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ORIGINAL ARTICLE

Helicobacter pylori rescue treatment with vonoprazan, metronidazole, and sitafloxacin in the presence of penicillin allergy

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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 sitafloxacin (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-SFTX 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,[1] and *H. pylori* eradication for all baseline risk levels is recommended by the World Health Organization.[2] 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,[3] and several studies have reported good results using a 7-day triple therapy with VPZ, AMPC, and clarithromycin (CAM).[4,5] We recently conducted the first registered prospective intervention study[6] 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 sitafloxacin. 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.[7] Sitafloxacin (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 levofloxacin.[8] 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* culture[11] (as reported previously[12]), 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 (%)	
Gastroduodenal 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 ^{13}C-urea breath test; UBT, ^{13}C-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 *H. 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 *H. 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 *H. pylori* eradication therapy in patients with penicillin allergy.

Table 2 Adverse effects of treatment with vonoprazan, metronidazole, and sitafloxacin assessed by questionnaire

	AEQ 1, 2, or 3	AEQ 2 or 3	AEQ 3
Diarrhea	50.0%	25.0%	6.3%
Dysgeusia	6.3%	0%	0%
Nausea	6.3%	0%	0%
Anorexia	12.5%	6.3%	6.3%
Abdominal pain	31.3%	6.3%	0%
Heartburn	12.5%	6.3%	6.3%
Hives	25.0%	6.3%	0%
Headache	12.5%	6.3%	6.3%
Abdominal fullness	50.0%	31.3%	6.3%
Belching	25.0%	12.5%	0%
Vomiting	0%	0%	0%
General malaise	12.5%	6.3%	0%
Other	6.3%	0%	0%

AEQ, adverse effect questionnaire; AEQ 1, weak; AEQ 2, moderate; AEQ 3, strong.

Results

As shown in Table 1, 17 patients with both penicillin allergy and a history of *H. 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, *H. pylori* infection was diagnosed by UBT (41.2%, $n = 7$), stool *H. pylori* antigen test (17.6%, $n = 3$), *H. 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,

Table 3 Safety of rescue treatment using VMS compared with treatment with VCM assessed by questionnaire

	AEQ 2 or 3			AEQ 3		
	VMS	VCM	*P*	VMS	VCM	*P*
Diarrhea	25%	5%	0.15	6.3%	0%	0.44
Dysgeusia	0%	0%	1	0%	0%	1
Nausea	0%	15%	0.24	0%	10%	0.49
Anorexia	6.3%	10%	1	6.3%	5%	1
Abdominal pain	6.3%	15%	0.61	0%	5%	1
Heartburn	6.3%	10%	1	6.3%	0%	0.44
Hives	6.3%	0%	0.44	0%	0%	1
Headache	6.3%	10%	1	6.3%	5%	1
Abdominal fullness	31.3%	30.0%	1	6.3%	15%	0.61
Belching	12.5%	5%	0.57	0%	0%	1
Vomiting	0%	0%	1	0%	0%	1
General malaise	6.3%	15%	0.61	0%	0%	1
Other	0%	5%	1	0%	0%	1

AEQ, adverse effect questionnaire; AEQ 2, moderate; AEQ 3, strong; VCM, vonoprazan/clarithromycin/metronidazole eradication therapy for 1 week; VMS, vonoprazan/metronidazole/sitafloxacin eradication therapy for 1 week.

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 study[6] 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 STFX[25] 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 Japan[27] 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 rescue 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.

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