg clarithromycin and 750mg amoxicillin twice daily for 7-day) (*n* = 1393) between April 2008 and February 2017 at Sadamoto GI Clinic, Japan were retrospectively analyzed. Patients who received 7-day P-CAB therapy (vonoprazan 20 mg twice daily; *n* = 498) were compared with those who received 7-day PPI therapy (lansoprazole 30 mg; *n* = 216, rabeprazole 10 mg; *n* = 331, esomeprazole 20 mg; *n* = 348 twice daily). Eradication rates were calculated by intention-to-treat (ITT) and by per-protocol (PP). Compliance and adverse events were also assessed for each study group.

Results: ITT and PP analysis of the first-line *H. pylori* eradication for vonoprazan, lansoprazole, rabeprazole, and esomeprazole were 75.5%/86.8%, 63.9%/76.2%, 68.0%/79.5%, and 63.2/70.8%, respectively. The vonoprazan eradication rates were significantly higher than those of these PPIs (*P* < 0.05), respectively. There was no significant difference in the adverse events between two therapies.

Conclusions: 7-day P-CAB based triple therapy is more effective than 7-day PPI based triple therapy as a first-line *H. pylori* eradication without differences in tolerability.

Keywords: *Helicobacter pylori*; Eradication; Vonoprazan; Potassium-Competitive Acid Blocker; Proton Pump Inhibitor

Introduction

According to the International Agency for Research of Cancer (IARC), gastric cancer is associated with *Helicobacter pylori* (*H. pylori*) infection in 80% of cases, and that successful *H. pylori* eradication can lead to a 30% - 40% reduction in the incidence of gastric cancer [1]. Eradication of *H. pylori* infection has also been reported as an effective strategy for the prevention of peptic ulcer and the treatment of gastric mucosa-associated lymphoid tissue lymphoma (MALToma), in addition to prevention of metachronous gastric cancer after endoscopic resection [2-4].

Use of conventional first-line triple therapy with a proton pump inhibitor (PPIs), clarithromycin (CAM) and amoxicillin (AMX) has been declining in recent years in Japan, mainly due to the insufficient effects of the antibiotics [5,6] and the increasing prevalence of antibiotic-resistant *H. pylori* [7,8].

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Maintenance of intragastric pH > 5 is necessary for AMX and CAM to exert adequate toxicity against anti-\textit{H. pylori} [9]. Vonoprazan (VPZ) is a novel potassium-competitive acid blocker (P-CAB), representing a new class of gastric acid-suppressant agents. It inhibits binding of potassium ions to $H^+, K^+$-ATPase in the parietal cells to exert a potent and long-lasting antisecretory effect, because of its high accumulation and slow clearance from gastric tissue [10]. In recent years, several reports have suggested that VPZ-based \textit{H. pylori} eradication therapy is superior to PPI-based \textit{H. pylori} eradication therapy in Japan [11-14]. In addition, some meta-analyses have also revealed the superior efficacy of VPZ-based \textit{H. pylori} eradication therapy [15-17]. However, the efficacy and safety of the VPZ-based regimen still remain controversial, especially in relation to the ability of VPZ to eradicate CAM-susceptible and CAM-resistant strains of \textit{H. pylori}.

In this study, the effectiveness and safety of VPZ-based triple therapy as compared to PPI-based triple therapy (using the same dose of CAM in both) as first-line therapy for \textit{H. pylori} eradication were evaluated at a single clinic in Japan.

Materials and Methods

Patients and study design

Data of patients who had received first-line \textit{H. pylori} eradication treatment (VPZ or a PPI with 400 mg CAM and 750 mg AMX twice daily for 7 days) (\textit{n} = 1393) between April 2008 and February 2017 at Sadamoto GI clinic, Japan, were retrospectively analyzed. Data were compared between patients who received P-CAB-based (VPZ 20 mg, \textit{n} = 498) triple therapy for 7 days were compared with those who received PPI-based (lansoprazole (LPZ) 30 mg, \textit{n} = 216; rabeprazole (RPZ) 10 mg, \textit{n} = 331; esomeprazole (EPZ) 20 mg, \textit{n} = 348) for 7 days.

All the patients treated before February 2015 received PPI-based triple therapy for 7 days as first-line therapy (LPZ was used between April 2008 and November 2010, RPZ between December 2012 and September 2011 and also between February 2014 and February 2015, and EPZ between October 2011 and January 2014). All the patients treated since March 2015 have received P-CAB-based triple therapy in place of PPI-based therapy. \textit{H. pylori} eradication therapy was not undertaken for patients who were pregnant or lactating, or in those with a history of allergic reactions to antibiotics.

Presence of \textit{H. pylori} infection was confirmed by at least one positive result among the rapid urease test (Helicocheck; Otsuka pharmaceutical, Tokyo, Japan), $^{13}$C-urea breath test (UBIT tablet/POCone; Otsuka pharmaceutical, Tokyo, Japan) and serological test for \textit{H. pylori} immunoglobulin G (E plate Eiken; Eiken Chemical, Tokyo, Japan). Successful eradication was defined as a result of < 2.5‰ in the $^{13}$C-urea breath test as a result at least 1 month after completion of treatment period.

Eradication rates were calculated by intention-to-treat (ITT) and per-protocol (PP) analyses. In the ITT analysis, all enrolled patients were included, and those who were lost to follow-up or did not undergo the follow-up urea breath test were regarded as cases of failed eradication. In the PP analysis, patients who did not undergo the follow-up urea breath test were excluded.

Compliance and adverse events were also assessed for each eradication group. The eradication rate and adverse events in the two groups were investigated

Statistical analysis

Comparison of categorical variables was conducted by the $\chi^2$ test, with calculation of the 95% confidence interval (CI). All $p$ values were two-sided, and $p$ values of < 0.05 were considered as indicative of selected to indicate statistical significance.

Results

Patient characteristics

The characteristics and overall treatment outcomes of the P-CAB-based and PPI-based treatment groups are presented in table 1. In total, 1393 patients received the protocol treatments as first-line treatment. There was no significant difference in the age or gender distribution between the two groups. In our study, most patients treated with RPZ, EPZ and VPZ were diagnosed as having \textit{H. pylori}-infected gastritis without any underlying lesions (75.8%, 65.2% and 89.2%, respectively), because this indication began to be covered by the national health insurance after February 2013. On the other hand, mainly LPZ was used between April 2008 and November 2010 for patients with peptic ulcer.

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### Table 1: Characteristics and treatment outcomes of 1393 patients.

<table>
<thead>
<tr>
<th>PPI or PCAB</th>
<th>LPZ (n = 216)</th>
<th>RPZ (n = 331)</th>
<th>EPZ (n = 348)</th>
<th>All PPIs (n = 895)</th>
<th>VPZ (n = 498)</th>
<th>p value all PPIs vs. P-CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (ys)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>55.5 ± 13.5</td>
<td>58.8 ± 12.9</td>
<td>58.0 ± 14.3</td>
<td>57.7 ± 13.6</td>
<td>56.5 ± 14.1</td>
<td>0.576</td>
</tr>
<tr>
<td>range</td>
<td>17 - 82</td>
<td>22 - 91</td>
<td>20 - 81</td>
<td>17 - 91</td>
<td>20 - 84</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>113 (52.3)</td>
<td>140 (42.3)</td>
<td>152 (43.7)</td>
<td>405 (45.3)</td>
<td>219 (44.0)</td>
<td>0.653</td>
</tr>
<tr>
<td>Female</td>
<td>103 (47.7)</td>
<td>191 (57.7)</td>
<td>196 (56.3)</td>
<td>490 (54.7)</td>
<td>279 (56.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Underlying disease (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>9 (4.2)</td>
<td>251 (75.8)</td>
<td>227 (65.2)</td>
<td>487 (54.4)</td>
<td>444 (89.2)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>101 (46.7)</td>
<td>47 (14.2)</td>
<td>69 (19.8)</td>
<td>217 (24.2)</td>
<td>34 (6.8)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>76 (35.2)</td>
<td>27 (8.2)</td>
<td>31 (8.9)</td>
<td>134 (15.0)</td>
<td>18 (3.6)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>Gastroduodenal Ulcer</td>
<td>16 (7.4)</td>
<td>4 (1.2)</td>
<td>14 (4.0)</td>
<td>34 (3.8)</td>
<td>2 (0.4)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>ESD</td>
<td>14 (6.5)</td>
<td>1 (0.3)</td>
<td>4 (1.1)</td>
<td>19 (2.1)</td>
<td>0 (0)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>MALToma</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>3 (0.1)</td>
<td>4 (0.4)</td>
<td>0 (0)</td>
<td>0.303</td>
</tr>
<tr>
<td><strong>Treatment outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication therapy completed</td>
<td>181</td>
<td>283</td>
<td>331</td>
<td>775</td>
<td>433</td>
<td>0.870</td>
</tr>
<tr>
<td>Successful eradication</td>
<td>138</td>
<td>225</td>
<td>220</td>
<td>583</td>
<td>376</td>
<td></td>
</tr>
<tr>
<td>Eradication rate</td>
<td>63.9%</td>
<td>68.0%</td>
<td>63.2%</td>
<td>65.1%</td>
<td>75.5%</td>
<td></td>
</tr>
<tr>
<td>Assessed by ITT analysis</td>
<td>138/216</td>
<td>225/331</td>
<td>220/348</td>
<td>583/895</td>
<td>376/498</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>58.5-69.2</td>
<td>64.1-71.9</td>
<td>59.4-67.1</td>
<td>63.4-67.0</td>
<td>73.2-77.8</td>
<td></td>
</tr>
<tr>
<td>Eradication rate</td>
<td>76.2%</td>
<td>79.5%</td>
<td>70.8%</td>
<td>75.2%</td>
<td>86.8%</td>
<td></td>
</tr>
<tr>
<td>Assessed by PP analysis</td>
<td>138/181</td>
<td>225/283</td>
<td>220/311</td>
<td>583/775</td>
<td>376/433</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>71.1 - 81.2</td>
<td>76.0 - 83.0</td>
<td>67.4 - 74.3</td>
<td>73.3 - 77.2</td>
<td>84.8 - 89.0</td>
<td></td>
</tr>
<tr>
<td>Cases in which treatment was discontinued because of occurrence of adverse events (%)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>0.231</td>
</tr>
</tbody>
</table>

In Japan, the costs of *H. pylori* eradication treatment for patients without peptic ulcers, post endoscopic resection for gastric cancer, and MALToma was not covered by the national health insurance before February 2013. In regard to the treatment outcomes, of the 1393 patients enrolled in the study, the treatment was completed in 1208 patients (86.7%). Treatment was discontinued in 12 patients (0.86%) because of the emergence of adverse events (Table 2). The remaining 173 patients (12.4%) dropped out of the study and did not undergo the follow-up breath test.

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As per the ITT analysis (Figure 1), the eradication rates associated with first-line treatment containing VPZ, LPZ, RPZ and EPZ were 75.5% (95% CI: 73.2 - 77.8), 63.9% (95% CI: 58.5 - 69.2), 68.0% (95% CI: 64.1 - 71.9) and 63.2% (95% CI: 59.4 - 67.1), respectively. As per the PP analysis (Figure 2), the eradication rates associated with first-line treatment containing VPZ, LPZ, RPZ and EPZ were 86.8% (95% CI: 84.8 - 89.0), 76.2% (95% CI: 71.1 - 81.2), 79.5% (95% CI: 76.0 - 83.0) and 70.7% (95% CI: 67.4 - 74.3), respectively. The eradication rates associated with PPI-based therapy was 65.1% (95% CI: 63.4 - 67.0) as per the ITT analysis and 75.2% (95% CI: 73.3 - 77.2) as per the PP analysis. Both the ITT and PP analyses revealed a significantly higher eradication rate associated with VPZ-based therapy than with PPI-based therapy, irrespective of the PPI used (p < 0.05) (Table 1). The ITT and PP analyses revealed no significant differences in the eradication rates among the PPI-based therapies using the three different PPIs.

### Table 2: Cases in which treatment discontinuation was necessitated because of occurrence of adverse events.

<table>
<thead>
<tr>
<th>P-CAB: A Potassium-Competitive Acid Blocker; LPZ: Lansoprazole; RPZ: Rabeprazole; EPZ: Esomeprazole; VPZ: Vonoprazan.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (n)</strong></td>
</tr>
<tr>
<td>LPZ Generalized fatigue (n = 1), nausea (n = 1), skin eruption (n = 1), bloating (n = 1)</td>
</tr>
<tr>
<td>RPZ Skin eruption (n = 1), diarrhea (n = 2), nausea (n = 1)</td>
</tr>
<tr>
<td>EPZ Skin eruption (n = 1), diarrhea (n = 1)</td>
</tr>
<tr>
<td>VPZ Generalized fatigue (n = 1), nausea (n = 1)</td>
</tr>
</tbody>
</table>

**Eradication rates**

As per the ITT analysis (Figure 1), the eradication rates associated with first-line treatment containing VPZ, LPZ, RPZ and EPZ were 75.5% (95% CI: 73.2 - 77.8), 63.9% (95% CI: 58.5 - 69.2), 68.0% (95% CI: 64.1 - 71.9) and 63.2% (95% CI: 59.4 - 67.1), respectively. As per the PP analysis (Figure 2), the eradication rates associated with first-line treatment containing VPZ, LPZ, RPZ and EPZ were 86.8% (95% CI: 84.8 - 89.0), 76.2% (95% CI: 71.1 - 81.2), 79.5% (95% CI: 76.0 - 83.0) and 70.7% (95% CI: 67.4 - 74.3), respectively. The eradication rates associated with PPI-based therapy was 65.1% (95% CI: 63.4 - 67.0) as per the ITT analysis and 75.2% (95% CI: 73.3 - 77.2) as per the PP analysis. Both the ITT and PP analyses revealed a significantly higher eradication rate associated with VPZ-based therapy than with PPI-based therapy, irrespective of the PPI used (p < 0.05) (Table 1). The ITT and PP analyses revealed no significant differences in the eradication rates among the PPI-based therapies using the three different PPIs.

**Figure 1: H.P. eradication rate (ITT analysis).**
Adverse events

Major adverse events were observed in 12 patients (0.86%) (diarrhea ($n = 3$), nausea ($n = 3$), skin eruption ($n = 3$), generalized fatigue ($n = 2$), and bloating ($n = 1$)). Treatment was discontinued prematurely in these patients. All of the above adverse events, except for skin eruption, resolved spontaneously without intervention. The patients with skin eruption needed oral anti-allergic agents or low-dose steroid therapy before the lesions resolved. None of the patients needed hospitalization for adverse events. There were no significant differences in the nature/frequencies of adverse events the patients receiving PPI-based and P-CAB-based $H. pylori$ eradication therapy (Table 2).

Discussion

According to both ITT and PP analyses in this study, the $H. pylori$ eradication rate was significantly higher in patients who received VPZ-based therapy than in patients who received the conventional PPI-based therapy, the dose of CAM and AMX remaining the same between the regimens, as first-line treatment.

One of the major factors reported to be associated with failure of $H. pylori$ eradication therapy is insufficient gastric acid inhibition [16]. Gastric acid secretion must be strongly suppressed (pH $> 5$) to prevent degradation of CAM and AMX during eradication therapy, as these two drugs show high acid-sensitivity [5,6,9]. The metabolic rate and acid-inhibitory effect of PPIs depend on gene polymorphism of the cytochrome P450 (CYP) 2C19 enzyme [13]. In addition, several doses of PPIs are required before maximal acid inhibition is obtained, because the acid inhibitory effect of this class of drugs is slow in onset and cumulative [18]. Therefore, PPIs may not yield sufficient gastric acid inhibition by day 7 of $H. pylori$ eradication therapy.

VPZ is a highly effective antacid drug as compared to PPIs. Sakurai., et al. compared the 24-hour mean gastric pH on day 1 and day 7 between patients (harboring the same CYP2C19 polymorphism) administered VPZ 20 mg and EPZ 20 mg, and reported that the intragastric pH after VPZ treatment (pH 5.2 and 6.1) was significantly higher than that after EPZ administration (pH 3.0 and 4.7) [19]. Therefore, the rapid and sustained acid-inhibitory effect of P-CAB might be responsible for the superior eradication rate associated with P-CAB-based therapy as compared to PPI-based $H. pylori$ eradication therapy. The acid-inhibitory effect of PPIs is affected by CYP2C19 polymorphism, and is especially attenuated in patients carrying the rapid metabolizer genotype of CYP2C19 [19]. On the other hand, the pharmacoki-

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Antibiotic resistance is another major factor known to affect the *H. pylori* eradication rates [16,17]. The eradication rates of both PPI-based and VPZ-based therapies were lower in patients with CAM-resistant *H. pylori* strains than in patients with CAM-susceptible *H. pylori* strains. Among patients with CAM-resistant *H. pylori* strains, however, the VPZ-based triple regimen appeared to be superior in efficacy to the PPI-based triple regimens (81.5% vs. 40.9%, p < .00001) [16]. These data emphasize the importance of antibiotic resistance in the failure of eradication therapy. Maintaining the intragastric pH at over 6 leads to a high *H. pylori* eradication rate, as increasing the pH to 6 or 7 allows the bacteria to enter the replicative state where they become susceptible to AMX [5]. In Inaba’s study, the eradication rate of VPZ-based triple therapy was 70% in patients with failure of the first-line PPI-based triple therapy with the same antibiotics [23]. This finding suggests that sufficient inhibition of intragastric acid secretion by VPZ might improve the toxicity of AMX against the CAM-resistant *H. pylori* strains. According to a randomized study reported as a conference abstract, the eradication rate of first-line dual therapy with VPZ and AMX (93.8%, 15/16) was not significantly different from that of VPZ-based triple therapy (87.5%, 14/16) [24]. This result shows that CAM might be unnecessary, as it has been shown that at least 80% of cases of *H. pylori* infection could be cured by a combination of VPZ plus AMX. However, this remains under debate and the study was limited by small sample size.

Drug interaction with antibiotics is yet another important factor that affects *H. pylori* eradication rates. Comparison of the pharmacokinetics of combined use of VPZ, AMX, and CAM with the single use each of these drugs revealed a higher mean C_{max} and area under the curve (AUC) of the drugs with combined use than with single use of the drugs. On the other hand, AMX has been reported to have no effect on the C_{min} or the AUC [25,26]. Both VPZ and CAM are predominantly metabolized by CYP3A4 and possibly inhibit CYP3A4 when used in combination. The plasma concentrations of both VPZ and CAM are about twofold higher when they are used in combination than when they are used singly because of mutual inhibition of each other’s metabolism. The sufficient intragastric acid inhibition induced by VPZ may be considered as one of the reasons for the more effective eradication associated with first-line VPZ-based triple therapy with AMX and CAM than with VPZ-based dual therapy with AMX alone.

Lastly, our study revealed no significant differences in the occurrence rates of adverse events between the VPZ-based and PPI-based therapies. One meta-analysis compared the safety of VPZ-based vs. PPI-based triple therapy for *H. pylori* eradication, and showed that VPZ was safer than PPI in the randomized controlled trial (RCT) subset (26.4% vs. 33.3%, p = .008), but that there was no significance in the occurrence rate of adverse events between the VPZ and PPI groups in the non-RCT subset (5.7% vs. 4.7%, p = .08) [16]. Therefore, the safety of VPZ-based triple therapy for *H. pylori* eradication is acceptable.

This study had the limitation that it was a retrospective cohort study, and was performed at a single clinic. In addition, the antibiotic susceptibility of *H. pylori* and polymorphism of CYP2C19 were not investigated. While the results of the meta-analyses demonstrated the superior benefit of VPZ-based therapy, the existence of significant heterogeneity cannot be ruled out, as in this study. This heterogeneity could arise from the different study settings among retrospective cohort studies. The VPZ-based triple therapy was typically used after February 2015 at our clinic, and while the period of use of PPI-based triple therapy varied among studies, it was mainly used before February 2015. Therefore, the eradication rates of the PPI-based triple therapies could be overestimated in retrospective studies, because the eradication rates of PPI-based triple therapies have gradually decreased. If both PPI- and VPZ-based regimens were used during the same period, the relative efficacy of VPZ-based triple therapy might increase.

**Conclusion**

P-CAB-based triple therapy is more effective than PPI-based triple therapy as first-line treatment for *H. pylori* eradication, with no difference in the tolerability between the two regimens.

**Conflict of Interest**

None of the authors has any conflicts of interests to disclose in relation to the submission of this manuscript.

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