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ORIGINAL ARTICLE

Retrospective Cohort Study

Usefulness of vonoprazan, a potassium ion-competitive acid blocker, for primary eradication of *Helicobacter pylori*

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Abstract

AIM

To investigate usefulness of triple therapy with vonoprazan, a potassium ion-competitive acid blocker and antibiotics, for *Helicobacter pylori* (*H. pylori*) eradication.

METHODS

The *H. pylori* eradication rate was examined in 2507 patients (2055 undergoing primary eradication and 452 undergoing secondary eradication, excluding patients with subtotal gastrectomy) at the Japanese Red Cross Kyoto Daiichi Hospital from March 2013 to September 2015. For patients treated from March 2013 to February 2015, a proton pump inhibitor (PPI) was used to reduce acid secretion, while vonoprazan was used after March 2015. The success rates of the 2 regimens (PPI + amoxicillin + clarithromycin/metronidazole, or vonoprazan + amoxicillin + clarithromycin/metronidazole) were compared.

RESULTS

The success rate of primary *H. pylori* eradication was significantly higher in the vonoprazan group. When stratified by the underlying disease, a significant increase of the *H. pylori* eradication rate was observed in patients with chronic gastritis. A significantly lower *H. pylori* eradication rate was observed in younger patients compared to older patients in the PPI group, but there was no difference according to age in the vonoprazan group. On the other

hand, the success rate of secondary eradication was similar at approximately 90% in both groups.

CONCLUSION

Vonoprazan is very useful for primary eradication of *H. pylori*, and may become a first-line acid secretion inhibitor instead of PPIs.

Key words: *Helicobacter pylori*; Eradication; Vonoprazan; Chronic gastritis; Potassium ion-competitive acid blocker

Core tip: Use of vonoprazan, a potassium ion-competitive acid blocker, is expected to achieve a higher eradication rate than conventional triple therapy. The success rates of the 2 regimens (use of proton pump inhibitor *vs* vonoprazan) were compared. The success rate of primary *Helicobacter pylori* (*H. pylori*) eradication was significantly higher in the vonoprazan group. When stratified by the underlying disease, a significant increase of the *H. pylori* eradication rate was observed in patients with chronic gastritis. Vonoprazan is very useful for primary eradication of *H. pylori*, and may become a first-line acid secretion inhibitor instead of proton pump inhibitors.

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INTRODUCTION

Since *Helicobacter pylori* (*H. pylori*) eradication therapy for chronic gastritis was approved for insurance cover in February 2013 in Japan, the number of patients undergoing eradication of *H. pylori* has greatly increased. In September 2014, the International Agency for Research of Cancer (IARC) reported that 80% of stomach cancer is caused by *H. pylori* infection, and the incidence of stomach cancer can be reduced by 30%-40% through *H. pylori* eradication[1]. However, the success rate of bacterial eradication by conventional primary triple therapy, involving the administration of a proton pump inhibitor (PPI) + amoxicillin (AMPC) + clarithromycin (CAM) for 1 wk, has steadily declined due to an increase of CAM resistance[2]. On the other hand, it is reported that secondary eradication therapy using metronidazole (MNZ) has a success rate exceeding 90%[3-7]. Reports about carcinogenicity of MNZ have appeared (although the risk is low)[8], and there is the possibility of resistance increasing due to its increased use in the near future. Consequently, development of new primary eradication therapy is desired.

Vonoprazan, a potassium ion-competitive acid blocker (P-CAB), was launched in Japan in February 2015 before its release on the world market[9]. Use of vonoprazan is expected to achieve a higher eradication rate than conventional triple therapy due to its strong inhibitory effect on gastric acid secretion[10,11]. Against this background, the current study aimed at evaluating the usefulness of triple therapy containing P-CAB compared with 7-d PPI-based triple therapy.

MATERIALS AND METHODS

This study is a retrospective analysis of prospectively collected data comparing outcomes of patients received *H. pylori* eradiation therapy by vonoprazan from March to September 2015 against a historical cohort of patient by a proton pump inhibitor (PPI) carried out from March 2013 to February 2015.

The subjects were 2507 patients (2055 undergoing primary eradication and 452 undergoing secondary eradication, excluding patients with subtotal gastrectomy) who tested positive for *H. pylori* at the Gastroenterology Department of the Japanese Red Cross Kyoto Daiichi Hospital from March 2013 to September 2015. In patients treated from March 2013 to February 2015, a PPI was used to inhibit gastric acid secretion, while vonoprazan was used for patients treated after March 2015. Patients were received 7-d course of triple therapy with amoxicillin 1500 mg and clarithromycin 400 mg plus lansoprazole 60 mg, esomeprazole 40 mg, rabeprazole 20 mg, or vonoprazan 40 mg as first-line treatment, and 7-d course of triple therapy with amoxicillin 1500 mg and metronidazole 500 mg plus lansoprazole 60 mg, esomeprazole 40 mg, rabeprazole 20 mg, or vonoprazan 40 mg as second-line treatment. Success rate was compared between the 2 *H. pylori* eradication methods.

Before starting the eradication therapy, patients underwent a medical interview concerning their drug allergy. Adverse effect was evaluated after eradication therapy by a medical interview.

The presence of *H. pylori* infection was confirmed by a positive result in any of the following tests: Urea breath test (n = 52), rapid urease test (n = 668), serum *H. pylori* IgG antibody (n = 1074), fecal *H. pylori* antigen (n = 7), and microscopy (n = 254). Eradication effect was confirmed by performing the urea breath test at two months after treatment, using a cut-off of 2.5‰. We did not investigate the strains and levels of resistance of *H. pylori* to the antimicrobial drugs planned to administer.

Patients who received eradication therapy were divided into a group treated with a PPI (lansoprazole, omeprazole, rabeprazole, or esomeprazole) and a group treated with vonoprazan, and success rates were compared, including the success rates stratified according to gender, age, and underlying disease.

The study protocol was approved by the Ethics Committee of Japanese Red Cross Kyoto Daiichi Hospital and was conducted in compliance with the Helsinki Declaration.

Table 1 Patient profile of primary eradication therapy

	PPI group	Vonoprazan group
Average age	62.8 (18-94)	62.7 (22-89)
Gender (male:female)	902:818	170:165
PPI		
Lansoprazole	1206	
Omeprazole	0	
Rabeprazole	62	
Esomeprazole	452	
Underlying disease		
Chronic gastritis	1362	255
Peptic ulcer	248	55
After endoscopic therapy for early gastric cancer	107	25
Other	3	0

PPI: Proton pump inhibitor.

Table 2 Patient profile of secondary eradication therapy

	PPI group	Vonoprazan group
Average age	62.3 (19-96)	63.6 (39-89)
Gender(male:female)	182:204	28:38
PPI		
Lansoprazole	266	
Omeprazole	1	
Rabeprazole	32	
Esomeprazole	87	
Underlying disease		
Chronic gastritis	313	48
Peptic ulcer	44	8
After endoscopic therapy for early gastric cancer	28	10
Other	1	0

PPI: Proton pump inhibitor.

For statistical analysis, the χ^2 test and Fischer's exact probability test were used, and significance was accepted at $P < 0.05$. All analyses were performed using the program GraphPad Prism 4 (GraphPad Soft ware, San Diego, CA).

RESULTS

Patient profile

Among the 2055 patients receiving primary eradication therapy, a PPI was used in 1720 and vonoprazan was used in 335. Lansoprazole was the PPI most commonly used to inhibit acid secretion (1206 patients), followed by esomeprazole and rabeprazole. Omeprazole was not used. In both the PPI group and the vonoprazan group, chronic gastritis was the underlying disease in more than 75% of the patients, followed by peptic ulcer and endoscopic therapy (Table 1).

Among the 452 patients receiving secondary eradication therapy, a PPI was used in 386 and vonoprazan was used in 66. The trends for PPI use and underlying cause were similar to those in the primary eradication group (Table 2).

Table 3 Results of eradication therapy

	PPI group	Vonoprazan group	*P* value
Primary eradication therapy			
ITT analysis	73.2% (1259/1720)	85.7% (287/335)	< 0.0001
PP analysis	76.4% (1259/1647)	90.3% (287/318)	< 0.0001
Secondary eradication therapy			
ITT analysis	89.9% (347/386)	89.4% (59/66)	0.87
PP analysis	92.8% (347/374)	96.7% (59/61)	0.4

PPI: Proton pump inhibitor.

Success rate of H. pylori eradication therapy

Regarding the success rate of primary eradication therapy in the PPI group, it was 73.2% by ITT analysis and 76.4% by PP analysis, while it was 85.7% by ITT analysis and 90.3% by PP analysis in the vonoprazan group. The *H. pylori* eradication success rate was significantly higher in the vonoprazan group by both ITT analysis and PP analysis.

Regarding the success rate of secondary eradication therapy in the PPI group, it was 89.9% by ITT analysis and 92.8% by PP analysis, while it was 89.4% by ITT analysis and 96.7% by PP analysis in the vonoprazan group, with no significant difference between the 2 groups (Table 3).

Success rate and underlying disease

In patients with chronic gastritis undergoing primary eradication therapy, a significantly higher success rate was observed in the vonoprazan group than the PPI group by both ITT analysis (86.7%) and PP analysis (90.6%). In patients with peptic ulcer undergoing primary eradication, the success rate was also higher in the vonoprazan group, but no significant difference was observed compared to the PPI group. In patients undergoing primary eradication after endoscopic therapy for early gastric cancer, there was little difference of the success rate between the PPI group and the vonoprazan group (Table 4). In patients undergoing secondary eradication, the PPI group and the vonoprazan group showed no differences of the success rate in relation to underlying diseases (Table 5).

Success rate and gender or age

No difference of the success rate according to gender was observed in either the PPI group or the vonoprazan group. Patients younger than 50 years were defined as younger and those older than 50 years were defined as older, and the success rates in both age groups were examined for PPI and vonoprazan therapy. In the PPI group, the success rate was significantly lower in younger patients, but there was no difference of the success rate based on age in the vonoprazan group (Table 6).

Table 4 Success rate and underlying disease: Primary eradication therapy

		PPI group	Vonoprazan group	*P* value
Chronic gastritis	ITT analysis	72.5% (988/1362)	86.7% (221/255)	< 0.0001
	PP analysis	75.1% (988/1316)	90.6% (221/244)	< 0.0001
Peptic ulcer	ITT analysis	75.4% (187/248)	83.6% (46/55)	0.22
	PP analysis	82.7% (187/226)	93.9% (46/49)	0.051
After endoscopic therapy for early gastric cancer	ITT analysis	76.6% (82/107)	80% (20/25)	0.8
	PP analysis	78.1% (82/105)	80% (20/25)	1

PPI: Proton pump inhibitor.

Table 5 Success rate and underlying disease: Secondary eradication therapy

		PPI group	Vonoprazan group	*P* value
Chronic gastritis	ITT analysis	91.5% (292/319)	89.6% (43/48)	0.59
	PP analysis	93.9% (292/311)	100% (43/43)	0.15
Peptic ulcer	ITT analysis	86.4% (38/44)	100% (8/8)	0.57
	PP analysis	95.0% (38/40)	100% (8/8)	1
After endoscopic therapy for early gastric cancer	ITT analysis	78.6% (22/28)	80% (8/10)	1
	PP analysis	78.6% (22/28)	80% (8/10)	1

PPI: Proton pump inhibitor.

Table 6 Success rate and age: Primary eradication therapy

		Younger than 50 yr	Older than 50 yr	*P* value
PPI group	ITT analysis	67.8% (185/273)	74.3% (1074/1446)	0.03
	PP analysis	72.3% (185/256)	77.2% (1074/1391)	0.09
Vonoprazan group	ITT analysis	84.8% (50/59)	86.2% (238/276)	0.84
	PP analysis	92.6% (50/54)	90.2% (238/264)	0.8

PPI: Proton pump inhibitor.

Adverse events

In the PPI group, 7 patients (0.4%) discontinued treatment due to adverse events during primary eradication therapy, including 2 cases of diarrhea, 4 cases of rash, and 1 other event. Two patients (0.5%) from the PPI group discontinued secondary eradication therapy, including 1 case of diarrhea and 1 other event. No cases of discontinuation of treatment due to adverse events were observed in the vonoprazan group. The incidence of major adverse effect such as diarrhea, dysgeusia and skin rash showed no difference between the two groups. No specific adverse effect was observed in the vonoprazan group.

DISCUSSION

In this investigation, the success rate of primary *H. pylori* eradication therapy was significantly higher in the vonoprazan group, and vonoprazan treatment achieved a significantly higher success rate in patients with chronic gastritis. In the PPI group, the success rate of *H. pylori* eradication therapy was significantly lower for younger patients than for older patients, but no difference related to age was observed in the vonoprazan group. On the other hand, the success rate of secondary *H. pylori* eradication therapy was similar (Approximately 90%) in the PPI group and the vonoprazan group.

Vonoprazan is a new potassium ion-competitive acid blocker, which is stable in an acid environment, and shows rapid and potent inhibition of gastric acid secretion[9]. Vonoprazan is instantly protonated in an acidic and even in a neutral environment, and is suggested to bind to and inhibit H^+,K^+-ATPase in the

protonated form[9]. Insufficient inhibition of gastric acid secretion has previously been reported to cause failure of *H. pylori* eradication[12]. Vonoprazan has been reported to rapidly increase the gastric pH for an extended period from the initial day of administration[10,11]. In this study, the success rate for young patients was much higher than that for older patients in the vonoprazan group. From these results, it can be inferred that the success rate of primary *H. pylori* eradication therapy was increased in the vonoprazan group due to vonoprazan improving the antibacterial activity of the antibiotics used in combination. In addition, the enzyme involved in metabolism of vonoprazan is another possible reason. The gene polymorphism of the liver enzyme cytochrome P450 (CYP) 2C19 affects the metabolic rate and the acid inhibitory effect of PPIs. However, vonoprazan is mainly metabolized in the liver by CYP3A4[12]. Therefore, vonoprazan exerts a potent inhibitory activity regardless of CYP2C19 polymorphism. CAM, which is used in primary *H. pylori* eradication therapy, is also metabolized by CYP3A4[13], and the $AUC_{0\text{-}12}$ and Cmax of vonoprazan are reported to be respectively increased 1.5 times and 1.6 times during combined administration of AMPC, CAM, and vonoprazan compared with single-agent administration[14]. In the present study, the success rate showed a significant increase with primary *H. pylori* eradication therapy, suggesting that the interaction of vonoprazan and CAM promoted the action of both agents. However, a smaller population was examined for secondary eradication therapy, so collection of more cases is needed in the future.

Moreover, regarding the *H. pylori* eradication rate in relation to the underlying disease in the vonoprazan group, a significantly higher success rate was seen in patients with chronic gastritis. While a similar trend to that for chronic gastritis was also observed for peptic ulcer, an almost equal *H. pylori* eradication rate was observed in the vonoprazan and PPI groups among patients treated after endoscopic therapy. Further investigation is also needed to determine if the difference in the eradication rate by underlying disease was due to the small number of subjects, host factors, or bacterial factors. In this study, we demonstrated that vonoprazan was very useful for primary eradication of *H. pylori.* However, the success rate of secondary *H. pylori* eradication therapy had no difference in the PPI group and the vonoprazan group. MNZ based conventional triple therapy has sufficiently high eradication success rate in Japan[3-7]. It has been reported that sufficient acid inhibition during eradication was more important in CAM based regimen than MNZ[15]. Therefore, we could not show the difference in secondary eradication therapy between the PPI group and the vonoprazan group.

Our study has some limitations. Although we used historical controls in the same institute, this was a retrospective study at a single center. Second, adverse effect was not precisely evaluated because we could not track patients who were not confirmed the effect of eradication therapy. Therefore, important events during the eradication therapy might have been lost. Although Murakami *et al*[16] reported that no marked differences were observed in adverse effects between the vonoprazan and the PPI group, Suzuki *et al*[17] indicated that the incidence of skin rash was significantly higher with vonoprazan therapy than with PPI therapy. Further investigation will be needed to clarify the adverse effect of vonoparazan in *H. pylori* eradication therapy. Third, factors which may affect success rate of *H. pylori* eradication therapy, such as alcohol, smoking, or the use of other medications were not recorded in the patients.

Despite these limitations, the results obtained were comparable to the *H. pylori* eradication rate at the time when vonoprazan was approved for patients with healed gastroduodenal ulcers[16], and the incidence of adverse events was similar to that with conventional eradication therapy using PPIs. In the future, *H. pylori* eradication therapy using the three-agent combination of AMPC, CAM, and vonoprazan may possibly become a first-line option.

In conclusion, vonoprazan is considered to be useful for triple therapy aimed at primary *H. pylori* eradication, and the possibility of using vonoprazan as first-line treatment to inhibit acid secretion instead of PPIs was suggested. For secondary eradication therapy, further investigation is needed to determine if the success rate is higher than that achieved with PPIs.

COMMENTS

Background

The International Agency for Research of Cancer reported that 80% of stomach cancer is caused by *Helicobacter pylori* (*H. pylori*) infection, and the incidence of stomach cancer can be reduced by 30%-40% through *H. pylori* eradication. Consequently, development of new primary eradication therapy is desired.

Research frontiers

The authors' group pioneered a novel primary eradication therapy for *H. pylori*, using vonoprazan. The number of patients undergoing eradication of *H. pylori* has greatly increased. However, the success rate of bacterial eradication by conventional primary triple therapy has steadily declined due to an increase of clarithromycin (CAM) resistance.

Innovations and breakthroughs

The success rate of bacterial eradication by conventional primary triple therapy, involving the administration of a proton pump inhibitor (PPI) + amoxicillin (AMPC) + CAM for 1 wk, has steadily declined due to an increase of CAM resistance. However, use of vonoprazan achieved a higher eradication rate than conventional triple therapy due to its strong inhibitory effect on gastric acid secretion.

Applications

Vonoprazan is considered to be useful for triple therapy aimed at primary *H. pylori* eradication, and the possibility of using vonoprazan as first-line treatment to inhibit acid secretion instead of PPIs was suggested.

Terminology

Vonoprazan is a novel oral potassium-competitive acid blocker, which is stable in an acid environment, and shows rapid and potent inhibition of gastric acid secretion.

Peer-review

The authors concluded that vonoprazan therapy for *H. pylori* eradication may be advantageous over those utilizing PPIs. The paper is well written, and the possible advantageous mechanism of vonoprazan action is adequately explored in the Discussion. Therefore, the paper should be of interest to the readership of the Journal.

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