Efficacy of Vonoprazan for *Helicobacter pylori* Eradication

Shu Kiyotoki¹, Jun Nishikawa² and Isao Sakaida³

Abstract:

*Helicobacter pylori* can infect the gastric mucosa and cause chronic inflammation, resulting in various diseases, including gastric cancer. Eradication of *H. pylori* in all infected subjects is recommended; however, the number of *H. pylori* strains with antibiotic resistance has increased, and the eradication rate has decreased. Vonoprazan, a potassium-competitive acid blocker, produces a stronger acid-inhibitory effect than proton pump inhibitors (PPIs). The *H. pylori* eradication rate with vonoprazan was found to be higher than that with PPIs. The *H. pylori* eradication rate with vonoprazan-based triple therapy (vonoprazan, amoxicillin, and clarithromycin) was approximately 90% and had an incidence of adverse events similar to that of PPIs. We review the current situation of *H. pylori* eradication in Japan, the first country in which vonoprazan was made available.

Key words: vonoprazan, *Helicobacter pylori*, eradication, potassium-competitive acid blocker (P-CAB), proton pump inhibitor (PPI)

(Intern Med 59: 153-161, 2020)

(DOI: 10.2169/internalmedicine.2521-18)

Introduction

*Helicobacter pylori* can infect the gastric mucosa and cause gastritis (1-3). Chronic inflammation caused by *H. pylori* in the gastric mucosa can lead to atrophic gastritis (4, 5), gastroduodenal ulcer (6), mucosa-associated lymphoid tissue (MALT) lymphoma (7), gastric adenocarcinoma (8-10), and even idiopathic thrombocytopenic purpura (11). These diseases can be prevented or treated by *H. pylori* eradication, so its eradication in all infected subjects is recommended in order to treat and prevent these diseases (12, 13).

The number of strains of *H. pylori* with antibiotic resistance has recently increased, and the eradication rate has decreased (14). Resistance to clarithromycin is an important cause of the failure to eradicate *H. pylori*. To overcome this, eradication regimens that use more kinds of drugs (quadruple therapy), higher doses of drugs, and longer treatment durations (10-14 days) have been recommended (13). The Maastricht V/Florence Consensus Report recommends bismuth-containing quadruple therapy or concomitant therapy in areas of high clarithromycin resistance (13).

It has been reported from Japan that triple therapy with vonoprazan, a potassium-competitive acid blocker (P-CAB), offers a higher rate of *H. pylori* eradication than that of proton pump inhibitors (PPIs). We herein review the current situation of *H. pylori* eradication in Japan, the first country in which vonoprazan was made available.

Vonoprazan, A Potassium-competitive Acid Blocker (P-CAB)

Vonoprazan fumarate is a P-CAB, which are agents that inhibit H⁺,K⁺-adenosine triphosphatase (ATPase) through reversible K⁺-competitive ionic binding that results in the inhibition of gastric acid secretion. Because vonoprazan has a relatively high pKa value and is stable in an acidic environment, it can accumulate in the acidic compartment of gastric parietal cells, unlike PPIs. In addition, vonoprazan does not require acid activation, in contrast to PPIs. Thus, vonoprazan can achieve stronger, longer-lasting suppression of gastric acid secretion than PPIs can (15, 16).

The metabolism of PPIs involves cytochrome P450 (CYP) 2C19, and the effects of PPIs are influenced by the CYP2C19 pharmacogenetic polymorphism (17, 18). How-

¹Department of Gastroenterology, Shuto General Hospital, Japan, ²Faculty of Laboratory Science, Yamaguchi University Graduate School of Medicine, Japan and ³Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Japan

Received: December 14, 2018; Accepted: April 1, 2019; Advance Publication by J-STAGE: June 27, 2019

Correspondence to Dr. Shu Kiyotoki, shu2026eb@hi.enjoy.ne.jp
ever, vonoprazan is not affected by CYP2C19, so sufficient inhibition of gastric acid secretion can be obtained in all subjects (19).

Vonoprazan produced rapid, profound, and sustained suppression of gastric acid secretion for over 24 hours in healthy subjects in Japan and the UK in Phase I clinical trials (19, 20). Jenkins et al. showed that the mean intragastric pH was >4.0 at 4 hours after the first administration of vonoprazan, and the acid-suppressing effect was sustained for 24 hours. The pH >5 holding time ratio after the administration of vonoprazan (40 mg) for 7 consecutive days was almost 100.0% among volunteers in Japan and the UK (20).

### H. pylori Eradication Rate with Vonoprazan

We searched for comparative studies that examined the rate of *H. pylori* eradication with vonoprazan-based triple therapies and PPI-based triple therapies using the key words “vonoprazan” and “pylori” in PubMed on November 1, 2018. Excluding the studies that did not show detailed data, 6 prospective studies (21-26) and 12 retrospective studies (27-38) were assessed. The results of the studies are presented in Table 1.

Vonoprazan is available mainly in Japan, and the *H. pylori* eradication regimens accepted in Japan are 7-day triple therapies: PPI or vonoprazan + amoxicillin + clarithromycin (PPI-AC or VAC) as first-line therapy and PPI or vonoprazan + amoxicillin + metronidazole (PPI-AM or VAM) as second-line therapy (12, 39). Thus, the results of all of the assessed studies pertain to these triple therapies.

#### 1) Efficacy of vonoprazan for first-line eradication

Murakami et al. compared the *H. pylori* eradication rate of vonoprazan with that of PPIs for patients with gastroduodenal ulcers in a randomized, double-blind, multicenter, parallel-group comparative study (21). The eradication rates of the VAC group (vonoprazan 20 mg in combination with amoxicillin 750 mg plus clarithromycin 200 mg or 400 mg, twice daily for 7 days) and the lansoprazole group (lansoprazole 30 mg in combination with amoxicillin 750 mg plus clarithromycin 200 mg or 400 mg, twice daily for 7 days) were 92.6% (95% confidence interval [CI], 89.2-95.2%) and 75.9% (95% CI, 70.9-80.5%) in the full analysis set, respectively, with the difference between the 2 groups being 16.7% (95% CI, 11.2-22.1%). This result demonstrated the non-inferiority of VAC to lansoprazole regarding the therapeutically significant effect on *H. pylori* eradication. Almost all studies reported that the eradication rate with vonoprazan was higher than that with PPIs (21-23, 27-32, 34-38), although Shinozaki et al. reported that no significant differences were shown compared with esomeprazole (33).

There have been two systematic reviews and one meta-analysis study of *H. pylori* eradication with vonoprazan (40-42). Jung et al. performed a systematic review with 10,644 patients in 10 studies (40). The *H. pylori* eradication rate according to an intention-to-treat (ITT) analysis was 88.1% (95% CI, 86.1-89.9%) in the vonoprazan-based triple therapy group and 72.8% (95% CI, 71.0-75.4%) in the PPI-based triple therapy group, and the *H. pylori* eradication rate with vonoprazan was superior to that with PPI [pooled risk ratio (95% CI) =1.19 (1.15-1.24)]. Dong et al. performed a meta-analysis including 14 studies with 14,636 patients. The odds ratio of the eradication rate with vonoprazan to that with PPIs was 2.44 (95% CI, 1.99-2.99) (41). However, these review articles by Dong et al., Jung et al., and Li et al. included retrospective observational studies. To show the superiority of PCAB in *H. pylori* eradication, further randomized control trials and meta-analyses (based on randomized controlled trials) are needed.

The remarkable effect of the VAC regimen for the eradication of clarithromycin-resistant *H. pylori* has been reported. In the randomized controlled trial by Murakami et al., the eradication rate of clarithromycin-resistant *H. pylori* was 40.0% with lansoprazole and 82.0% with vonoprazan (21). The subgroup analysis of the systematic review by Jung et al. showed the pooled risk ratio of the eradication rate of vonoprazan for clarithromycin-resistant *H. pylori* to that of PPI to be 1.94 (95% CI, 1.63-2.31) (40), and the meta-analysis by Dong et al. reported that the odds ratio was 5.92 (95% CI, 3.70-9.49) (41). The retrospective studies showed a comparable result (28, 30). Sue et al. reported that no significant difference was observed between the VAC and PPI-AC regimens in treatment of clarithromycin-susceptible *H. pylori* (43). Li et al. showed through their meta-analysis that vonoprazan- and conventional PPI-based therapies are similarly effective for the eradication of clarithromycin-susceptible *H. pylori* strains. The superiority of VAC to PPI-AC was emphasized against clarithromycin-resistant *H. pylori* (42).

A multivariate logistic regression analysis of the prospective study by Murakami et al. showed that the difference in clarithromycin dose (200 mg or 400 mg) had no significant effect on the eradication rate (21). This result is the same as that of a previous Japanese study of a PPI (44). Although vonoprazan increases the blood concentration of clarithromycin (45) and stabilizes clarithromycin in gastric juice by suppressing gastric acid secretion (46), an increase in only the clarithromycin dose does not have a positive impact on *H. pylori* eradication.

Vonoprazan has been shown not to have anti-*H. pylori* activity in vitro (47). The main mechanism of the high eradication rate of vonoprazan is its strong inhibition of gastric acid secretion. Protein-targeted antibiotics, such as amoxicillin and clarithromycin, effectively work in the bacterial growth phase. *H. pylori* grows between pH 6.0 and 8.0 in the same band of pH values, providing increased sensitivity for these antibiotics (48-50). As described above, vonoprazan can produce a more rapid, profound, and sustained suppression of gastric acid secretion than PPIs and can elevate the intragastric pH (19, 20). These features of vonoprazan help enhance the sensitivity of antibiotics and thus promote the high eradication rate.
| References | Study design | Eradication rate (95% CI) | Adverse events (discontinuation) |
|------------|--------------|---------------------------|----------------------------------|
|            |              | ITT/FAS | PP  | ITT/FAS | PP  | PP  | PP  | PP  |
| (24)       | Prospective, non-randomized, open-label, multicenter | VPZ 20 mg + AMX 750 mg + CAM 200 mg or 400 mg, twice-daily, 7 days, n=1,688 | VPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=76 (RPZ), 71 (EPZ) | NA | 90.8% | NA | RPZ 68.4%, EPZ 77.5% | NA (0%) | NA (0%) |
| (27)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg or 400 mg, twice-daily, 7 days, n=111 | RPZ 10 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=498 | 94.6% (88.6-98.0) | 95.5% (89.7-98.5) | 86.7% (78.4-92.7) | 86.7% (78.4-92.7) | 2.7% (NA) | 3.1% (NA) |
| (23)       | Randomized, single-blind, single-center, parallel-group comparison | VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=72 | RPZ 20 mg or LPZ 30 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=69 | 95.8% (88.3-99.1) | 95.7% (88.0-99.1) | 69.6% (57.3-80.1) | 71.4% (58.7-82.1) | 26.3% (NA) | 37.7% (NA) |
| (28)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=125 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=295 | 89.6% (84-95) | 89.6% (84-95) | 71.9% (67-77) | 73.1% (68-78) | 11.9% (0%) | 10.7% (5 dropouts) |
| (21)       | Randomized, double-blind, multicenter, parallel-group comparison | VPZ 20 mg + AMX 750 mg + CAM 200 mg or 400 mg, twice-daily, 7 days, n=329 | LPZ 30 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=321 | 92.6% (89.2-95.2) | NA | 75.9% (70.9-80.5) | NA | 34.0% (0.9%) | 41.4% (0.6%) |
| (38)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=308 | LPZ 30 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=272 | NA | 91.0% | NA | 84.7% | NA |
| (29)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=353 | LPZ 30 mg or RPZ 10 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=2,173 | 62.3% | 89.4% | 47.1% | 66.8% | 8.4% (NA) | 5.7% (NA) |
| (30)       | Prospective and retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 400 mg, twice-daily, 7 days, n=146 | LPZ 30 mg, RPZ 10 mg, OPZ 20 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=1,305 | NA | 89.7% (87.9-91.3) | NA | 73.9% (66.0-80.8) | NA |
| (31)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=546 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=211 (LPZ), 89 (RPZ), 507 (EPZ) | 87.9% (84.9-90.5) | NA | LPZ 57.3% (50.4-64.1), RPZ 62.9% (52.0-72.9), EPZ 71.6% (67.5-75.5) | NA | 11.2% (0%) | LPZ 5.7%, RPZ 10.1%, EPZ 7.7% (0%) |
| (32)       | Retrospective, multicenter | VPZ 20 mg + AMX 750 mg + CAM 200 mg or 400 mg, twice-daily, 7 days, n=422 | LPZ 30 mg, RPZ 10 mg, OPZ 20 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=2,293 | 87.2% | NA | 72.4% | NA | 6.2% (NA) | 6.2% (NA) |
| (33)       | Retrospective, two-institution | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=117 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=198 (LPZ), 138 (RPZ), 120 (EPZ) | 83% (75-89) | 85% (77-91) | LPZ 66% (59-72), RPZ 67% (58-74), EPZ 83% (75-89) | LPZ 69% (62-76), RPZ 70% (61-77), EPZ 87% (79-93) | 5% (NA) | LPZ 1.1%, RPZ 6%, EPZ 3% (NA) |

**Table 1.** Comparative Studies of *H. Pylori* First-line Eradication Therapy with Vonoprazan and Proton Pump Inhibitors.
Table 1. Comparative Studies of *H. Pylori* First-line Eradication Therapy with Vonoprazan and Proton Pump Inhibitors. (continued)

| References | Study design | Triple therapy regimen | Eradication rate (95% CI) | Adverse events (discontinuation) |
|------------|--------------|-------------------------|---------------------------|---------------------------------|
|            |              | Vonoprazan | PPI | ITT/FAS | PP | ITT/FAS | PP | Vonoprazan | PPI |
| (22)       | Non-randomized, open-label, multicenter, parallel-group comparison | VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=623 | LPZ 30 mg, RPZ 10 mg, OPZ 20 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=608 | 84.9% (81.9-87.6) | 86.4% (83.5-89.1) | 78.8% (75.3-82.0) | 79.4% (76.0-82.6) | NA | NA |
| (25)       | Randomized, open-label, multicenter | VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=55 [CAM-susceptible *H. pylori*] | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=42 (LPZ), 4 (RPZ), 5 (EPZ [CAM-susceptible *H. pylori*]) | 87.3% (75.5-94.7) | 88.9% (77.4-95.8) | 76.5% (62.5-87.2) | 86.7% (73.2-94.9) | NA (0%) | NA (1 dropout) |
| (34)       | Retrospective, single-center, propensity score matching analysis | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=181 | LPZ 30 mg or RPZ 10 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=480 | 89.0% (84.4-93.5) [89.1% (84.5-93.8) in propensity score matching] | 91.5% (87.3-95.6) [91.2% (87.0-95.5)] | 74.2% (70.3-78.1) [70.9% (64.1-77.6)] | 77.9% (74.1-81.7) [71.7% (64.9-78.4)] | 12.7% (0%) | 14.4% (0%) |
| (37)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=363 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=207 (LPZ), 450 (RPZ), 123 (EPZ) | 91.5% (88.6-94.3) | 97.4% (95.7-99.1) | LPZ 77.3% (71.6-83.0) | LPZ 85.6% (80.5-90.6) | NA | NA |
| (35)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=443 | EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=431 | 84.6% | 86.3% | 79.1% | 79.9% | 0.68% (1 dropout) | 1.17% (3 dropouts) |
| (36)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=335 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + CAM 200 mg, twice-daily, 7 days, n=1,720 | 85.7% | 90.3% | 73.2% | 76.4% | NA (0%) | NA (0.4%) |

PPI: proton pump inhibitor; CI: confidence interval; ITT: intention to treat analysis; FAS: full analysis set; PP: per protocol analysis; VPZ: vonoprazan, AMX: amoxicillin, CAM: clarithromycin, LPZ: lansoprazole, RPZ: rabeprazole, OPZ: omeprazole, EPZ: esomeprazole; NA: not available
PPIs are influenced by the CYP2C19 polymorphism. The intragastric pH during eradication with PPIs in extensive metabolizers of CYP2C19 is lower than in poor metabolizers, resulting in a decrease in the rate of *H. pylori* eradication (17, 51, 52). Because vonoprazan is mainly metabolized by CYP3A4/5 (53), it can strongly inhibit gastric acid in all patients without this individual variability, thus further contributing to its overall high eradication rate.

Adverse events of eradication therapy with vonoprazan were also investigated by a systematic review and a meta-analysis study. Jung et al. reported adverse event rates of 8.1% for vonoprazan-based triple therapy (95% CI, 3.8-16.3%) and 8.2% for PPI-based triple therapy (95% CI, 3.6-17.4%), and the difference between the two groups was not significant [pooled risk ratio of vonoprazan-based therapy (95% CI) = 1.02 (0.78-1.34)] (40). Dong et al. reported that the vonoprazan group had a lower occurrence of adverse events than the PPI group in their randomized control trial subgroup analysis [odds ratio of vonoprazan-based therapy (95% CI) = 0.70 (0.54-0.91)], but when adding the non-randomized control trials into the overall analysis, there was no significant difference between the vonoprazan and PPI groups [odds ratio (95% CI) = 1.04 (0.77-1.42)] (41). In two randomized control trials and one propensity score-matched analysis (21, 23, 34), the vonoprazan group had a lower incidence of adverse events than the PPI group. However, the incidence of adverse events in the vonoprazan group was higher than that in the PPI group in three of the non-randomized control trials (28, 29, 31).

These results imply that the safety of *H. pylori* eradication therapy with vonoprazan is comparable to that of PPI-based triple therapy.

**2) Efficacy of vonoprazan for second-line eradication**

The second-line eradication regimen in Japan is vonoprazan or PPI + amoxicillin + metronidazole (VAM or PPI-AM). We summarized the results of second-line eradication therapy in Table 2. Sue et al. compared the VAM regimen (vonoprazan 20 mg + amoxicillin 750 mg + metronidazole 250 mg, twice a day for 7 days) with the PPI-AM regimen (lansoprazole 30 mg, rabeprazole 10 mg, or esomeprazole 20 mg + amoxicillin 750 mg + metronidazole 250 mg, twice a day for 7 days) in a prospective, non-randomized, open-label trial (22). The eradication rates with VAM in the ITT analysis and per protocol (PP) analysis were 80.5% (95% CI, 74.6-85.6%) and 82.4% (95% CI, 76.6-87.3%), respectively, and those with PPI-AM were 81.5% (95% CI, 74.2-87.4%) and 82.1% (95% CI, 74.8-87.9%), respectively, with no significant difference noted. The other four retrospective studies showed no significant difference between the eradication rate with vonoprazan and that with PPIs (29, 31, 35, 36). Unlike amoxicillin and clarithromycin (49), metronidazole is a DNA-targeted antibiotic, and its effect does not depend on the cell division of bacteria. Therefore, eradication regimens containing metronidazole do not benefit from the strong suppression of gastric acid secretion by vonoprazan.

There are a few studies concerning the adverse events of second-line eradication therapy with vonoprazan (21, 24, 29, 31, 36). These studies showed that adverse events occurred in 0-30% of patients receiving VAM-containing regimens, with diarrhea being the main adverse effect.

**3) Efficacy of vonoprazan for third-line eradication**

Sue et al. also performed a prospective, randomized trial of the efficacy of vonoprazan-based and PPI-based 7-day triple regimens with amoxicillin and sitafloxacin as a third-line therapy for eradicating *H. pylori* after failure of clarithromycin-based and metronidazole-based therapies (26). Their regimen contained vonoprazan 20 mg or PPI + amoxicillin 750 mg + sitafloxacin 100 mg, twice a day for 7 days (VAS or PPI-AS). The ITT and PP eradication rates of the vonoprazan group were 75.8% (95% CI, 57.7-88.9%) and 83.3% (95% CI, 65.3-94.4%), respectively, and those of the PPI group were 53.3% (95% CI, 34.3-71.7%) and 57.1% (95% CI, 37.2-75.5%), respectively. In the PP analyses, the eradication rate of the VAS group was significantly higher than that of the PPI-AS group (p = 0.043). However, no significant differences were detected in the ITT analyses (p=0.071). In Japan, third-line therapy is not covered under the Japanese national health insurance system, so we do not have enough information for a thorough review.

**Can Vonoprazan-based Triple Therapy Be Applied to Other Populations and Regions?**

Vonoprazan is currently available mainly in Japan, and there have been no large-scale studies of vonoprazan in other countries. Differences in populations and regions may lead to different results from those of Japanese studies.

The first concern is whether the inhibition of gastric acid is as strong in other populations as in Japanese. In two Phase I clinical trials including healthy subjects in Japan and the UK, the intragastric pH >4 or 5 holding time ratio of the UK population tended to be lower than that of the Japanese population (19, 20). If the suppression of gastric acid by vonoprazan affects the eradication rate, then the rate in the UK population may be lower than that in the Japanese population. Vonoprazan is mainly metabolized by CYP3A4/5 (53). Sugimoto et al. reported that the CYP3A4/5 genotype status might affect the pharmacokinetics and pharmacodynamics of vonoprazan and thereby affect the *H. pylori* eradication rate (54). The CYP3A4/5 genotype may cause individual variability regarding the effect of vonoprazan.

Second, we must consider the various patterns of antibiotic resistance of *H. pylori* among regions. The Japanese studies described above investigated roughly the same eradication regimens: vonoprazan 20 mg + amoxicillin 750 mg + clarithromycin 200/400 mg or metronidazole 250 mg, twice
Table 2. Comparative Studies of *H. pylori* Second-line Eradication Therapy with Vonoprazan and Proton Pump Inhibitors.

| References | Study design | Triple therapy regimen | Eradication rate (95% CI) | Adverse events (discontinuation) |
|------------|--------------|-------------------------|----------------------------|----------------------------------|
|            |              | Vonoprazan | PPI | ITT/FAS | PP | ITT/FAS | PP | Vonoprazan | PPI |
| (29)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=85 | LPZ 30 mg or RPZ 10 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=650 | 71.8% | 96.8% | 73.7% | 90.5% | 6% (NA) | 3.3% (NA) |
| (31)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=76 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=57 (LPZ), 24 (RPZ), 104 (EPZ) | 96.1% | NA | 89.5% (88.9-99.2) | NA | 7.9% (0%) | LPZ 12.3%, RPZ 12.5%, EPZ 13.5% (0%) |
| (22)       | Non-randomized, open-label, multicenter, parallel-group comparison | VPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=216 | LPZ 30 mg, RPZ 10 mg, OPZ 20 mg, or EPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=146 | 80.5% (74.6-85.6) | 82.4% (76.6-87.3) | 81.5% (74.2-87.4) | 82.1% (74.8-87.9) | NA | NA |
| (35)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=46 | EPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=54 | 89.1% | 91.1% | 83.3% | 88.2% | NA | NA |
| (36)       | Retrospective, single-center | VPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=66 | LPZ 30 mg, RPZ 10 mg, or EPZ 20 mg + AMX 750 mg + MNZ 250 mg, twice-daily, 7 days, n=386 | 89.4% | 96.7% | 89.9% | 92.8% | NA (0%) | NA (0.5%) |

PPI: proton pump inhibitor, CI: confidence interval, ITT: intention to treat analysis, FAS: full analysis set, PP: per protocol analysis, VPZ: vonoprazan, AMX: amoxicillin, MNZ: metronidazole, LPZ: lansoprazole, RPZ: rabeprazole, OPZ: omeprazole, EPZ: esomeprazole, NA: not available
a day for 7 days (21-38). In Japan, the rate of clarithromycin resistance of *H. pylori* is more than 30%, whereas that of metronidazole resistance is less than 5% (55). The Maastricht V/Florence Consensus Report recommended that clarithromycin-containing triple therapy as first-line therapy be abandoned when the clarithromycin resistance rate in the region exceeded 15%, with PPI-amoxicillin-metronidazole triple therapy, concomitant treatment, or bismuth-containing quadruple therapy recommended instead (13). The review article by Graham and Fischbach showed that 4-drug treatment (i.e., concomitant therapy or sequential therapy, etc.) achieved an eradication rate of more than 90%, even in a region with high clarithromycin resistance (56). The studies of quadruple therapy in Japan showed high eradication rates, but the number of cases was relatively small, and the evidence level was low (57-63).

In Japan, *H. pylori* eradication therapies have been approved for patients with *H. pylori*-related chronic gastritis under the Japanese national health insurance system since 2013 (64), resulting in increasing cases of *H. pylori* eradication. Due to the fact that *H. pylori* eradication for gastric cancer prevention is epochal, it is therefore necessary to develop more efficient eradication methods. Eradication regimens that use more kinds of drugs (quadruple therapy), higher doses of drugs, and longer treatment durations (10-14 days) have been recommended (13, 56, 65). The use of vonoprazan for concomitant therapy and sequential therapy might further improve the eradication rate. Developing optimal regimens with vonoprazan will be an important issue in the future.

**Conclusion**

We reviewed *H. pylori* eradication therapies with vonoprazan in Japan. First-line triple therapy with vonoprazan has a higher rate of eradication than that with PPI. The effect of vonoprazan on gastric acid secretion is outstanding. Vonoprazan should be administered as an assisting agent in *H. pylori* eradication therapy, regardless of the number of treatments performed. However, multiple studies of various populations and regions will be needed to develop optimal regimens of treatment with vonoprazan that can be applied globally.

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

**References**

1. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1: 1273-1275, 1983.
2. Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfil Koch’s postulates for pyloric *Campylobacter*. Med J Aust 142: 436-439, 1985.
3. Morris A, Nicholson G. Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. Am J Gastroenterol 82: 192-199, 1987.
4. Asaka M, Kato M, Kudo M, et al. Atrophic changes of gastric mucosa are caused by *Helicobacter pylori* infection rather than aging: studies in asymptomatic Japanese adults. Helicobacter 1: 52-56, 1996.
5. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Marganitis G. The long-term impact of *Helicobacter pylori* eradication on gastric histology: a systematic review and meta-analysis. Helicobacter 12 (Suppl 2): 32-38, 2007.
6. Ford AC, Gurusamy KS, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive people. Cochrane Database Syst Rev 4: CD003840, 2016.
7. Nakamura S, Sugiyama T, Matsumoto T, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. Gut 61: 507-513, 2012.
8. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ 348: g3174, 2014.
9. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 372: 392-397, 2008.
10. Yoon SB, Park JM, Lim CH, Cho YK, Choi MG. Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter 19: 243-248, 2014.
11. Satake M, Nishikawa J, Fukagawa Y, et al. The long-term efficacy of *Helicobacter pylori* eradication therapy in patients with idiopathic thrombocytopenic purpura. J Gastroenterol Hepatol 22: 2233-2237, 2007.
12. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. Helicobacter 15: 1-20, 2010.
13. Malfertheiner P, Megraud F, O’Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut 66: 6-30, 2017.
14. Smith SM, O’Morain C, McNamara D. Antimicrobial susceptibility testing for *Helicobacter pylori* in times of increasing antibiotic resistance. World J Gastroenterol 20: 9912-9921, 2014.
15. Hori Y, Imanishi A, Matsukawa J, et al. 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. J Pharmacol Exp Ther 335: 231-238, 2010.
16. Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+-ATPase. Aliment Pharmacol Ther 42: 1315-1326, 2015.
17. Furuta T, Shirai N, Sagimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet 20: 153-167, 2005.
18. Chong E, Ensom MH. Pharmacogenetics of the proton pump inhibitors: a systematic review. Pharmacotherapy 23: 460-471, 2003.
19. Sakurai Y, Nishimura A, Kennedy G, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. Clin Transl Gastroenterol 6: e94, 2015.
20. Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 41: 636-648, 2015.
21. Murakami K, Sakurai Y, Shinoh M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind
study. Gut 65: 1439-1446, 2016.
22. Sue S, Kawashima H, Iwata Y, et al. The superiority of vonoprazan-based first-line triple therapy with clarithromycin: a prospective multi-center cohort study on Helicobacter pylori eradication. Intern Med 56: 1277-1285, 2017.
23. Maruyama M, Tanaka N, Kubota D, et al. Vonoprazan-based regimen is more useful than PPI-based one as a first-line Helicobacter pylori eradication: a randomized controlled trial. Can J Gastroenterol Hepatol 2017: 4385161, 2017.
24. Ozaki H, Harada S, Takeuchi T, et al. Vonoprazan, a novel potassium-competitive acid blocker, should be used for the Helicobacter pylori eradication therapy as first choice: a large sample study of vonoprazan in real world compared with our randomized control trial using second-generation proton pump inhibitors for Helicobacter pylori eradication therapy. Digestion 97: 212-218, 2018.
25. Sue S, Ogushi M, Arima I, et al. Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-resistant Helicobacter pylori: a multicenter, prospective, randomized trial. Digestion 24: e12456, 2018.
26. Sue S, Shibata W, Sasaki T, et al. Randomized trial of vonoprazan-based versus proton-pump inhibitor-based third-line triple therapy with sitafloxacin for Helicobacter pylori. J Gastroenterol Hepatol 2018 (Epub ahead of print).
27. Kajihara Y, Shimoyama T, Mizuki I. Analysis of the cost-effectiveness of using vonoprazan-ampicillin-clarithromycin triple therapy for first-line Helicobacter pylori eradication. Scand J Gastroenterol 52: 238-241, 2017.
28. Matsumoto H, Shiotti T, Katsumata R, et al. Helicobacter pylori eradication with proton pump inhibitors or potassium-competitive acid blockers: the effect of clarithromycin resistance. Dig Dis Sci 61: 3215-3220, 2016.
29. Nishizawa T, Suzuki H, Fujimoto A, et al. Effects of patient age and choice of antisecretory agent on success of eradication therapy for Helicobacter pylori infection. J Clin Biochem Nutr 60: 208-210, 2017.
30. Noda H, Noguchi S, Yoshimine T, et al. A novel potassium-competitive acid blocker improves the efficacy of clarithromycin-containing 7-day triple therapy against Helicobacter pylori. J Gastroenterol 15: 234-238, 2016.
31. Sakurai K, Suda H, Ido Y, et al. Comparative study; vonoprazan and proton pump inhibitors in Helicobacter pylori eradication therapy. World J Gastroenterol 23: 668-675, 2017.
32. Shichijo S, Hirata Y, Niihara R, et al. Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori: a multicenter retrospective study in clinical practice. J Dig Dis 17: 670-675, 2016.
33. Shinozaki S, Nomoto H, Kondo Y, et al. Comparison of vonoprazan and proton pump inhibitors for eradication of Helicobacter pylori. Kaohsiung J Med Sci 32: 255-260, 2016.
34. Suzuki S, Gotoda T, Kusano T, Iwatsuka K, Moriyama M. The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day ppi-based low-dose clarithromycin triple therapy. Am J Gastroenterol 111: 949-956, 2016.
35. Tsujimae M, Yamashita H, Hashimura H, et al. A comparative study of a new class of gastric acid suppressant agent named vonoprazan versus esomeprazole for the eradication of Helicobacter pylori. Digestion 94: 240-246, 2016.
36. Yamada S, Kawakami T, Nakatsugawa Y, et al. Usefulness of vonoprazan, a potassium ion-competitive acid blocker, for primary eradication of Helicobacter pylori. World J Gastrointest Pharmacol Ther 7: 550-555, 2016.
37. Tanabe H, Yoshino K, Ando K, et al. Vonoprazan-based triple therapy is non-inferior to susceptibility-guided proton pump inhibitor-based triple therapy for Helicobacter pylori eradication. Ann Clin Microbiol Antimicrob 17: 29, 2018.
38. Mori N, Nishiu H, Suga D, et al. Second-line triple therapy in failures with vonoprazan-based triple therapy for eradication of Helicobacter pylori. Biomed Rep 9: 169-174, 2018.
39. Lee SY. Current progress toward eradicating Helicobacter pylori in East Asian countries: differences in the 2013 revised guidelines between China, Japan, and South Korea. World J Gastroenterol 20: 1493-1502, 2014.
40. Jung YS, Kim EH, Park CH. Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on Helicobacter pylori eradication. Aliment Pharmacol Ther 46: 106-114, 2017.
41. Dong SQ, Singh TP, Wei X, Yao H, Wang HL. Review: a Japanese population-based meta-analysis of vonoprazan versus PPI for Helicobacter pylori eradication therapy: is superiority an illusion? Helicobacter 2017 (Epub ahead of print).
42. Li M, Oshima T, Horiwaka T, et al. Systematic review with meta-analysis: vonoprazan, a potent acid blocker, is superior to proton-pump inhibitors for eradication of clarithromycin-resistant strains of Helicobacter pylori. Helicobacter 23: e12456, 2018.
43. Sue S, Ogushi M, Arima I, et al. Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-resistant Helicobacter pylori: a multicenter, prospective, randomized trial. Helicobacter 23: e12456, 2018.
44. Asaka M, Sugiyama T, Kato M, et al. A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of Helicobacter pylori in Japanese peptic ulcer patients. Helicobacter 6: 254-261, 2001.
45. Sakurai Y, Shino M, Okamoto H, Nishimura A, Nakamura K, Hasegawa S. Pharmacokinetics and safety of triple therapy with vonoprazan, amoxicillin, and clarithromycin or metronidazole: a phase I, open-label, randomized, crossover study. Adv Ther 33: 1519-1535, 2016.
46. Erh PO, Goddard AF, Barrett DA, Shaw PN, Spiller RC. The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection. J Antimicrob Chemother 39: 5-12, 1997.
47. Takeda Pharmaceutical Company Limited. Takecad® 10mg/20mg Interview Form [Internet]. [cited 2018 Nov 1]. Available from: http://www.takedamed.com/mcm/medicine/download.jsp?id=162&type=INTERVIEW_FORM (in Japanese)
48. Sachs G, Meyer-Rosberg K, Scott DR, Melchers K. Acid, protons and Helicobacter pylori. Yale J Biol Med 69: 301-316, 1996.
49. Scott D, Weeks D, Melchers K, Sachs G. The life and death of Helicobacter pylori. Gut 43 (Suppl 1): S56-S60, 1998.
50. Sachs G, Scott DR, Wen Y. Gastric infection by Helicobacter pylori. Curr Gastroenterol Rep 13: 540-546, 2011.
51. Furuta T, Shirai N, Takashima M, et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 69: 158-168, 2001.
52. Sugimoto M, Furuta T, Shirai N, et al. Evidence that the degree and duration of acid suppression are related to Helicobacter pylori eradication by triple therapy. Helicobacter 12: 317-323, 2007.
53. Yamasaki H, Kawaguchi N, Nonaka M, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker. Xenobiotica 47: 1027-1034, 2017.
54. Sugimoto M, Ban H, Hira D, et al. Letter: CYP3A4/5 genotype status and outcome of vonoprazan-containing Helicobacter pylori eradication therapy in Japan. Aliment Pharmacol Ther 45: 1009-1010, 2017.
55. Okamura T, Suga T, Nagaya T, et al. Antimicrobial resistance and characteristics of eradication therapy of Helicobacter pylori in Japan: a multi-generational comparison. Helicobacter 19: 214-220, 2014.
56. Graham DY, Fischbach L. Helicobacter pylori treatment in the era
of increasing antibiotic resistance. Gut 59: 1143-1153, 2010.
57. Yanai A, Sakamoto K, Akanuma M, Ogura K, Maeda S. Non-bismuth quadruple therapy for first-line *Helicobacter pylori* eradication: a randomized study in Japan. World J Gastrointest Pharmacol Ther 3: 1-6, 2012.
58. Okada M, Nishimura H, Kawashima M, et al. A new quadruple therapy for *Helicobacter pylori*: influence of resistant strains on treatment outcome. Aliment Pharmacol Ther 13: 769-774, 1999.
59. Okada M, Oki K, Shirotani T, et al. A new quadruple therapy for the eradication of *Helicobacter pylori*. Effect of pretreatment with omeprazole on the cure rate. J Gastroenterol 33: 640-645, 1998.
60. Koizumi W, Tanabe S, Nakatani K, et al. Quadruple therapy with ecabet sodium, omeprazole, amoxicillin and metronidazole is effective for eradication of *Helicobacter pylori* after failure of first-line therapy (KDOG0201 Study). J Clin Pharm Ther 35: 303-307, 2010.
61. Nagahara A, Miwa H, Ogawa K, et al. Addition of metronidazole to rabeprazole-amoxicillin-clarithromycin regimen for *Helicobacter pylori* infection provides an excellent cure rate with five-day therapy. Helicobacter 5: 88-93, 2000.
62. Nagahara A, Miwa H, Yamada T, Kurosawa A, Ohkura R, Sato N. Five-day proton pump inhibitor-based quadruple therapy regimen is more effective than 7-day triple therapy regimen for *Helicobacter pylori* infection. Aliment Pharmacol Ther 15: 417-421, 2001.
63. Ueki N, Miyake K, Kusunoki M, et al. Impact of quadruple regimen of clarithromycin added to metronidazole-containing triple therapy against *Helicobacter pylori* infection following clarithromycin-containing triple-therapy failure. Helicobacter 14: 91-99, 2009.
64. Asaka M. A new approach for elimination of gastric cancer deaths in Japan. Int J Cancer 132: 1272-1276, 2013.
65. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. Cochrane Database Syst Rev 2013 (Epub ahead of print).

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).