

Vonoprazan improves the efficacy of *Helicobacter pylori* eradication therapy with a regimen consisting of clarithromycin and metronidazole in patients allergic to penicillin

Shoko Ono¹ | Mototsugu Kato² | Soichi Nakagawa³ | Katsuhiro Mabe² | Naoya Sakamoto³

¹Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan

²Department of Gastroenterology, National Hospital Organization Hakodate Hospital, Hakodate, Japan

³Department of Gastroenterology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence

Shoko Ono, Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan.
Email: onosho@med.hokudai.ac.jp

Abstract

Background: Although all *Helicobacter pylori* (*H. pylori*)-positive patients should receive eradication therapy, the therapy is a challenge for patients allergic to penicillin. There have been a few reports on the efficacy of eradication therapy for such patients.

Objective: To analyze the efficacy of vonoprazan or proton pump inhibitor (PPI)-based 7-day triple therapy in patients allergic to penicillin.

Materials and Methods: A total of 88 consecutive patients allergic to penicillin who received *H. pylori* eradication therapy were retrospectively analyzed. Thirty-one patients had a history of failed eradication therapy. Four 7-day regimens were prescribed during the study period: clarithromycin-metronidazole-PPI (13 patients), clarithromycin-metronidazole-vonoprazan (14 patients), metronidazole-sitafloxacin-PPI (44 patients) and metronidazole-sitafloxacin-vonoprazan (17 patients). A ¹³C-urea breath test was used for confirmation of eradication, and efficacy of eradication was evaluated by "intention-to-treat" analysis and "per-protocol" analysis.

Results: Intention-to-treat and per-protocol eradication rates were 46.2%/54.6% for patients who received clarithromycin-metronidazole-PPI, 92.9%/92.9% for patients who received clarithromycin-metronidazole-vonoprazan, 100%/100% for patients who received metronidazole-sitafloxacin-PPI and 88.2%/93.8% for patients who received metronidazole-sitafloxacin-vonoprazan. For first eradication, vonoprazan significantly raised the intention-to-treat efficacy of the triple therapy including clarithromycin-metronidazole (vonoprazan: 92.9%, PPI: 46.2%, $P=.0128$). A 7-day regimen consisting of metronidazole and sitafloxacin was effective for patients allergic to penicillin with or without past failure of eradication.

Conclusion: For first eradication in patients allergic to penicillin, a 7-day triple therapy consisting of clarithromycin, metronidazole and vonoprazan could be a candidate eradication regimen.

KEYWORDS

eradication therapy, *Helicobacter pylori*, penicillin allergy, vonoprazan

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) was declared a human carcinogen in 1994, and *H. pylori* screening and treatment programs in all countries are recommended by the International Agency for Research on Cancer Working Group.^{1,2} The Kyoto global consensus report in 2015 stated that all *H. pylori*-positive individuals should receive eradication therapy; however, eradication is a challenge in some patients.³ Penicillin allergy is the most common drug allergy and occurs in about 3%-7% of Japanese and 8% of Americans.^{4,5} Although amoxicillin (AMX) is one of the most effective antibiotics against *H. pylori*, AMX-based regimens cannot be used in such patients. Instead of regimens including AMX, a proton-pump inhibitor (PPI)-based triple therapy with metronidazole (MTZ) and clarithromycin (CLR) or sitafloxacin (STX) or tetracycline (TC) and a bismuth-containing quadruple therapy (PPI-bismuth-TC-MTZ) were recommended in previous reports.⁶⁻⁸ However, the Japanese government insurance does not cover STX, TC, and bismuth for *H. pylori* eradication, and increase in CLR-resistant *H. pylori* is problematic.⁹

Vonoprazan (VPZ) is a novel potassium-competitive blocker and inhibits gastric H^+K^+ -ATPase, and it is more advantageous than PPIs in the speed and strength of the acid-inhibitory effect.¹⁰ Recently, there have been some reports about the effectiveness of VPZ for eradication of *H. pylori* including CLR-resistant strains.¹¹⁻¹³ Therefore, we conducted a pilot study on *H. pylori* eradication therapy using a regimen with CLR, MTZ, and VPZ for patients allergic to penicillin.

2 | PATIENTS AND METHODS

2.1 | Patients

A total of 90 patients (14 men and 76 women, mean age of 59 years) allergic to penicillin who received *H. pylori* eradication therapy from March 2009 to July 2016 were retrospectively analyzed. All of the patients received esophagogastroduodenoscopy (EGD) before visiting our institution, including patients with gastric and/or duodenal ulcers (n=16), gastric polyp (n=5), and gastritis only (n=69). Of the 90 patients, 27 patients (30%) experienced an allergic reaction during past *H. pylori* eradication therapy that included AMX. The remaining 63 patients (70%) were diagnosed as being allergic to past penicillin derivatives. Furthermore, four patients received eradication therapy with regimens that did not include AMX and the eradication therapy failed.

2.2 | *H. pylori* tests

A ¹³C-urea breath test (Ubit[®], Otsuka Pharmaceutical, Tokyo, Japan) was used for diagnosis of *H. pylori* infection before and more than 8 weeks after the completion of eradication treatment. The cutoff value was 2.5‰.

2.3 | Eradication regimens

VPZ has been available since March 2015 in our institution, and PPIs were changed to VPZ after became available. The following four

TABLE 1 Doses of drugs prescribed in the eradication regimens

Drugs	Dose
Proton-pump inhibitors (PPIs)	
Lansoprazole	30 mg b.i.d. ^a
Rabeprazole	20 mg b.i.d.
Vonoprazan (VPZ)	20 mg b.i.d.
Clarithromycin (CLR)	200 mg b.i.d
Metronidazole (MTZ)	250 mg b.i.d.
Sitafloxacin (STX)	100 mg b.i.d.

^ab.i.d., bis in die.

7-day regimens were prescribed within the study period: (1) CLR-MTZ-PPI, (2) CLR-MTZ-VPZ, (3) MTZ-STX-PPI, and (4) MTZ-STX-VPZ. Doses of the drugs used are summarized in Table 1. Generally, the combination of MTZ and STX was prescribed for patients who previously received eradication therapy. For eradication in naive patients, selection of the regimen depended on the doctor who interviewed the patient.

2.4 | Measured outcome parameters

Analysis of *H. pylori* eradication efficacy was performed on an "intention-to-treat (ITT)" basis and on a "per-protocol (PP)" basis. Compliance with therapy and adverse events were determined with a questionnaire at the time of judgment of *H. pylori* eradication. Mean values were calculated for continuous variables, and percentages were provided for categorical data. Categorical data were compared using Fisher's exact test, and numerical data were compared using Student's *t* test. A *P* value of <.05 in each analysis was considered statistically significant.

The study was approved by the Ethics Committee of Hokkaido University Hospital (approval number 015-0457).

3 | RESULTS

Of the 90 patients, two patients did not wish to receive *H. pylori* eradication therapy after a medical interview. The remaining patients were prescribed the following medication: (1) CLR-MTZ-PPI for 13 patients, (2) CLR-MTZ-VPZ for 14 patients, (3) MTZ-STX-PPI for 44 patients, and (4) MTZ-STX-VPZ for 17 patients. Characteristics of the patients according to regimens are shown in Table 2. In the MTZ-STX-PPI group, the percentage of patients who had a history of *H. pylori* eradication therapy was significantly higher than the percentages in other groups (*P*=.0011). There were only four patients who completed eradication therapy using regimens different from AMX-CLR-PPI, but for whom eradication therapy failed.

A flow diagram for treatment of patients is shown in Figure 1. One patient discontinued the medication due to skin eruption and two patients did not visit for judgment of eradication. Compliance with the protocol was 100% from the questionnaire. The efficacy

TABLE 2 Characteristics of patients

	(a) CLR/MTZ/PPI	(b) CLR/MTZ/VPZ	(c) MTZ/STX/PPI	(d) MTZ/STX/VPZ
n	13	14	44	17
Age, mean, y	58.0	62.4	57.8	61.8
Gender (M/F)	2: 11	2: 12	8: 36	2: 15
Height, mean, cm	154.3	154.0	158.0	153.3
Body weight, mean, kg	56.3	52.8	54.6	54.5
Having history of eradication, n (%)	3 (23.1)	1 (7.1)	24 ^a (54.5)	3 (17.6)

CLR, clarithromycin; MTZ, metronidazole; PPI, proton-pump inhibitor; VPZ, vonoprazan; STX, sitafloxacin.

^a $P < .01$ (MTZ/STX/PPI vs CLR/MTZ/PPI, CLR/MTZ/VPZ and MTZ/STX/VPZ).

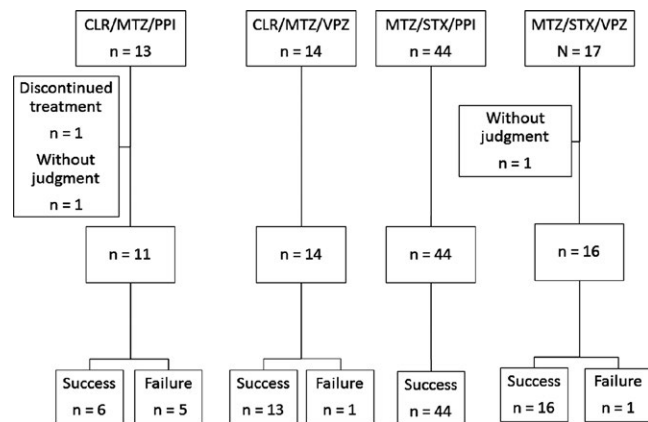


FIGURE 1 Flow diagram of treatment for patients. In the clarithromycin-metronidazole-PPI group, one patient discontinued treatment due to skin eruption. The overall eradication rate in per-protocol analysis was 91.8% (78/85). CLR, clarithromycin; MTZ, metronidazole; PPI, proton-pump inhibitor; VPZ, vonoprazan; STX, sitafloxacin

and safety of *H. pylori* eradication therapy for the patients allergic to penicillin is shown in Table 3. ITT and PP eradication rates with (1) CLR-MTZ-PPI were 46.2% and 54.6%, respectively, and those with (2) CLR-MTZ-VPZ were significantly higher (92.9%, vs CLR-MTZ-PPI, PP: $P = .0561$, ITT: $P = .0128$). On the other hand, there were no significant differences in efficacy between (c) MTZ-STX-PPI and (d) MTZ-STX-VPZ. In six patients in whom first-line eradication with the combination of CLR and MTZ failed, 2nd-line eradication with MTZ-STX was successful.

Adverse events were observed in 13 patients (14.8%). Major events were diarrhea and soft stools and severe adverse events that needed medication occurred in three patients (skin eruption $n = 2$, bloody stool $n = 1$).

Table 4 shows the history of *H. pylori* eradication therapy and the efficacy of eradication. For first-line therapy, the eradication rate of (1) CLR-MTZ-PPI was significantly lower than that of other regimens (ITT: $P = .0009$, PP: $P = .0078$). Furthermore, (3) MTZ-STX-PPI and (4) MTZ-STX-VPZ were effective for patients allergic to penicillin with or without past eradication failure.

4 | DISCUSSION

The Maastricht V Florence Consensus Report stated that only regimens that reliably produce eradication rates of $\geq 90\%$ in any region should be used.¹⁴ The rates of *H. pylori* resistance to antibiotics are increasing in many countries, and the rates of successful eradication rates of *H. pylori* have been concordantly declining.¹⁵ In particular, CLR resistance has been rapidly increasing in many countries and the resistance rate in Japan is about 30%.¹⁶ CLR susceptibility testing in a population or region with documented high CLR resistance is recommended before a standard first-line CLR-based treatment.¹⁴

The Japanese government insurance has allowed first-line (PPI-AMX-CLR) and second-line (PPI-AMX-MTZ) eradication therapy. The eradication rate using traditional first-line therapy is low (70%) due to the increase in CLR resistance.^{11,17,18} Fortunately, MTZ-resistant *H. pylori* has not been increasing, and the eradication rate of second-line treatment using a PPI-AMX-MTZ regimen therefore remains high.¹⁹ VPZ has been available for *H. pylori* eradication since 2015, and the efficacy of first-line eradication therapy in Japan has dramatically improved. Recently, Murakami et al. reported superior efficacy of 7-day triple therapy with VPZ in combination with CLR and AMX and also reported that the eradication rate for patients infected with CLR-resistant strains was surprisingly high.¹¹ Although its mechanism is unclear, the rapid and potent gastric acid-inhibitory effect of VPZ would provide a good environment for effective antibacterial action.

For eradication therapy in patients allergic to penicillin, a PPI-CLR-MTZ regimen in areas of low CLR resistance and a PPI-bismuth-tetracycline-MTZ regimen in areas of high CLR resistance are recommended in the Maastricht V/Florence Consensus Report.¹⁴ Our data showed that the eradication rate using a combination of CLR and MTZ with a PPI was only 54.6% (PP), which is not acceptable. Gisbert et al. reported that the eradication rate of a 7-day regimen using these antibiotics with PPIs for patients allergic to penicillin was 59%, similar to the rate in our study.⁸ However, these eradication rates were lower than those in previous studies on first-line therapy with CLR-MTZ-PPIs, and the percentage of CAM-resistant strains in patients allergic to penicillin may be higher than that in the general population. Unfortunately, we could not determine the presence of CLR resistance

TABLE 3 Efficacy and safety of *H. pylori* eradication therapy according to the regimens in patients allergic to penicillin

	(a) CLR/MTZ/PPI	(b) CLR/MTZ/VPZ	(c) MTZ/STX/PPI	(d) MTZ/STX/VPZ
n	13	14	44	17
Eradication rate (ITT ^a), %	46.2 ^c (6/13)	92.9 (13/14)	100 (44/44)	88.2 (15/17)
Eradication rate (PP ^b), %	54.6 ^d (6/11)	92.9 ^e (13/14)	100 (44/44)	93.8 (15/16)
Severe adverse events, %	7.7 (1/13)	0 (0/14)	2.3 (1/44)	5.9 (1/17)

CLR, clarithromycin; MTZ, metronidazole; PPI, proton-pump inhibitor; VPZ, vonoprazan; STX, sitafloxacin.

^aITT: intention-to-treat.

^bPP, per-protocol.

^cP<.0001 (CLR/MTZ/PPI vs CLR/MTZ/VPZ, MTZ/STX/PPI, MTZ/STX/VPZ).

^dP<.0001 (CLR/MTZ/PPI vs CLR/MTZ/VPZ, MTZ/STX/PPI, MTZ/STX/VPZ).

^eP=.0128 (CLR/MTZ/VPZ vs CLR/MTZ/PPI).

	(a) CLR/MTZ/PPI	(b) CLR/MTZ/VPZ	(c) MTZ/STX/PPI	(d) MTZ/STX/VPZ
n	13	14	44	17
First line				
ITT ^a (%)	5/10 ^c (50.0)	12/13 (92.3)	20/20 (100)	13/14 (92.9)
PP ^b (%)	5/9 ^d (55.6)	12/13 (92.3)	20/20 (100)	13/13 (100)
Second- or third line				
ITT and PP (%)	1/3 ^e (33.3)	1/1 (100)	24/24 (100)	2/3 (66.7)

CLR, clarithromycin; MTZ, metronidazole; PPI, proton-pump inhibitor; VPZ, vonoprazan; STX, sitafloxacin.

^aITT, intention-to-treat.

^bPP, per-protocol.

^cP=.0009 (CLR/MTZ/PPI vs CLR/MTZ/VPZ, MTZ/STX/PPI, MTZ/STX/VPZ).

^dP=.0078 (CLR/MTZ/PPI vs CLR/MTZ/VPZ, MTZ/STX/PPI, MTZ/STX/VPZ).

^eP=.0017 (CLR/MTZ/VPZ vs CLR/MTZ/PPI).

TABLE 4 History of *H. pylori* eradication therapy and efficacy of eradication

in this study; however, VPZ significantly raised the efficacy of eradication therapy in the combination of CLR and MTZ and provided a high eradication rate.

Failure of eradication increases *H. pylori* resistant to antibiotics.²⁰ We selected regimens with the combination of MTZ and STX for patients allergic to penicillin for whom past eradication therapy failed, and the efficacy was excellent in our study. Furuta et al. reported the perfect eradication with a regimen of PPI-MTZ-STX for patients allergic to penicillin.⁷ STX-resistant *H. pylori* has not yet influenced the efficacy of eradication therapy in Japan.²¹ Although STX is still not covered by Japanese government insurance, the combination of MTZ and STX might to be prescribed to patients allergic to penicillin with failed past eradication therapy using regimens including CAM and frequently used macrolide.

The present study has several limitations. This was a retrospective pilot study with a small sample size. Furthermore, we did not perform CLR susceptibility testing in our patients. All future studies should have susceptibility testing for reduced treatment failures and less antibiotic resistance.

In conclusion, a VPZ-based 7-day triple therapy with the combination of CLR and MTZ could be a candidate eradication regimen especially for patients allergic to penicillin without a history of eradication therapy.

COMPETING INTERESTS

The authors have no competing interests.

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