**ORIGINAL ARTICLE**

**Helicobacter pylori** rescue treatment with vonoprazan, metronidazole, and sitafl oxacin in the presence of penicillin allergy

Soichiro Sue, Tomohiko Sasaki, Hiroaki Kaneko, Kuniyasu Irie, Masaaki Kondo and Shin Maeda

Department of Gastroenterology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

**Key words**

Helicobacter pylori, hypersensitivity, metronidazole, sitafl oxacin, vonoprazan.

Accepted for publication 5 January 2021.

**Correspondence**

Shin Maeda, Yokohama City University, Fukuura 3-9, Kanazawa-ku, Yokohama City, Kanagawa 236-0004, Japan.

Email: shinmaeda2-gi@umin.ac.jp

**Declaration of conflict of interest:** None of the authors has any conflict of interest.

**Author contribution:** Soichiro Sue and Shin Maeda contributed to the study concept and design. Soichiro Sue, Sasaki Tomohiko, Hiroaki Kaneko, Kuniyasu Irie, Masaaki Kondo, and Shin Maeda contributed to the data acquisition. Soichiro Sue and Shin Maeda contributed to the data analysis and interpretation. Soichiro Sue contributed to the drafting of the manuscript. Sasaki Tomohiko, Hiroaki Kaneko, and Shin Maeda contributed to the critical revision of the manuscript for important intellectual content. Soichiro Sue contributed to the statistical analysis. Shin Maeda obtained funding. Shin Maeda contributed to the study supervision.

**Funding support:** Yokohama City University

**Abstract**

**Background and Aim:** To assess the efficacy and safety of 7-day **Helicobacter pylori** rescue treatment consisting of a vonoprazan (VPZ), metronidazole (MNZ), and sitafl oxacin (STFX) regimen (VPZ-MNZ-STFX therapy) in patients with penicillin allergy.

**Methods:** This was a registered prospective intervention study. Patients with penicillin allergy who were diagnosed with **H. pylori** infection and had a history of **H. pylori** eradication were eligible for inclusion. Seventeen patients were prospectively treated with VPZ 20 mg bid, MNZ 250 mg bid, and STFX 100 mg bid for 7 days. Safety was evaluated using a questionnaire on adverse effects.

**Results:** The eradication rate of 7-day VPZ-MNZ-STFX therapy was 88.2% (95% confidence interval: 63.6–98.5%; n = 17) in both intention-to-treat and per-protocol analyses. On the questionnaire, 25% of patients reported experiencing diarrhea, with a score of 2 or 3. All patients undergoing VPZ-MNZ-STFX therapy completed 100% of their medication course.

**Conclusion:** Rescue **H. pylori** eradication with VPZ-MNZ-STFX therapy is effective and well tolerated in patients with penicillin allergy (UMIN000016335, jRCTs031180133).

**Introduction**

**Helicobacter pylori** eradication reduces the incidence of gastric cancer, and **H. pylori** eradication for all baseline risk levels is recommended by the World Health Organization. In patients with penicillin allergy, **H. pylori** eradication is performed without amoxicillin (AMPC). In February 2015 (i.e. at the start of this study), vonoprazan (VPZ) was approved in Japan for **H. pylori** eradication, and several studies have reported good results using a 7-day triple therapy with VPZ, AMPC, and clarithromycin (CAM). We recently conducted the first registered prospective intervention study of VPZ, CAM, and metronidazole (MNZ)-based 7-day first-line triple therapy in patients with penicillin allergy and reported better results compared to a Proton Pump Inhibitor (PPI), CAM, and MNZ regimen. A retrospective study of VPZ-based triple therapy for patients with penicillin allergy was recently reported after registration of the current study; 17 cases were eradicated with vonoprazan, metronidazole, and sitafl oxacin. A 92.9% eradication rate (n = 14) for first-line and 66.7% eradication rate (n = 3) for second- or third-line therapies were reported. Sitafl oxacin (STFX) is a quinolone drug that is used as the main third-line regimen in Japan because the eradication rate (ER) of a 7-day triple therapy including STFX was significantly higher than that of a regimen including the quinolone drug levofloxacain. We
believe that VPZ, CAM, and MNZ as the 7-day triple therapy is a good regimen for first-line eradication of *H. pylori* because of its reported high ER and safety.6,7 However, evidence supporting the use of VPZ, MNZ, and STFX (VPZ-MNZ-STFX) as a rescue regimen in patients allergic to AMPC or CAM or with prior eradication failure is very limited. Consequently, we conducted this prospective registry study to investigate 7-day VPZ-MNZ-STFX triple therapy as a rescue regimen for *H. pylori* patients with penicillin allergy.

**Methods**

**Study design and ethical issues.** This is the first prospective registry study to assess the efficacy and safety of 7-day VPZ-MNZ-STFX triple therapy for *H. pylori* eradication, as a second-line eradication therapy, in patients with penicillin allergy. We previously reported high efficacy and safety of VPZ, CAM, and MNZ as a first-line therapy for patients with *H. pylori* infection and penicillin allergy.6 This was a single-center, open-label, single-arm intervention study that began registering patients in February 2015, that is, when VPZ was approved in Japan.

This study was approved by the Ethics Committee Institutional Review Board of Yokohama City University Hospital, Japan, in January 2015 (no. B150108015). When the Clinical Trials Act took effect in 2019, this study was rereviewed and approved by the Institutional Review Board of Yokohama City University, as required by law (CRB18-022). All of the studies were performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2017, Japanese Ministry of Health, Labor, and Welfare). The study protocol complied with the Clinical Trials Act of Japan.

This study was registered at the University Hospital Medical Information Network (UMIN) trial registry under UMIN000016335. This study was also registered at the Japan Registry of Clinical Trials (jRCTs), which was established in 2019 by the Japanese Government based on the Clinical Trials Act, under jRCTs031180133 (https://jRCT.niph.go.jp/latest-detail/jRCTs031180133). The UMIN and jRCT are recognized by the International Committee of Medical Journal Editors.

All participants provided written informed consent before study enrollment.

**Study population.** This study evaluated second-line *H. pylori* rescue therapy. Patients who met all of the following criteria were eligible to participate in this study: male or female, aged ≥20 years, penicillin allergy and *H. pylori* infection, and failed first-line *H. pylori* eradication.

*H. pylori* infection was defined as a positive result on the urea breath test (UBT),9 stool *H. pylori* antigen test,10 *H. pylori* culture11 (as reported previously15), pathological (histological) diagnosis of *H. pylori*,13,14 or anti-*H. pylori* immunoglobulin G (HpIgG).15 Endoscopy was performed within 1 year of enrollment in all patients.

Penicillin allergy was defined as a diagnosis thereof by a physician not involved in this study. In such patients, penicillin was contraindicated.

Patients with any of the following conditions were ineligible to participate in this study: history of second-line *H. pylori* eradication therapy; pregnancy or lactation; history of allergy to VPZ, MNZ, or STFX; severe liver, renal, or heart dysfunction; or disqualification by a physician.

**Treatment.** Eligible patients who provided written informed consent were enrolled in this study. A registration form, which included gender, age, endoscopic findings, method of diagnosing *H. pylori* infection, and prior eradication regimens, was completed. The patients were assigned to receive triple therapy for 7 days with VPZ 20 mg twice daily (bid), MNZ 250 mg bid, and STFX 100 mg bid. A treatment duration of 7 days was used based on a previous randomized controlled trial that found no significant difference between 7- and 14-day therapy with rabeprazole (10 mg bid or qid), MNZ (250 mg bid), and STFX (100 mg bid).16

All of the patients were prohibited from taking VPZ, proton pump inhibitors; histamine-s blockers; and antibiotics except VPZ, MNZ, and STFX during the study period.

**Procedures.** After completion of eradication therapy, a physical examination was performed by a physician who also evaluated compliance with the regimen. Adverse events and compliance data were added to the medical records according to the study protocol. An adverse effect questionnaire (AEQ) was completed by the patients during therapy. The AEQ contained 13 questions pertaining to diarrhea, dysgeusia, nausea, anorexia, abdominal pain, heartburn, urticaria, headache, abdominal fullness, eructation, vomiting, fatigue, and other, with the following

| Table 1 Patient characteristics and *Helicobacter pylori* eradication rates |
|----------------------------|------------------|
| **Characteristics**                        | **Total (n = 17)** |
| Age (mean ± SE) (years)                       | 61.6 ± 12.3 |
| Males (%)                                      | 23.5 |
| Smokers (%)                                    | 5.9 |
| Evaluation by UBT (%)                         | 100 |
| Endoscopic findings (%)                      |                |
| Gastrroduodenal ulcer                        | 23.5 |
| Gastric cancer                                | 5.9 |
| Gastritis only                                | 70.6 |
| Diagnosis of *H. pylori* infection (%)        |                |
| UBT                                           | 41.2 |
| *H. pylori* stool antigen                      | 17.6 |
| *H. pylori* culture                           | 17.6 |
| Pathology (histology)                         | 17.6 |
| *H. pylori* IgG                               | 5.9 |
| Eradication result, success/failure           | 15/2 |
| Eradication rate, % (95% CI) (ITT)            | 88.2% (63.6–98.5%) |
| Eradication rate, % (95% CI) (PP)             | 88.2% (63.6–98.5%) |

Evaluation by urea breath test (UBT), %, eradication success rate determined by the 13C-urea breath test; UBT, 13C-urea breath test; diagnosis of *H. pylori* infection, %, *H. pylori* status before eradication therapy. CI, confidence interval; ITT, intention-to-treat analysis; PP, per-protocol analysis; SE, standard error.
subjective responses: none (AEQ 0), weak (AEQ 1), moderate (AEQ 2), and strong (AEQ 3), as reported previously.17

The 13C-UBT was used to assess 

*Helicobacter pylori* eradication success at 4 weeks. UBT was performed using UBIT 100 mg tablets with the standard cutoff of 2.5‰ (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). UBT samples were collected by a nurse in the hospital and transported to an external agency for clinical inspection. These procedures are identical to those for nonstudy cases in the hospital.

A physical examination was performed by a physician at the same time the eradication results were imparted to the patients. The physician also completed a case report form, the data in which were subsequently analyzed.

**Outcome.** The primary end-point was the 

*Helicobacter pylori* eradication rate using the VPZ-MNZ-SFTX 7-day rescue triple therapy in patients with penicillin allergy. The secondary end-point was safety as evaluated by the AEQ.

**Statistical analysis.** For the primary end-point, frequencies and two-sided 95% confidence intervals (CIs) were calculated. As an exploratory analysis, the AEQ scores associated with the VPZ-MNZ-STFX and VPZ-CAM-MNZ therapy regimens were compared using Fisher’s exact test, with *P* < 0.05 taken to indicate statistical significance.

The required sample size was calculated based on the maximum feasible number in the 5-year period of this study according to the referral consultation number from another institution for 

*Helicobacter pylori* eradication therapy in patients with penicillin allergy.

**Results**

As shown in Table 1, 17 patients with both penicillin allergy and a history of 

*Helicobacter pylori* eradication were enrolled. All patients receiving VPZ-MNZ-STFX therapy were enrolled prospectively between February 2015 and May 2019. The mean age of the patients was 61.6 ± 12.3 years, and 23.5% were male. UBT was performed at 10.1 ± 2.4 weeks after drug withdrawal. No patient failed to return for follow-up. Endoscopic findings revealed gastritis (70.6%, *n* = 12), gastroduodenal ulcer (23.5%, *n* = 4), and gastric cancer (5.9%, *n* = 1). The cancer was resected endoscopically, and curative resection was confirmed before registration.

Before the rescue therapy, 

*Helicobacter pylori* infection was diagnosed by UBT (41.2%, *n* = 7), stool 

*Helicobacter pylori* antigen test (17.6%, *n* = 3), 

*Helicobacter pylori* culture (17.6%, *n* = 3), pathology (histology) (17.6%, *n* = 3), or HpIgG (5.9%, *n* = 1).

The ER was 88.2% (95% CI: 63.6–98.5%; *n* = 17) in the intention-to-treat and per-protocol analyses with 7-day VPZ-MNZ-STFX therapy. All 17 patients showed 100% adherence to their medication regimen.

Table 2 shows the AEQ results. One patient failed to submit the AEQ; consequently, 16 patients participated in this assessment. AEQ scores of 2/3 for diarrhea, abdominal fullness,
and belch were reported by 25, 31.3, and 12.5%, respectively. AEQ scores of 2/3 for anorexia, abdominal pain, heartburn, hives, headache, and general malaise were reported by 6.3%. AEQ scores of 3 for diarrhea, anorexia, heartburn, headache, or abdominal fullness were reported by 8.3% of the patients.

Discussion
This study showed the efficacy and safety of rescue VPZ-MNZ-STFX therapy in patients with penicillin allergy. The 88.2% (95% CI: 63.6–98.5%) success rate and 100% compliance rate indicate that this novel regimen is a good rescue therapy option for patients with penicillin allergy. The grading of the VPZ-MNZ-STFX therapy as a rescue therapy was fair (85–89%), as defined by Graham.18

The Maastricht V guidelines stated that, in patients with penicillin allergy, PPI, CAM, and MNZ may be prescribed as a first-line treatment because of lower adverse event rates compared with the PPI, STFX, and MNZ,19 PPI, tetracycline, and MNZ,20 bismuth, PPI, tetracycline, and MNZ,21 and bismuth, PPI, tetracycline, and furazolidone regimens.22 Because the VPZ, CAM, and MNZ regimen showed an excellent ER and safety profile in patients allergic to penicillin in areas with high rates of CAM resistance,6 we believe that the VPZ, CAM, and MNZ regimen should be used as the first-line treatment in patients with penicillin allergy. The Maastricht V guidelines also stated that a fluoroquinolone-containing regimen is an empirical second-line rescue option for patients with penicillin allergy and that an STFX-based regimen is also an option; this has been tested successfully in Japan.23 A PPI, MNZ, and STFX regimen showed good efficacy as a third-line treatment (90.9%; 95% CI: 78.3–97.5%; n = 44); however, diarrhea (21.4 and 32.0% in the first and third-line studies, respectively) and loose stools (35.7 and 68% in the first- and third-line studies, respectively) were reported as adverse events,16 with higher rates than those reported with the VPZ, CAM, and MNZ regimen.6

This study demonstrated the safety of VPZ-MNZ-STFX based on the AEQ scores. As shown in Table 3, AEQ scores were compared between the current study, for VMS, and our previous study6 using the VPZ-CAM-MNZ regimen. No significant differences were observed, but there was a trend toward a higher diarrhea score with VPZ-MNZ-STFX therapy compared with VPZ-CAM-MNZ therapy (25 vs 5%, AEQ 2/3, P = 0.15). The current study also showed that the incidence of diarrhea was the same with VPZ-MNZ-STFX therapy as with PPI-MNZ-STFX therapy. We believe that both the VMS and VPZ-CAM-MNZ therapies are safe but that the VPZ-CAM-MNZ therapy is more desirable because of potentially less frequent diarrhea.

This study also demonstrated the efficacy of VPZ-MNZ-STFX therapy as a rescue regimen. We observed a higher ER with VPZ-AMPC-STFX therapy, even after first-line VPZ-AMPC-CAM and second-line VPZ-AMPC-MNZ therapy failure.24 This implies that the difference in ERs is due to the combination of VPZ and STFX. The mechanism behind this observation may be related to the acid-sensitive antimicrobial property of STFX25 and to the rapid and long-acting acid-inhibitory effect of VPZ.26

The limitations of this study were as follows. First, this study had a small sample size. However, it is very difficult to conduct a larger-scale study of a rescue regimen in patients with penicillin allergy. The prevalence of penicillin allergy is 3–7% in Japan27 and elsewhere,28 but higher ERs with VPZ regimens (VPZ-AMPC-CAM therapy and VPZ-CAM-MNZ therapy) make it difficult to assess rescue regimens in patients with penicillin allergy. There were only three cases who received VPZ-MNZ-STFX therapy in the current study, even with its retrospective design, highlighting the difficulty of conducting a large-scale study. Second, in most cases, we could not assess resistance to MNZ and STFX (14/17). One of the VPZ-MNZ-STFX therapy cases had the following minimum inhibitory concentrations (mg/L): MNZ, 8; STFX, 0.12; AMPC, 0.06; and CAM, 16 (this patient had an allergic reaction to the VPZ-AMPC-CAM therapy, which failed, but eradication was achieved using VPZ-MNZ-STFX therapy). The minimum inhibitory concentrations (mg/L) of the other two VPZ-MNZ-STFX therapy cases were as follows: MNZ, 2; STFX, <0.03; AMPC, <0.03; and CAM, 8 in one and MNZ, 4; STFX, 0.25; AMPC, <0.03; and CAM, 8 in the other. Further studies of VPZ-MNZ-STFX therapy in patients with MNZ and STFX resistance are needed.

In conclusion, our assessment of 7-day VPZ-MNZ-STFX therapy as a rescue regimen for patients with penicillin allergy demonstrated a fair ER and safety profile. The prospective data obtained from this small-scale prospective study are rare and valuable.

Acknowledgment
This study was supported by Yokohama City University (basic research expenditures).

References
1 Lee YC, Chiang TH, Chou CK et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology. 2016; 150: 1113.e5–24.e5.
2 Herrero R, Park JY, Forman D. The fight against gastric cancer - the IARC Working Group report. Best Pract. Res. Clin. Gastroenterol. 2014; 28: 1107–14.
3 Murakami K, Sakurai Y, Shiino 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. 2016; 65: 1439–46.
4 Dong SQ, Singh TP, Wei X, Yao H, Wang HLA. Japanese population-based meta-analysis of vonoprazan versus PPI for Helicobacter pylori eradication therapy: is superiority an illusion? Helicobacter. 2017; 22: e12438.
5 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. 2017; 46: 106–14.
6 Sue S, Suzuki N, Shibata W et al. First-line Helicobacter pylori eradication with vonoprazan, clarithromycin, and metronidazole in patients allergic to penicillin. Gastroenterol. Res. Prat. 2017; 2017: 2019802.
7 Ono S, Kato M, Nakagawa S, Mabe K, Sakamoto N. Vonoprazan improves the efficacy of Helicobacter pylori eradication therapy with a regimen consisting of clarithromycin and metronidazole in patients allergic to penicillin. Helicobacter. 2017; 22: e12374.
8 Murakami K, Furuta T, Ando T et al. Multi-center randomized controlled study to establish the standard third-line regimen for
Helicobacter pylori eradication in Japan. J. Gastroenterol. 2013; 48: 1128–35.
9 Ohara S, Kato M, Saito M et al. Comparison between a new 13C-urea breath test, using a film-coated tablet, and the conventional 13C-urea breath test for the detection of Helicobacter pylori infection. J. Gastroenterol. Hepatol. 2004; 39: 621–8.
10 Sato M, Shimoyama T, Takahashi R et al. Characterization and usefulness of stool antigen tests using a monoclonal antibody to Helicobacter pylori catalase. J. Gastroenterol. Hepatol. 2012; 27(Suppl 3): 23–8.
11 Cutler AF. Diagnostic tests for Helicobacter pylori infection. Gastroenterologist. 1997; 5: 202–12.
12 Sue S, Ogushi M, Arima I et al. Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-susceptible Helicobacter pylori: a multicenter, prospective, randomized trial. Helicobacter. 2018; 23: e12456.
13 Loffeld RJ, Stobberingh E, Flendrig JA, Arends JW. Helicobacter pylori in gastric biopsy specimens. Comparison of culture, modified giemsa stain, and immunohistochemistry. A retrospective study. J. Pathol. 1991; 165: 69–73.
14 Shimizu T, Akamatsu T, Ota H, Katsuyama T. Immunohistochemical detection of Helicobacter pylori in the surface mucous gel layer and its clinicopathological significance. Helicobacter. 1996; 1: 197–206.
15 Kosunen TU, Seppala K, Sama S, Sipponen P. Diagnostic value of decreasing IgG, IgA, and IgM antibody titres after eradication of Helicobacter pylori. Lancet. 1992; 339: 893–5.
16 Furuta T, Sugimoto M, Kodaira C et al. Sitaflaxacin-based third-line rescue regimens for Helicobacter pylori infection in Japan. J. Gastroenterol. Hepatol. 2014; 29: 487–93.
17 Sue S, Kuwashima 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. 2017; 56: 1277–85.
18 Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter. 2007; 12: 275–8.
19 Furuta T, Sugimoto M, Yamade M et al. Eradication of H. pylori infection in patients allergic to penicillin using triple therapy with a PPI, metronidazole and sitafloxacin. Intern. Med. 2014; 53: 571–5.
20 Rodriguez-Torres M, Salgado-Mercado R, Rios-Bedoya CF et al. High eradication rates of Helicobacter pylori infection with first- and second-line combination of esomeprazole, tetracycline, and metronidazole in patients allergic to penicillin. Dig. Dis. Sci. 2005; 50: 634–9.
21 Gisbert JP, Gisbert JL, Marcos S, Olivaeres D, Pajares JM. Helicobacter pylori first-line treatment and rescue options in patients allergic to penicillin. Aliment. Pharmacol. Ther. 2005; 22: 1041–6.
22 Gisbert JP. “Rescue” regimens after Helicobacter pylori treatment failure. World J. Gastroenterol. 2008; 14: 5385–402.
23 Malferttheiner P, Megraud F, O’Morain CA et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. Gut. 2017; 66: 6–30.
24 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. 2019; 34: 686–92.
25 Sugimoto M, Sahara S, Ichikawa H et al. Four-times-daily dosing of rabeprazole with sitafloxacin, high-dose amoxicillin, or both for metronidazole-resistant infection with Helicobacter pylori in Japan. Helicobacter. 2017; 22: e12319.
26 Sakurai Y, Mori Y, Okamoto H et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment. Pharmacol. Ther. 2015; 42: 719–30.
27 Muranaka M, Okumura H, Takeda K, Koizumi K, Igarashi H. Population studies on drug hypersensitivities. Acta Allergol. 1973; 28: 50–61.
28 Harandian F, Pham D, Ben-Shoshan M. Positive penicillin allergy testing results: a systematic review and meta-analysis of papers published from 2010 through 2015. Postgrad. Med. 2016; 128: 557–62.