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Vonoprazan-Based Triple-Therapy Could Improve Efficacy of the Tailored Therapy of *Helicobacter pylori* Infection

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ABSTRACT

Background & Aims: The prevalence of clarithromycin resistant bacteria is increasing, and the effectiveness of *Helicobacter pylori* (*H. pylori*) triple therapy is gradually decreasing in Japan. Vonoprazan, a potassium-competitive acid blocker, has been reported for its effectiveness in eradicating *H. pylori*. We aimed to evaluate the efficacy of tailored vonoprazan-based triple therapy in patients with *H. pylori*. This study is the first to compare the efficacy of vonoprazan-based tailored triple therapy to that of vonoprazan-based conventional therapy.

Method: This retrospective cohort study evaluated the treatment efficacy in 920 patients. Of these, 541 received conventional and 379 received tailored therapy. Successful eradication was confirmed by a negative ^{13}C-urea breath test 6–8 weeks following completion of *H. pylori* eradication therapy, and the data were evaluated using the Chi-square test, or Fisher's exact test, as appropriate.

Results: The eradication rate of tailored therapy was 90% and 96.3% by intent-to-treat analysis and per protocol analysis, respectively, which was significantly higher than the 85% and 90.2% found for conventional therapy ($p < 0.05$ and $p < 0.001$, respectively). Amoxicillin- or clarithromycin-resistant bacteria did not affect treatment outcomes. By univariate and multivariate analysis, both amoxicillin- and clarithromycin-resistant bacteria and conventional therapy were detected as risk factors for eradication failure (odds ratio = 6.267, 95% CI [1.056–119.924], $p < 0.05$, and odd ratio = 3.113, 95% confidence interval [1.688–6.160], $p < 0.001$, by multivariate analysis).

Conclusion: Vonoprazan-based triple therapy could be a more effective treatment for *H. pylori* infection than conventional therapy when combined with a therapy regimen tailored according to bacterial antibiotic susceptibility.

Key words: *Helicobacter pylori* – conventional therapy – clarithromycin – amoxicillin – drug resistance – microbial drug resistance - vonoprazan.

Abbreviations: AMX: amoxicillin; AMX-R: amoxicillin resistant; AMX-S: amoxicillin sensitive; CAM: clarithromycin; CAM-R: clarithromycin resistant; CAM-S: clarithromycin sensitive; *H. pylori: Helicobacter pylori*; ITT: intent-to-treat; MNZ: metronidazole; PPI: proton pump inhibitor; PPS: per protocol set; VPZ: vonoprazan.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most prevalent bacterial pathogens and is associated with upper gastrointestinal disorders such as gastritis, peptic ulcer, functional dyspepsia, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer [1-3]. Eradication of *H. pylori* infection provides an effective approach for curing or preventing the associated diseases [4-6]. However, the effectiveness of the most commonly recommended first-line regimen has declined.

The treatment success of *H. pylori* involves many factors, including point mutation conferring antibiotic resistance and the genetic polymorphisms influencing drug metabolism, which vary by the geographic area [7, 8]. Therefore, the same regimen may be extremely effective in one geographic area but ineffective in another. The Japanese Society for Helicobacter Research recommends a 7-day triple therapy using a proton pump inhibitor (PPI) or vonoprazan (VPZ) with amoxicillin (AMX) and clarithromycin (CAM) [9]; this is the only first-line regimen currently covered by the Japanese national health

insurance system. In the rescue therapy, a 7-day triple therapy using PPI or VPZ with AMX and metronidazole (MNZ) is the only second-line regimen currently covered by the Japanese national health insurance system. The resistance rate of MNZ in Japan is very low (from 1.1% to 2.5%) [10]; therefore 99% of patients with *H. pylori* infection are cured by first- and second-line regimens. In Japan, CAM-based 7-day triple therapy was approved for gastric and duodenal ulcers in 2000, when the initial eradication rate was approximately 90% [11]. However, the eradication rate of triple therapy has decreased with the increase of CAM resistant (CAM-R) strains [12]. The Maastricht IV/Florence Consensus Report recommended that anti-*H. pylori* regimen should consider the local CAM resistance rate, with regions of high or low resistance identified using a 15–20% threshold [13]. A working group from the Japanese Society of Helicobacter Research performed a surveillance study to determine the temporal antimicrobial susceptibility profiles of *H. pylori* isolated during 2002–2006 and 2010–2011 in 67 institutions; this resulted in the analysis of 7,735 isolates. Primary CAM-R increased from 19% to 31% as CAM use increased; therefore, CAM treatment should not be used without an antibiotic susceptibility test.

Recently, VPZ, a novel potassium-competitive acid blocker, has been used in *H. pylori* eradication therapy in order to increase the eradication rate [14, 15]. Our previous study demonstrated that the first-line eradication rate of VPZ-based triple therapy was 89.7%, significantly higher than that of PPI-based triple therapy in per protocol set (PPS) analysis. Additionally, even in patients with CAM-R bacteria, the eradication rate was significantly higher for those treated with VPZ compared to those treated with a PPI (87.5% vs. 53.8%) [14]. However, concerns related to the CAM-R strains remain, because this eradication rate failed to achieve an acceptable grade according to the report card for grading *H. pylori* therapies proposed by Graham [16]. It has been reported that tailoring therapy according to bacterial CAM susceptibility can improve the eradication rate in PPI-based triple therapy, but no study has examined the efficacy of VPZ-based triple therapy. Additionally, the influence of bacterial amoxicillin (AMX) susceptibility in VPZ-based triple therapy is unclear.

This study aimed to find out whether tailoring *H. pylori* treatment according to CAM susceptibility could improve the eradication rate in VPZ-based triple therapy, and to assess the influence of bacterial AMX susceptibility in eradication therapy.

METHODS

Statement of ethics

This study conformed to the code of ethics stated in the Declaration of Helsinki. The research protocols were approved by the appropriate Ethics Committee (approval number 2018-H057).

Study population

This was a retrospective cohort study. All patients who had an initial *H. pylori* infection treatment from October 2015 to December 2018 were enrolled. Patients who underwent PPI-based triple therapy, a MNZ-containing regimen without an antibiotic susceptibility test, a MNZ-based regimen against CAM sensitive (CAM-S) *H. pylori* or had both CAM-R and MNZ resistant (MNZ-R) bacteria were excluded from the study.

H. pylori eradication therapies

The treatment regimen selection was dependent upon the attending doctor. Basically, the patients who did not undergo a bacterial susceptibility test by esophagogastroduodenoendoscopic examination received conventional therapy (VPZ-based CAM-containing 7-day triple therapy: 20 mg VPZ, twice daily (b.i.d.); 750 mg AMX, b.i.d.; and 200 mg CAM, b.i.d.). The patients who did not yet have a bacterial susceptibility test result prior to the start of treatment also received conventional therapy. Patients who already had a bacterial susceptibility test result prior to starting treatment received tailored therapy (VPZ-based CAM-containing 7-day triple therapy: 20 mg VPZ, b.i.d.; 750 mg AMX, b.i.d.; and 200 mg CAM, b.i.d. in the case of CAM-S bacteria and VPZ-based MNZ-containing 7-day triple therapy: 20 mg VPZ, b.i.d.; 750 mg AMX, b.i.d.; and 250 mg MNZ, b.i.d. in the case of CAM-R bacteria).

Diagnosis of *H. pylori* infection

Positive diagnosis for *H. pylori* infection was defined as endoscopic active gastritis and positivity in one of four tests (rapid urease test, histology, serum antibody, or culture). Successful eradication was confirmed by a negative ^{13}C-urea breath test 6–8 weeks following completion of *H. pylori* eradication therapy.

H. pylori susceptibility to amoxicillin, clarithromycin, and metronidazole

H. pylori isolates were obtained from gastric biopsy specimens before treatment. AMX-R, CAM-R, and MNZ-R were defined using the flat dilution method as a minimum inhibitory concentration of ≥ 0.06 μg/ml, ≥ 1 μg/ml, and ≥ 16 μg/ml for *H. pylori*, respectively.

Statistical analyses

The results are presented as the mean ± standard division (SD), and as numbers and percentages. The quantitative data were analyzed using the *t*-test, and categorical data were analyzed using the Chi-squared test or Fisher's exact test, as appropriate. Logistic regression was used to obtain the eradication failure odds ratio. The variable was included in the multivariate analysis when a p-value < 0.2 was observed in the univariate analysis. All data were analyzed using JMP® Version 14.2 (SAS Institute Inc., Cary, NC, USA). A p-value < 0.05 was considered significant.

RESULTS

A total of 1,001 patients were candidates for this study. Eighty-one patients were excluded: 52 underwent PPI-based triple therapy, 14 underwent an MNZ-containing regimen without an antibiotic susceptibility test, 9 underwent an MNZ-containing regimen against CAM-S bacteria, and 6 had both CAM-R and MNZ-R bacteria. A total of 541 patients

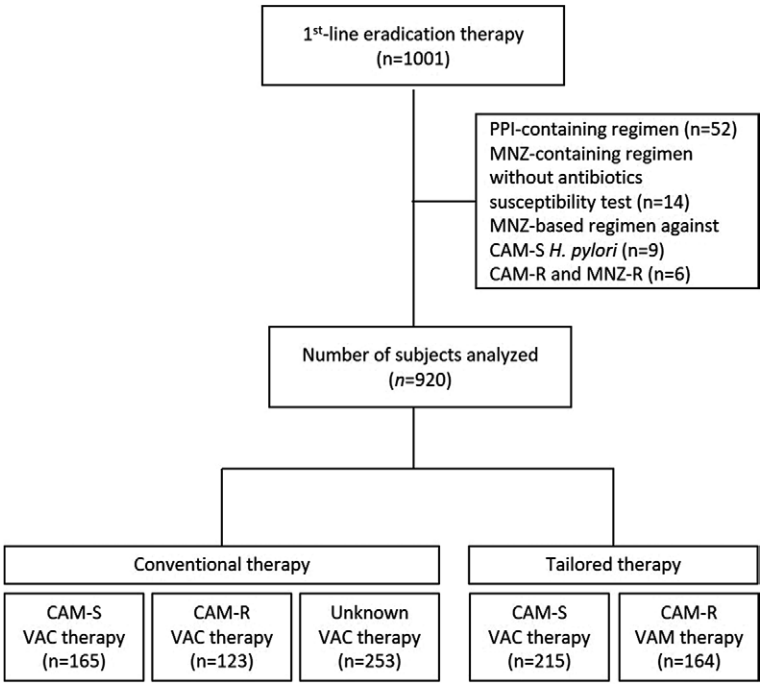

Fig. 1. Patient enrolment flow chart.

received conventional therapy: 165 had CAM-S bacteria and 123 had CAM-R bacteria. A total of 379 patients received tailored therapy: 215 had CAM-S bacteria and received CAM-containing triple therapy, and 164 had CAM-R bacteria and received MNZ-containing triple therapy (Fig. 1). Patient characteristics are shown in Table I. There were no differences in patient characteristics between the conventional and tailored therapy groups. The resistance rates of AMX and CAM were 14.4% and 43.0%, respectively.

The eradication rate of tailored therapy by intent-to-treat (ITT) analysis and PPS analysis was 90.0% (95% confidence interval - CI 86.5%–92.6%) and 96.3% (95%CI 93.8%–97.8%), respectively, which was significantly higher than that of conventional therapy: 85.0% (95%CI 81.8%–87.8%) and 90.2% (95%CI 87.4%–92.5%), p = 0.0 028 and p = 0.0008, respectively (Fig. 2).

In the conventional therapy group, the eradication rate of patients with CAM-R bacteria (85.8%, 95%CI 78.5%–91.0%) was significantly lower than in those with CAM-S (93.2%, 95%CI 88.2%–96.1%) (p = 0.046). In the tailored therapy group, the eradication rate of patients with CAM-R bacteria (98.1%, 95%CI 94.4%–99.3%) did not differ from those with CAM-S bacteria (95.0%, 95%CI 91.0%–97.3%), and was significantly increased compared to those with CAM-R bacteria in the

Table I. Characteristics of patients who received first-line vonoprazan-based triple therapy for *H. pylori*.

	Conventional therapy n=541		Tailored therapy n=379		p value
Gender					
Female, n	250	(46.2%)	176	(46.4%)	0.947
Male, n	291	(53.8%)	203	(53.6%)	
Age, years	62.5±13.9	63.8±12.6			0.129
Diagnosis					
Gastritis, n	444	(82.1%)	316	(83.4%)	0.846
Peptic ulcer, n	58	(10.7%)	39	(10.3%)	
Others, n	39	(7.2%)	24	(6.3%)	
AMX susceptibility					
sensitive, n	255	(88.5%)	316	(83.4%)	0.074
resistant, n	33	(11.5%)	63	(16.6%)	
CAM susceptibility					
sensitive, n	165	(57.3%)	215	(56.7%)	0.937
resistant, n	123	(42.7%)	164	(43.3%)	

AMX: amoxicillin, CAM: clarithromycin

conventional therapy group (p = 0.0002). In patients with CAM-S bacteria, there was no difference in the eradication rate between conventional and tailored therapies.

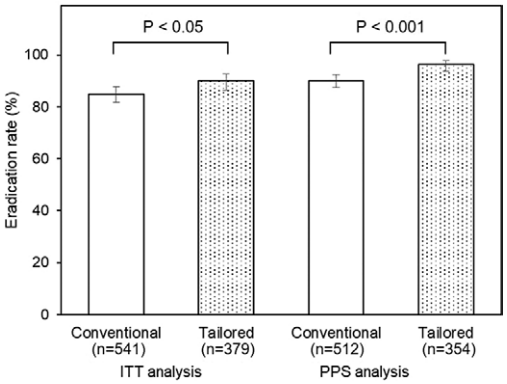

Fig. 2. Comparison of *H. pylori* eradication rate between conventional therapy and tailored therapy. By ITT analysis, the eradication rate of tailored therapy was 90.0%, which was increased compared to 85.0% of conventional therapy (p<0.05). By PPS analysis, the eradication rate of tailored therapy was increased compared to conventional therapy (96.3% vs 90.2%, p < 0.001).

In the conventional therapy group, the eradication rate of the patients with CAM-S and AMX-R bacteria, and CAM-R and AMX-S bacteria was 92.3% (95%CI 66.7%–98.6%) and 90.0% (95%CI 82.6%–94.5%), respectively, which did not differ from the 93.2% (95%CI 88.0%–96.3%) of patients with CAM-S and AMX-S bacteria. The eradication rate of patients with CAM-R and AMX-R bacteria (65.0%, 95%CI 43.3%–81.9%) was significantly lower than that of patients with CAM-S and AMX-S bacteria (p = 0.001). However, in the tailored therapy group, bacterial antibiotic susceptibility had no influence on the eradication rate (Fig. 3).

By univariate analysis, having both AMX-R and CMA-R, and conventional therapy was detected as a risk factor for eradication failure (p = 0.017, and p = 0.0008, respectively) (Table II). By multivariate analysis using the factors with p < 0.2 by univariate analysis, AMX-R and CAM-R, and conventional therapy were detected as risk factors for the failure of VPZ-based triple therapy (p = 0.042 and p = 0.0005, respectively) (Table II).

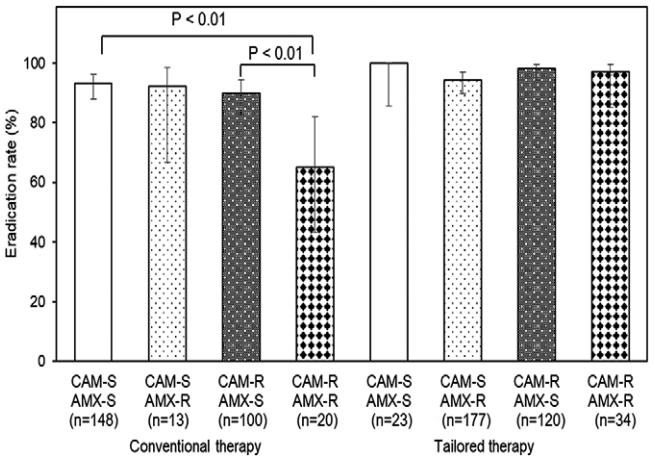

Fig. 3. Comparison of the *H. pylori* eradication rate according to antibiotic susceptibility of bacteria. In the conventional therapy, the eradication rate for both CAM-R and AMX-R was significantly decreased compared to CAM-R (p < 0.01) and antibiotics sensitive (p < 0.05).

DISCUSSION

In the present study, tailored therapy showed the best eradication rate (90.0%) by ITT analysis, which reached an acceptable grade B according to the report card for grading *H. pylori* therapies proposed by Graham [16]. As far as we know, this is the first report comparing the efficacy of VPZ-based tailored triple therapy to VPZ-based conventional therapy.

Antibiotic susceptibility, especially CAM susceptibility, has been attracting attention regarding its role in the triple therapy success of *H. pylori* eradication because the efficacy of regimens containing CAM is greatly affected by CAM resistance [12].

In 2000, the resistance rate for CAM was 7.0%; however, while it increased to 27.7% in 2004 [10, 17], the eradication rate has inversely decreased. In this study the resistance rates of AMX and CAM were 14.4% and 43.0%, respectively; these rates are the same as those reported previously [10, 18]. Our previous study showed that a VPZ-based CAM-containing triple regimen achieved a higher eradication rate than a PPI-based CAM-containing triple regimen in first-line eradication therapy [14]. VPZ-containing therapy was more effective than PPI-containing therapy for patients with CAM-R bacteria

Table II. Risk factors for eradication failure.

	Univariate analysis			Multivariate analysis		
Factor	OR	95% CI	p value	OR	95% CI	p value
Female	0.973	[0.582–1.628]	0.919			
Age ≥ 60	0.998	[0.583–1.706]	0.993			
Gastritis	1.090	[0.541–2.196]	0.809			
AMX-R	1.781	[0.820–3.869]	0.139	0.497	[0.026–2.424]	0.450
CAM-R	1.275	[0.677–2.402]	0.452			
AMX-R+CAM-R	2.608	[1.269–5.360]	0.017	6.267	[1.056–119.924]	0.042
Conv. therapy	2.839	[1.518–5.309]	0.0008	3.113	[1.688–6.160]	0.0005

OR: odd ratio, CI: confidence interval, AMX-R: amoxicillin resistance, CAM-R: clarithromycin resistance, Conv.: conventional

in randomized controlled trials [19]. Furthermore, a recent meta-analysis showed the advantage of VPZ use compared to PPI [20]. Similar to previous reports [15, 20], the eradication rate of conventional therapy in this study was 85.0% by ITT analysis, suggesting the long-lasting stability of the increased eradication rate from VPZ-based triple therapy, even in areas where the CAM-R bacteria rate was over 40%. This high eradication rate in VPZ-based triple therapy has been attributed to a rapid and prolonged (24-h) acid suppression (pH > 4, holding time ratio 100%) [21], which affects *H. pylori* eradication [22, 23]. Unlike PPI, which is activated by acid to function, VPZ inhibits potassium intake and the subsequent release of hydrogen ions by selectively binding to parietal cells [24-27]. However, no report has investigated the advantage provided by VPZ in direct use and acid inhibition during VPZ based eradication therapy. While the eradication rate of regimens containing AMX is affected by AMX-R [28], the effect of bacterial AMX susceptibility in VPZ-based triple therapy has never been considered. In this study, the effect of AMX and CAM antibiotic susceptibility were analyzed in terms of eradication success. The eradication rate of only AMX or CAM resistant bacteria did not differ from that of non-antibiotic resistant bacteria. The eradication rate in patients with both AMX and CAM resistant bacteria in conventional therapy was extremely decreased compared to those with single strain or non-antibiotic resistant bacteria. Combined resistance to AMX and CAM, but not AMX or CAM resistance alone, was a significant risk factor for eradication failure in VPZ-based triple therapy. The AMX resistance rate in our study was 14.4%, higher than the 5.5% reported in 2004 [10], and suggests an increasing AMX resistance rate. Hereafter, the eradication rate of VPZ-based triple therapy might decrease owing to the increasing number of AMX and CAM resistant bacteria.

The main reason for eradication failure is the rapid increase in antibiotic resistance of bacteria, poor patient compliance, and the rapid metabolism of conventional PPIs. Additionally, there are geographic differences in bacterial antibiotic resistance and genotype in the rapid metabolism of conventional PPIs. The frequency of AMX resistance is quite low worldwide, except in Cameroon, Iran, and Japan [10, 29, 30]. In eastern countries, the frequency of the A2143G mutation, which has a much stronger impact on conferring antibiotic resistance, is lower than that in western countries. The frequency of poor CYP2C19 metabolizers is higher in the Japanese population compared to the Caucasian populations [7, 8]. Therefore, it is necessary to consider the geographic area where the trial was performed when interpreting research results.

Before VPZ appeared on the market, a study on a tailored treatment regimen based on CAM susceptibility was performed to improve the *H. pylori* eradication rate, and achieved approximately 95% by PPI-based triple therapy [31, 32]. In our study, the efficacy of tailored VPZ-based triple therapy was shown for the first time. Tailored therapy significantly increased the eradication rate from 85.0% to 90.2% by ITT analysis, and up-graded the treatment from grade C (acceptable) to grade B (good) based on Graham's reporting system [16]. Per-protocol set analysis indicated the tailored therapy eradication rate was 96.3%, which is considered 'excellent' by the report card system [16].

The eradication rate of conventional triple therapy was improved by the use of VPZ instead of PPI. However, the eradication rate of patients with CAM-R bacteria ranged from 73.2% to 87.5% [15], which is an unacceptable level. In this study, the reason for *H. pylori* eradication failure in VPZ-based triple therapy was elucidated for the first time. As antibiotics are widely used, combined AMX and CAM resistant bacteria continue to increase. Therefore, the eradication rate of VPZ-based conventional therapy may decrease in the future, as the eradication rate of PPI-based conventional therapy decreased over the past decades [12]. Tailored therapy could be the best option to achieve an optimal eradication result. Heteroresistance (simultaneous presence of both susceptible and resistant strains at different sites in the same stomach) should be considered in patients with pangastritis, because *H. pylori* is not uniformly distributed in the stomach [33]. To avoid this problem, two biopsy specimens were obtained from the antrum and corpus for the antibiotic susceptibility examination in this study. This might be the reason for the improved eradication rate, even in the VPZ-based triple therapy.

Our results must be interpreted within the limitations of our study. First, the study design was a retrospective single-center cohort study. Antibiotic resistance related data should be considered in light of the varying responses obtained in different geographic areas, even those within the same district. A worldwide, multicenter, prospective randomized trial is necessary to show the superiority of tailored therapy. Nonetheless, it is impossible to perform trials examining VPZ efficacy in *H. pylori* infected populations in countries other than Japan. Second, eradication success might be influenced by several factors such as antibiotic susceptibility, insufficient acid inhibition, bacterial genotypes that reduce virulence, and compliance [34, 35], but bacterial genotypes and compliance could not be analyzed. Tailored therapy effectiveness measured by molecular tests has achieved higher success rates than that measured by traditional culture-based tests [36]. Further research is necessary to compare the eradication rate of tailored therapy by both molecular and culture testing.

CONCLUSION

Vonoprazan improved the eradication rate of the first-line triple-therapy. In addition, VPZ could improve even a tailored therapy based on the antibiotic susceptibility of bacteria.

Conflicts of interest: M.S. received a joint research grant from Amano Enzyme Inc., and K.K. received lecture fees from Daiichi Sankyo Co., Ltd., Astra Zeneca Co., Ltd., EA Pharma Co., Ltd., Mylan Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., and Takeda Pharmaceutical Co., Ltd. K.K. received research grants from Astellas Co., Ltd., Daiichi Sankyo Co., Ltd., EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., and Takeda Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to declare.

Authors' contribution: M.S. concept and design of; T.S., K.A., Y.Y., S.I., Y. H., M.E., Y.F., N.O., and K.K. data acquisition; M.S. statistical analysis. T.S. analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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