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【 REVIEW ARTICLE 】

Efficacy of Vonoprazan for *Helicobacter pylori* Eradication

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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)

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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-

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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 therapeutic 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.

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

References	Study design	Triple therapy regimen		Eradication rate (95% CI)				Adverse events (discontinuation)	
		Vonoprazan	PPI	Vonoprazan		PPI			
				ITT/FAS	PP	ITT/FAS	PP	Vonoprazan	PPI
(24)	Prospective, non-randomized, open-label, multicenter	VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=1,688	RPZ 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 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=98	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 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 (2 dropouts)	NA (2 dropouts)
(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	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 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 11%, RPZ 6%, EPZ 3% (NA)

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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	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)
		VPZ 20 mg + AMX 750 mg + CAM 200 or 400 mg, twice-daily, 7 days, n=41 [CAM-resistant *H. pylori*]		82.9% (67.9-92.8)	82.9% (67.9-92.8)				
(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), RPZ 79.8% (76.1-83.5), EPZ 81.3% (74.4-88.2)	LPZ 85.6% (80.5-90.6), RPZ 86.1% (82.8-89.4), EPZ 88.5% (82.6-94.4)	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

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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

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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	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% (88.9-99.2)	NA	LPZ 89.5% (78.5-96.0), RPZ 95.8% (78.5-99.9), EPZ 88.5% (80.7-93.9)	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.

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