World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 July 21; 30(27): 3304-3313

DOI: 10.3748/wjg.v30.i27.3304

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Vonoprazan-amoxicillin dual therapy for *Helicobacter pylori* eradication in Chinese population: A prospective, multicenter, randomized, two-stage study

Xue-Ping Huang, Yi-Juan Liu, Shao-Wei Lin, Yan-Feng Shao, Feng Qiu, Qing-Wu Qiu, Zhang-Kun Xu, Jin-Xian Chen, Liang-Huo Chen, Zhen-Qun Lin, Wen-Hua Dai, Ming-Qing Zhang, Qi Jiang, Zhong-Qin Xiao, Xian-Xing Cheng, Xiang-Fei Zhang, Wen-Bin You, Wei Chen, Long-Qin Li, Wei-Xing Lin, Yong-Fu Wang, Fu-Jin Lai, Long-Qun Chen, Zhong-Hua Huang, Wen-Qi Zheng, Jin-Qi Wei, Zhi-Hui Lin

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade A, Grade B

P-Reviewer: Kansu A; Khalil G

Received: March 22, 2024

Revised: June 12, 2024

Accepted: June 25, 2024

Published online: July 21, 2024

Processing time: 111 Days and 3.4 Hours

Xue-Ping Huang, Zhi-Hui Lin, Department of Gastroenterology, Shengli Clinical Medical College of Fujian Medical University, Fuzhou 350000, Fujian Province, China

Xue-Ping Huang, Zhi-Hui Lin, Department of Gastroenterology, Fujian Provincial Hospital, Fuzhou 350001, Fujian Province, China

Yi-Juan Liu, Department of Gastroenterology, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350000, Fujian Province, China

Shao-Wei Lin, School of Public Health, Fujian Medical University, Fuzhou 350000, Fujian Province, China

Yan-Feng Shao, Department of Gastroenterology, The Third People's Hospital of Fujian Province, Fuzhou 350000, Fujian Province, China

Feng Qiu, Department of Gastroenterology, Fujian Provincial Hospital North Brance Fujian Provincial Geriatric Hospital, Fuzhou 350000, Fujian Province, China

Qing-Wu Qiu, Department of Gastroenterology, Xiaoao Hospital, Fuzhou 350000, Fujian Province, China

Zhang-Kun Xu, Department of Gastroenterology, The General Hospital of Fujian Energy Group, Fuzhou 350000, Fujian Province, China

Jin-Xian Chen, Department of Gastroenterology, The Second Hospital of Zhangzhou, Zhangzhou 363000, Fujian Province, China

Liang-Huo Chen, Department of Gastroenterology, Anxi Country Hospital, Quanzhou 362000, Fujian Province, China

Zhen-Qun Lin, Department of Gastroenterology, Zhangzhou Municipal Hospital of TCM, Zhangzhou 363000, Fujian Province, China

Wen-Hua Dai, Department of Gastroenterology, Zhangpu Hospital, Zhangzhou 363000, Fujian Province, China

Ming-Qing Zhang, Department of Gastroenterology, The Affiliated Dongnan Hospital of Xiamen University, Zhangzhou 363000, Fujian Province, China

Qi Jiang, Department of Gastroenterology, First Hospital of Nanping City, Nanping 353000, Fujian Province, China

Zhong-Qin Xiao, Department of Gastroenterology, Fujian Nanping Second Hospital, Nanping 353000, Fujian Province, China

Xian-Xing Cheng, Department of Gastroenterology, Wuyishan Municipal Hospital, Nanping 353000, Fujian Province, China

Xiang-Fei Zhang, Department of Gastroenterology, Fuzhou Changle District Hospital, Fuzhou 350000, Fujian Province, China

Wen-Bin You, Wei Chen, Department of Gastroenterology, Changle City Second Hospital, Fuzhou 350000, Fujian Province, China

Long-Qin Li, Department of Gastroenterology, Jinjiang Municipal Hospital, Quanzhou 362000, Fujian Province, China

Wei-Xing Lin, Department of Gastroenterology, Fuding Hospital Affiliated to Fujian University of Traditional Chinese Medicine, Ningde 352000, Fujian Province, China

Yong-Fu Wang, Department of Gastroenterology, Liancheng Hospital, Longyan 364000, Fujian Province, China

Fu-Jin Lai, Department of Gastroenterology, Xiapu County Hospital, Ningde 352000, Fujian Province, China

Long-Qun Chen, Department of Gastroenterology, Jinjiang Second Hospital, Quanzhou 362000, Fujian Province, China

Zhong-Hua Huang, Department of Gastroenterology, The First Hospital of Putian City, Putian 351100, Fujian Province, China

Wen-Qi Zheng, Department of Gastroenterology, Putian Fude Hospital, Putian 351100, Fujian Province, China

Jin-Qi Wei, Department of Gastroenterology, The 5th Affiliated Hospital of Sun Yat-sen University, Zhuhai 519000, Guangdong Province, China

Co-first authors: Xue-Ping Huang and Yi-Juan Liu.

Co-corresponding authors: Jin-Qi Wei and Zhi-Hui Lin.

Corresponding author: Zhi-Hui Lin, MD, PhD, Chief Doctor, Department of Gastroenterology, Shengli Clinical Medical College of Fujian Medical University, No. 134 Dongjie, Gulou District, Fuzhou 350000, Fujian Province, China. fjslyylzh@fjmu.edu.cn

Abstract

BACKGROUND

The efficacy of Vonoprazan-amoxicillin dual therapy (VAT) in the treatment of *Helicobacter pylori* (*H. pylori*) is controversial.

AIM

To evaluate the efficacy of VAT in the Chinese population.

METHODS

This prospective, multicenter, randomized, open-label, and two-stage study was conducted at 23 centers in Fujian, China (May 2021-April 2022). *H. pylori*-infected patients were randomized to bismuth quadruple therapy (BQT), BQT-Vonoprazan (BQT-V), seven-day VAT (VAT-7), ten-day VAT (VAT-10), and fourteen-day VAT (VAT-14) groups. The primary endpoint was the *H. pylori* eradication rate. The secondary endpoint was the frequency of adverse events. This study was registered with the Chinese Clinical Trial Registry, ChiCTR2100045778.

RESULTS

In the first stage, VAT-7 and BQT-V groups were selected for early termination because less than 23 among 28 cases were eradicated. In the second stage, the eradication rates for BQT, VAT-10, and VA-14 were 80.2% [95% confidence interval (95%CI): 71.4%-86.8%], 93.2% (86.6%-96.7%), 92.2% (85.3%-96.0%) in the intention-to-treat (ITT) analysis, and 80.9% (95%CI: 71.7%-87.5%), 94.0% (87.5%-97.2%), and 93.9% (87.4%-97.2%) in the per-protocol analysis. The ITT analysis showed a higher eradication rate in the VAT-10 and VAT-14 groups than in the BQT group (P = 0.022 and P = 0.046, respectively). The incidence of adverse events in the VAT-10 and VAT-14 groups was lower than in the BQT group (25.27% and 13.73% *vs* 37.62%, respectively; P < 0.001).

CONCLUSION

VAT with a duration of 10 or 14 days achieves a higher eradication rate than the BQT, with a more tolerable safety profile in *H. pylori*-infected patients in Fujian.

Key Words: *Helicobacter pylori*; Vonoprazan; Amoxicillin; Dual therapy; Bismuth quadruple therapy

Core Tip: Our study was a prospective, multicenter, randomized, two-stage study for *Helicobacter pylori* (*H. pylori*) eradication in Chinese population. We found that a daily dose of 20 mg of Vonoprazan was sufficient to eradicate *H. pylori*. We also found that compared to bismuth quadruple therapy, Vonoprazan-amoxicillin dual therapy with a duration of 10 days or 14 days, rather than 7 days, achieved higher eradication rates and that the safety profile of this dual therapy was more tolerable and manageable in Chinese patients. These results will guide further research and clinical practice for *H. pylori* eradication.

Citation: Huang XP, Liu YJ, Lin SW, Shao YF, Qiu F, Qiu QW, Xu ZK, Chen JX, Chen LH, Lin ZQ, Dai WH, Zhang MQ, Jiang Q, Xiao ZQ, Cheng XX, Zhang XF, You WB, Chen W, Li LQ, Lin WX, Wang YF, Lai FJ, Chen LQ, Huang ZH, Zheng WQ, Wei JQ, Lin ZH. Vonoprazan-amoxicillin dual therapy for *Helicobacter pylori* eradication in Chinese population: A prospective, multicenter, randomized, two-stage study. *World J Gastroenterol* 2024; 30(27): 3304-3313
URL: https://www.wjgnet.com/1007-9327/full/v30/i27/3304.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i27.3304

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped, Gram-negative bacterium affecting approximately 50% of the global population[1]. However, the *H. pylori* eradication rate has decreased to less than 80% in some countries, primarily prompted by increasing antibiotic resistance[2]. Recent international guidelines recommend bismuth quadruple therapy (BQT) or non-BQT as the first-line treatment for *H. pylori* in regions with high *H. pylori* clarithromycin (CLA) resistance[3,4]. However, these quadruple therapy regimens have some disadvantages, including high cost, numerous adverse reactions, and poor treatment compliance due to the use of numerous drugs. These drawbacks have prevented the widespread implementation of BQT in the treatment of *H. pylori* infection. As a result, there is increased interest in developing effective and easier treatment options.

Unge *et al*[5] first reported the use of dual therapy in 1989, consisting of a combination of proton pump inhibitors (PPIs) and amoxicillin (AMX), to eradicate *H. pylori*. However, the eradication rate of this regimen was only 55%-75% at the standard dosage and frequency rate, and the efficacy was low[6,7]. As a result, dual therapy was gradually replaced by triple therapy. In recent years, some studies have attempted to improve dual therapy by increasing the dosage and frequency of the drugs. The results show that high-dose dual therapy has achieved good efficacy and fewer adverse reactions[8,9].

For the eradication of *H. pylori*, maintaining a near-neutral gastric pH during treatment is critical to the success of the dual therapy regimen. Vonoprazan, a new type of potassium-competitive acid blocker, has been proven to have a stronger and more durable effect on the inhibition of gastric acid secretion than other PPIs. Therefore, Vonoprazan is expected to be more effective than other PPIs when used in combination with AMX to treat *H. pylori* infection. Several randomized studies in Japan[10], China[11], Europe, and the United States[12] have demonstrated the effectiveness of Vonoprazan-amoxicillin dual therapy (VAT) in eradicating *H. pylori*. However, the duration and dosages of VAT regimen are still controversial, and large multicenter randomized studies on this regimen in the Chinese population are still lacking.

This study aimed to evaluate the safety and efficacy of different dosages and duration of treatment with VAT regimens. The goal was to provide a safer and more effective regimen to be used in clinical practice to optimize treatment outcomes for patients in China with *H. pylori* infections.

MATERIALS AND METHODS

Patient selection

The inclusion criteria included patients with *H. pylori* infection, treatment naive, and if they are 18 to 70 years old, no use of antibiotics, bismuth, or traditional Chinese medicine four weeks prior to treatment, no use of PPIs or histamine type 2 receptor antagonists (H2 blockers) two weeks prior to treatment, and informed and consenting to participate in the study. Exclusion criteria included: The presence of serious medical conditions, such as severe heart, lung, or kidney dysfunction, compromised immune functioning, allergies to medications used in the study, mental illness, communication difficulties, pregnancy or lactation, and any organic diseases, such as gastrointestinal tumors and gastrointestinal hemorrhage.

Study design

This was a prospective, multicenter, randomized, open-label and phase II study according to Simon's two-stage optimal design. This study was conducted on patients with *H. pylori* infection in the Gastroenterology Departments of 23 centers from May 2021 to April 2022 in Fujian province, Southeast China. Esomeprazole-amoxicillin dual regimen was abandoned at the beginning of the clinical trial because esomeprazole could not be obtained in Fujian hospital for medical policy adjustment reasons. Patients were randomly assigned 1:1:1:1:1 to five study groups. Simon's two-stage optimal design was used for each group, which was performed according to the following hypothesis: The minimum eradication rate was set at 80%, and the expected eradication rate was set at 90%, with a one-tailed type I error = 5%, and power equal to 80%. In the first stage, 28 eligible patients were entered into each group. If fewer than 23 of 28 patients responded to a treatment, that treatment group would be valid for early termination. Otherwise, an additional 69 patients would be accrued to a maximum size of 97. If more than 83 patients achieved an objective response after the completion of the second stage, the treatment group was considered worthy of further investigation. The probability of early termination was 0.69.

Randomization was done centrally with a random number-generating system and an interactive internet and voice-response system. Clinicians and patients were not masked to treatment assignment. Treatment continued unless intolerable or unsafe adverse effects developed, or consent was withdrawn. A demographic data and medical history were recorded for each patient, including: Age, sex, medical history, coffee, tea, and alcohol consumption, and smoking habits. Coffee or tea consumption was defined as consumption of one or more cups per day. Alcohol consumption was defined as consuming more than 50 g of alcohol per day in the past six months. Smoking was defined as smoking at least one pack of cigarettes per week. Patients with duodenal and/or gastric ulcers were defined as having peptic ulcers, while those without ulcers were defined as having non-ulcer dyspepsia. The esomeprazole-amoxicillin dual regimen was abandoned at the beginning of the clinical trial because esomeprazole could not be obtained at Fujian Hospital due to medical policy adjustments, as presented in Supplementary Table 1.

Diagnosis and treatment regimens for H. pylori infection

Patients were diagnosed with *H. pylori* infection by using 13C-/14C- urea breath test (13C-UBT/14C-UBT), or rapid urease test (San Qiang Bio & Che, Fujian, China). After being diagnosed with *H. pylori* infection, patients were randomly assigned (1:1:1:1:1) to five treatment groups: BQT group (ilaprazole 10 mg, bismuth potassium citrate 220 mg, amoxicillin 1000 mg, and clarithromycin 500 mg, twice daily, for 14 days); BQT-V group (Vonoprazan 20 mg, once daily, bismuth potassium citrate 220 mg twice daily, amoxicillin 1000 mg, twice daily, and clarithromycin 500 mg, twice daily, for 14 days); VAT-7 group (Vonoprazan 20 mg, twice daily, and amoxicillin 1000 mg, three times daily, for 7 days); VAT-10 group (Vonoprazan 20 mg, twice daily, and amoxicillin 1000 mg, three times daily, for 10 days); and VAT-14 group (Vonoprazan 20 mg, once daily, and amoxicillin 1000 mg, three times daily, for 14 days). Eprazole and Vonoprazan were suggested to be taken half an hour before meals, while CLA and AMX were suggested to be taken postprandially.

The study drug information was as follows: ilaprazole (Group Lizhu Pharmaceutical Factory), Vonoprazan (Takeda), amoxicillin (Zhejiang Jinhua Kangenbei Biopharmaceutical Co. LTD), clarithromycin (Guangdong East Sunshine Pharmaceutical Co. LTD), and bismuth potassium citrate (Yuekang Pharmaceutical Group Co. LTD).

Study outcomes

The primary endpoint in this study was the *H. pylori* eradication rate assessed by 13C-urea or 14C-urea breath tests, at least 6 weeks after completing the regimen. The secondary endpoints were the severity and frequency of adverse events, and the rate of clinical symptom remission. The adverse events were recorded in a questionnaire by investigators for 14 days following the commencement of therapy, and symptom severity was evaluated according to a four-point scale system: None, mild (discomfortable or annoying, but not interfering with daily life), moderate (discomfort sufficient to interfere with daily life), and severe (discomfort resulting in discontinuation of eradication therapy)[13]. Patients were asked to recall all unused medications and empty bags to assess compliance.

Statistical analysis

The primary analyses were determined by intention-to-treat (ITT) and per-protocol (PP) analyses. The ITT analysis was defined to include all randomized patients. The patients who were lost to follow-up or who did not undergo 13C-/14C-urea breath tests were considered as treatment failures in the ITT analysis. The PP analysis included patients who achieved > 80% drug compliance and underwent urea breath testing. Drug compliance was recorded in a specific questionnaire form by patients. Efficacy and safety analyses were performed on the intent-to-treat population. Response rates were reported with exact two-sided 95% confidence intervals. Differences among groups were analyzed using Pearson's χ^2 test for categorical variables, and ANOVA for continuous variables, with post hoc analysis using the Bonferroni method. All *P* values were two sided and were considered statistically significant if the *P* value was < 0.05. All analyses were computed using the R V.3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria).

Statement of ethics

This study was approved by the independent Ethics Committees of the Fujian Provincial Hospital (Approval No. K2020-006-02). This study is registered with the Chinese Clinical Trial Registry, ChiCTR2100045778. All subjects signed written informed consents prior to receiving treatment. This study was carried out in accordance with the guidelines of the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT).

RESULTS

Patient enrolment and demographic data

The study flowchart is shown in Figure 1. A total of 362 patients were enrolled within the 1-year study period. In the first stage, 28 patients were enrolled in each group. The numbers of cases eradicated in the VAT-7 group and BQT-V group were 19 and 21, respectively. Since the proportion of responses was not sufficiently high to recommend this regimen to go to the next step in the clinical trial, this group was selected for early termination. The numbers of cases eradicated in the other three groups were 24 for BQT, 26 for VAT-10, and 25 for VAT-14, respectively, which were all greater than 23, therefore these groups were selected for further study. At the second stage, 222 patients were enrolled and randomly assigned to three treatment groups. Demographic data of these participants are presented in Table 1. There was a significant difference in gender. There was no significant difference in age, diagnosis, cigarette smoking, or alcohol, coffee, and tea consumption amongst the three randomized groups.

Eradication rates of H. pylori

The *H. pylori* eradication rates for each regimen are presented in Figure 2. In the ITT analysis, the *H. pylori* eradication rate was 80.2% [95% confidence interval (95%CI): 71.4%-86.8%] in the BQT group, 93.2% (95%CI: 86.6%-96.7%) in the VAT-10 group, and 92.2% (95%CI: 85.3%-96.0%) in the VAT-14 group. In the PP analysis, the *H. pylori* eradication rate was 80.9% (95%CI: 71.7%-87.5%) in the BQT group, 94.0% (95%CI: 87.5%-97.2%) in the VAT-10 group, and 93.9% (95%CI: 87.4%-97.2%) in the VAT-14 group. The results of ITT analysis proved that the *H. pylori* eradication rate in both the VAT-10 (93.2%) and VAT-14 (92.2%) groups was higher than that of the BQT group (80.2%), with rate differences of 13.9% between the BQT and VAT-10 groups, and 12.0% between the BQT and VAT-14 groups. All reported differences were statistically significant. PP analysis also showed significant differences, which were consistent with the results of ITT analysis (Figure 2). These results demonstrated that VAT-10 or VAT-14 was superior to BQT.

Compliances and adverse events

All participants received at least one dose of medication and the adverse events were assessed using the Adverse Event Analysis. The reported adverse events are displayed in Table 2. In total, the incidence of adverse events in the VAT-10 and VAT-14 groups was lower than in the BQT group (25.27% and 13.73% *vs* 37.62%, respectively; $P < 0.001$). Additionally, reported adverse events were more severe in the BQT group than in the VAT-10 and VAT-14 groups. Bitter taste was the most commonly reported adverse event in the BQT group. This adverse effect was more frequently reported in the BQT compared to the VAT-10 group (18.81% *vs* 3.88%; $P = 0.005$), and in the BQT compared to VAT-14 group (18.81% *vs* 5.88%; $P = 0.019$). Nausea was the second most commonly reported adverse event: BQT *vs* VAT-10 (14.85% *vs* 3.88%; $P = 0.042$), and BQT *vs* VAT-14 (14.85% *vs* 3.92%; $P = 0.042$). The other adverse events included dizziness: BQT *vs* VAT-10 (14.85% *vs* 3.88%; $P = 0.028$), and BQT *vs* VAT-14 (14.85% *vs* 1.96%; $P = 0.007$); abdominal discomfort: BQT *vs* VAT-10 (10.89% *vs* 0.97%; $P = 0.02$), and BQT *vs* VAT-14 (10.89% *vs* 3.92%; $P = 0.206$); and anorexia: BQT *vs* VAT-10 (9.90% *vs* 2.91%; $P = 0.158$), and BQT *vs* VAT-14 (9.90% *vs* 1.96%; $P = 0.107$). Patient compliance in the VAT-10 and VAT-14 groups was better than in the BQT group (97.09% and 97.06% *vs* 93.07%, respectively), although no statistical differences were found in these three groups ($P = 0.263$).

There are 4 patients in total who failed to take at least 80% of the study drugs due to adverse events. Among these 4 patients, 1 patient in the VAT-10 group ceased treatment due to dizziness, 1 patient in the VAT-14 group ceased treatment due to skin rash, and 2 patients in the BQT group ceased treatment due to diarrhea and nausea.

Remission of clinical symptoms for each regimen

The clinical symptom relief for the VAT-14 regimen (complete remission rate 58.82%, partial remission rate 33.33%, and no remission rate 7.84%), was significantly better than that of the BQT regimen (complete remission rate 40.59%, partial remission rate 41.58%, and no remission rate 17.82%) ($P = 0.014$). However, the clinical symptom relief for the VAT-10 regimen (complete remission rate 44.66%, partial remission rate 29.12%, and no remission rate 26.21%) was not better than that of the BQT regimen ($P = 1.000$) (Table 3).

Cost-effectiveness analysis of each regimen

Cost-effectiveness analysis showed that the cost-effectiveness ratio (CER) of VAT-10 and VAT-14 were both less than that of BQT (Table 4). Considering that the reported effectiveness for VAT-10 and VAT-14 were equal (Table 4), the VAT-14 regimen, which demonstrated the lowest CER, was the most cost-effective therapy.

DISCUSSION

Research on Vonoprazan has been conducted firstly in Japan. Recently, there have been some studies of Vonoprazan in other countries. Differences in populations may lead to different results from those observed in studies conducted in Japan. In the current study, we conducted a multicenter trial in Fujian, China to assess the efficacy and safety of VAT with different duration and dosages in the first-line treatment of *H. pylori* infection. Vonoprazan plus AMX was approved by the FDA and has been packaged in the Voquezna Dual Pak. However, the product has not been released on the market due to the detection of trace levels of a nitrosamine impurity[14].

Table 1 Baseline characteristics of patients, *n* (%)

	Total	BQT	VAT-10	VAT-14	*P* value
Age (years, mean ± SD)	45.15 ± 12.53	43.84 ± 14.26	45.52 ± 11.26	45.69 ± 12.39	0.428
Range	12.00-80.00	15.00-72.00	27.00-80.00	12.00-77.00	
Gender					0.027
Male	164 (53.59)	48 (51.06)	64 (64.00)	45 (45.45)	
Female	142 (46.41)	46 (48.94)	36 (36.00)	54 (54.55)	
Diagnosis					0.754
Peptic ulcer	42 (13.73)	15 (14.85)	12 (11.65)	15 (14.71)	
Non-ulcer dyspepsia	264 (86.72)	86 (85.15)	91 (88.35)	87 (85.29)	
Cigarette smoking	33 (10.78)	12 (12.77)	9 (9.00)	9 (9.09)	0.618
Alcohol drinking	14 (4.58)	6 (6.38)	4 (4.00)	3 (3.03)	0.524
Tea drinking	41 (13.40)	15 (15.96)	14 (14.00)	10 (10.10)	0.473
Coffee drinking	18 (5.88)	6 (6.38)	2 (2.00)	9 (9.09)	0.097
Family history of gastric cancer	17 (5.56)	4 (4.26)	4 (4.00)	5 (5.05)	0.940
H. pylori family gathering	51 (16.67)	15 (15.96)	15 (15.00)	19 (19.19)	0.581

H. pylori: *Helicobacter pylori*; VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy.

Table 2 Adverse events for each regimen, *n* (%)

Adverse events	BQT	VAT-10	VAT-14	*P* value		
				Total	BQT *vs* VAT-10	BQT *vs* VAT-14
Total	38 (37.62)	25 (25.27)	14 (13.73)	< 0.001	0.112	0.001
Bitter taste	19 (18.81)	4 (3.88)	6 (5.88)	< 0.001	0.005	0.019
Nausea	15 (14.85)	4 (3.88)	4 (3.92)	0.003	0.042	0.042
Dizziness	15 (14.85)	4 (3.88)	2 (1.96)	< 0.001	0.028	0.007
Diarrhea	11 (10.89)	4 (3.88)	10 (9.80)	0.144	-	-
Abdominal discomfort	11 (10.89)	1 (0.97)	4 (3.92)	0.005	0.020	0.206
Abdominal pain	10 (9.90)	4 (3.88)	7 (6.86)	0.236	-	-
Anorexia	10 (9.90)	3 (2.91)	2 (1.96)	0.022	0.158	0.107
Constipation	9 (8.91)	6 (5.83)	5 (4.90)	0.481	-	-
Belching	9 (8.91)	2 (1.94)	4 (3.92)	0.062	-	-
Vomiting	8 (7.92)	1 (0.97)	4 (3.92)	0.040	0.114	0.719
Skin rash	7 (6.93)	1 (0.97)	2 (1.96)	0.054	-	-
Bloating	7 (6.93)	6 (5.83)	4 (3.92)	0.638	-	-
Heartburn	7 (6.93)	1 (0.97)	3 (2.94)	0.060	-	-
Insomnia	6 (5.94)	1 (0.97)	3 (2.94)	0.107	-	-

VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy.

The physiological basis for an effective dual therapy is thought to be associated with the ability of the anti-secretory component of the therapy to maintain an intragastric pH above 6. Theoretically, raising the gastric pH above 6 causes bacteria to begin replicating and increases bacterial sensitivity to amoxicillin[15]. A high-dose, high-frequency dual therapy of AMX (≥ 2.0 g/day) and a PPI (at least twice daily) for 14 days has been reported to be effective in eradicating *H. pylori* as a first-line therapy[16,17]. However, the high medication doses and frequent medication administration

Table 3 Remission of clinical symptoms for each regimen, *n* (%)

Remission	BQT	VAT-10	VAT-14	*P* value		
				Total	BQT *vs* VAT-10	BQT *vs* VAT-14
Complete remission	41 (40.59)	46 (44.66)	60 (58.82)	< 0.001	1.000	0.014
Partial remission	42 (41.58)	30 (29.12)	34 (33.33)			
No remission	18 (17.82)	27 (26.21)	8 (7.84)			

VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy.

Table 4 Cost-effectiveness analysis of each regimen

	BQT	VAT-10	VAT-14
Cost (CNY per percent)	334.18	216.80	163.52
Effectiveness (%)	80.90	94.00	93.90
CER (CNY per percent)	4.13	2.31	1.74
ICER (CNY per percent)		-1.82	-2.39

Effectiveness, the eradication rate in the per-protocol analysis (%). VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy; CER: Cost-effectiveness ratio; Cost: Direct drug costs per patient; ICER: Incremental cost-effectiveness ratio.

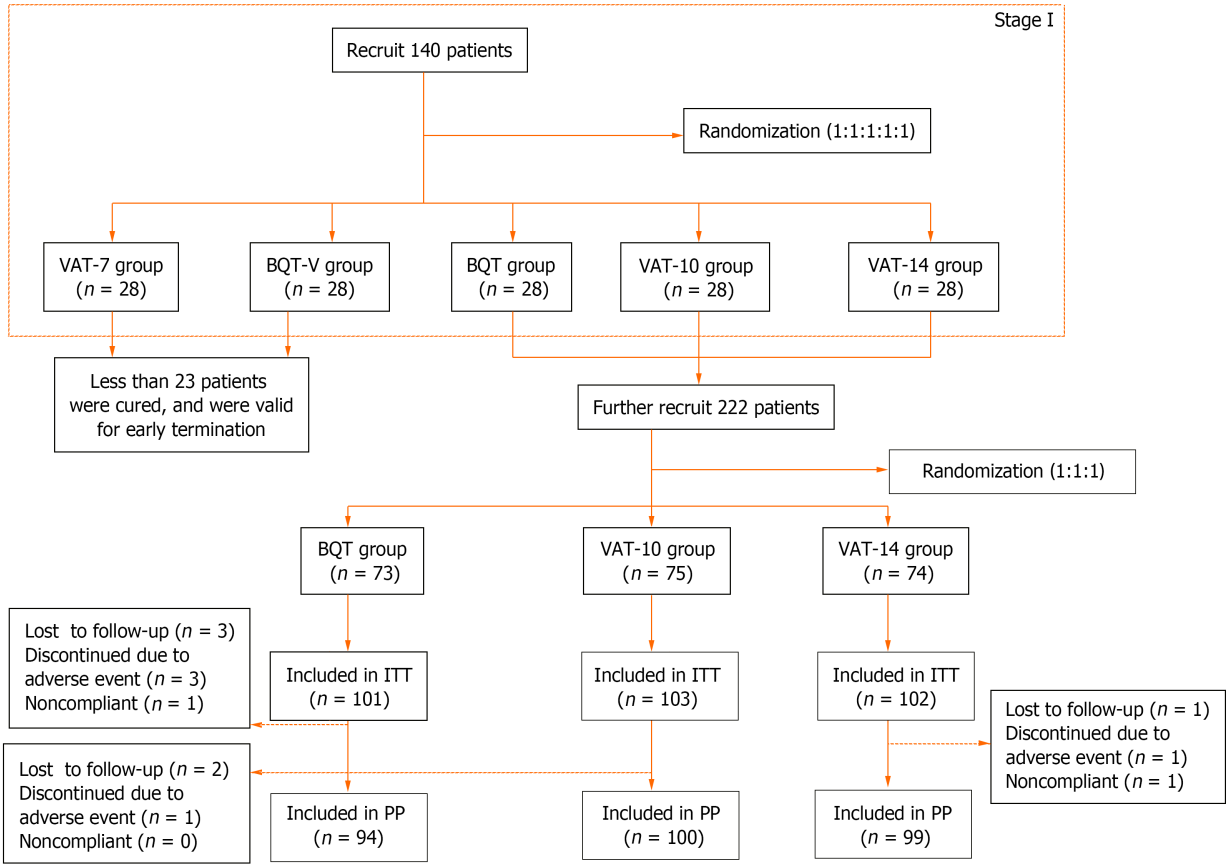

Figure 1 Flowchart of the clinical trial. VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy; ITT: Intention-to-treat; PP: Per-protocol.

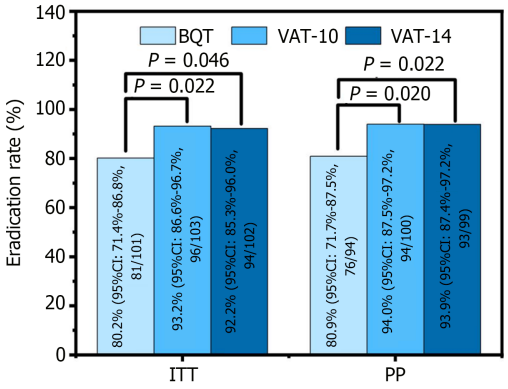

Figure 2 Intention-to-treat and per-protocol analyses of *Helicobacter pylori* eradication rates attained by bismuth quadruple therapy, Vonoprazan-amoxicillin dual therapy-10 and Vonoprazan-amoxicillin dual therapy-14. There were statistically significant differences in the eradication rates among the three regimens. VAT: Vonoprazan-amoxicillin dual therapy; BQT: Bismuth quadruple therapy; ITT: Intention-to-treat; PP: Per-protocol; 95%CI: 95% confidence interval.

required in such dual therapy regimens may induce some adverse events, resulting in poor patient compliance.

A dual therapy using Vonoprazan and AMX was first studied in Japan[18]. The therapy consisted of Vonoprazan (20 mg twice/day) and AMX (750 mg twice/day) for 7 days. This dual therapy regimen achieved an eradication rate of 92.9%, and was noninferior to Vonoprazan-amoxicillin-clarithromycin triple therapy in the ITT analysis. However, VAT-7 regimen in our study achieved a low eradication rate, which is similar to the results of two clinical studies in China[19,20]. As the course of VAT was extended to 10 or 14 days, the eradication rate of *H. pylori* increased to more than 90%. However, the eradication rate of 14 days VAT in Europe and the United States[12] was much lower than those of our study and other studies in China[21,22]. The underlying reason is unknown. It may be related to different species of *H. pylori* endemic in different areas around the world, leading to varied treatment outcomes. As for the dosage of Vonoprazan used in VAT, most studies proposed 20 mg twice a day. While we tried to use the dose of 20 mg a day in the VAT-14 group, we also achieved a satisfactory eradication rate. We showed that the dose of 20 mg a day for Vonoprazan was enough to maintain a sufficient intragastric pH for *H. pylori* eradication. A 10 or 14 days regimen is better than 7 days regimens, as previous numerous regimens.

The plasma concentration of amoxicillin decreases significantly after 6 to 8 hours. The effective blood concentration of amoxicillin can be maintained by increasing the frequency of administration. Compared with the frequency of twice a day, amoxicillin administered 3 to 4 times a day can improve the eradication rate of *H. pylori*[23]. As for the dosage of amoxicillin, a multicenter randomized trial in Japan showed low-dose amoxicillin (1.5 g/day) dual therapy provided acceptable and similar *H. pylori* eradication rates compared to Vonoprazan-based triple therapy in regions with high clarithromycin resistance[10]. However, the data from China indicated such regimen didn't provide the satisfactory eradication rate[20]. Thus, our study used a high dose of amoxicillin (1000 mg three times a day) to increase the eradication rate of *H. pylori* in VAT.

Due to its cytochrome P4502C19 (CYP2C19) polymorphism, Vonoprazan is less likely to interact with other drugs, such as warfarin and clopidogrel, than are PPIs, such as lansoprazole and omeprazole. CYP2C19 polymorphisms are not significant independent factors of *H. pylori* eradication using VAT. Furthermore, VAT regimens contain only two drugs and induce fewer adverse events than traditional BQT regimen. VAT regimens were also found to be more economical than BQT regimen. The eradication rate for BQT regimen was only 80.90% in our study. Our previous study showed that the rates of *H. pylori* antimicrobial resistance to amoxicillin, metronidazole, clarithromycin, and levofloxacin in Fujian were 14.90%, 50.96%, 38.94%, and 35.10%, respectively[24]. Hence, the treatment failure of BQT and BQT-V regimen may be due to the high resistance rate of CLA in Fujian. Therefore, under these circumstances, empiric treatment with a VAT regimen will have the potential to achieve higher eradication rates, and suppress the emergence of multidrug-resistant *H. pylori* strains, especially in areas where antibiotic resistance is growing or antimicrobial sensitivity tests are not readily available.

VAT regimen is also suitable for areas where bismuth cannot be obtained. If the patient is forbidden to use bismuth or cannot tolerate its adverse reactions, VAT regimen should be considered. VAT regimen is especially useful for elderly patients or patients with underlying diseases, such as liver and kidney dysfunctions. However, the VAT regimen is not suitable for patients who are allergic to penicillin antibiotics, such as amoxicillin. New regimens including other antibiotics combined with Vonoprazan warrants further investigation.

It should be noted that antibiotic resistance is not the sole reason for the failure of the effectiveness of *H. pylori* treatments in clinical practice. Poor patient compliance may also lead to treatment failure. In this study, medication side effects were the main reason for poor patient compliance. Failure of patients to take the full course of prescribed antibiotics increases the risk of bacteria developing antibiotic resistance. In the current study, the adverse reaction rate was higher in the BQT group than that in the VAT-10 group or VAT-14 group. However, overall patient compliance was excellent in all three groups. In our experience, patient education, including explanation of possible medication side effects and emphasis on the importance of treatment compliance is helpful in increasing patient compliance.

There are several limitations in our study. Firstly, the number of subjects in this study was small. The continuous involvement of more patients will be implemented in future studies since the *H. pylori* eradication rates observed were highly encouraging. Secondly, since most of the dual therapy studies published were performed in Asia, there might be bias caused by population characteristics. Therefore, a randomized, multicenter trial involving Europe, Africa, and other regions of the world should be designed to observe the effectiveness of VAT regimens in these regions in the future.

CONCLUSION

In summary, VAT with a duration of 10 days or 14 days, but not 7 days, achieved higher eradication rates than BQT with a more tolerable and manageable safety profile in patients in Fujian, China with *H. pylori* infection.

FOOTNOTES

Author contributions: Lin ZH and Wei JQ should be considered co-corresponding authors because of their significant contributions throughout the research; Lin ZH and Wei JQ conceived, designed, and supervised the study; Huang XP and Liu YJ contributed equally to the study; Huang XP and Liu YJ designed and performed the experiments, analyzed the data, prepared figures and tables, and authored and reviewed drafts of the article; Lin SW, Shao YF, Qiu F, Qiu QW, Xu ZK, Chen JX, Chen LH, Lin ZQ, Dai WH, Zhang MQ, Jiang Q, Xiao ZQ, Cheng XX, Zhang XF, You WB, Chen W, Li LQ, Lin WX, Wang YF, Lai FJ, Chen LQ, Huang ZH, and Zheng WQ collected and analyzed the data; and all authors have read and approved the final manuscript.

Supported by the Natural Science Foundation of Fujian Province, No. 2020J011087 and No. 2022J011025; Medical Innovation Project of Fujian Provincial Health Commission, No. 2020CXA006; and Zhuhai Science and Technology Project, No. 20181117E030040.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Fujian Provincial Hospital Institutional Review Board (Approval No. K2021-006-02).

Clinical trial registration statement: This study is registered at https://www.chictr.org.cn/showprojEN.html?proj=121897. The registration identification number is ChiCTR2100045778.

Informed consent statement: All study participants or their legal guardians provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country of origin: China

ORCID number: Xue-Ping Huang 0000-0003-2803-2277; Wei-Xing Lin 0000-0002-3274-996X; Jin-Qi Wei 0000-0001-5308-4920; Zhi-Hui Lin 0000-0002-2165-9280.

S-Editor: Chen YL
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Burucoa C**, Axon A. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2017; **22**: Suppl 1 [PMID: 28891138 DOI: 10.1111/hel.12403]

2 **Thung I**, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of Helicobacter pylori antibiotic resistance. *Aliment Pharmacol Ther* 2016; **43**: 514-533 [PMID: 26694080 DOI: 10.1111/apt.13497]

3 **Megraud F**, Bruyndonckx R, Coenen S, Wittkop L, Huang TD, Hoebeke M, Bénéjat L, Lehours P, Goossens H, Glupczynski Y; European Helicobacter pylori Antimicrobial Susceptibility Testing Working Group. Helicobacter pylori resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut* 2021; **70**: 1815-1822 [PMID: 33837118 DOI: 10.1136/gutjnl-2021-324032]

4 **Liu WZ**, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou LY, Chen Y, Wang JB, Du YQ, Lu NH; Chinese Society of Gastroenterology, Chinese Study Group on Helicobacter pylori and Peptic Ulcer. Fifth Chinese National Consensus Report on the management of Helicobacter pylori infection. *Helicobacter* 2018; **23**: e12475 [PMID: 29512258 DOI: 10.1111/hel.12475]

5 **Unge P**, Gad A, Gnarpe H, Olsson J. Does omeprazole improve antimicrobial therapy directed towards gastric Campylobacter pylori in patients with antral gastritis? A pilot study. *Scand J Gastroenterol Suppl* 1989; **167**: 49-54 [PMID: 2617169 DOI: 10.3109/00365528909091311]

6 **van der Hulst RW**, Keller JJ, Rauws EA, Tytgat GN. Treatment of Helicobacter pylori infection: a review of the world literature. *Helicobacter* 1996; **1**: 6-19 [PMID: 9398908 DOI: 10.1111/j.1523-5378.1996.tb00003.x]

7 **Attumi TA**, Graham DY. Increasing the duration of dual amoxicillin plus omeprazole Helicobacter pylori eradication to 6 weeks: a pilot study. *J Gastroenterol Hepatol* 2012; **27**: 59-61 [PMID: 21793914 DOI: 10.1111/j.1440-1746.2011.06876.x]

8 **Hwong-Ruey Leow A**, Chang JV, Goh KL. Searching for an optimal therapy for H pylori eradication: High-dose proton-pump inhibitor dual therapy with amoxicillin *vs* standard triple therapy for 14 days. *Helicobacter* 2020; **25**: e12723 [PMID: 32713104 DOI: 10.1111/hel.12723]

9 **Gao CP**, Zhou Z, Wang JZ, Han SX, Li LP, Lu H. Efficacy and safety of high-dose dual therapy for Helicobacter pylori rescue therapy: A systematic review and meta-analysis. *J Dig Dis* 2016; **17**: 811-819 [PMID: 27977071 DOI: 10.1111/1751-2980.12432]

10 **Suzuki S**, Gotoda T, Kusano C, Ikehara H, Ichijima R, Ohyauchi M, Ito H, Kawamura M, Ogata Y, Ohtaka M, Nakahara M, Kawabe K. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line Helicobacter pylori treatment: a multicentre randomised trial in Japan. *Gut* 2020; **69**: 1019-1026 [PMID: 31915235 DOI: 10.1136/gutjnl-2019-319954]

11 **Qian HS**, Li WJ, Dang YN, Li LR, Xu XB, Yuan L, Zhang WF, Yang Z, Gao X, Zhang M, Li X, Zhang GX. Ten-Day Vonoprazan-Amoxicillin Dual Therapy as a First-Line Treatment of Helicobacter pylori Infection Compared With Bismuth-Containing Quadruple Therapy. *Am J Gastroenterol* 2023; **118**: 627-634 [PMID: 36729890 DOI: 10.14309/ajg.0000000000002086]

12 **Chey WD**, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan Triple and Dual Therapy for Helicobacter pylori Infection in the United States and Europe: Randomized Clinical Trial. *Gastroenterology* 2022; **163**: 608-619 [PMID: 35679950 DOI: 10.1053/j.gastro.2022.05.055]

13 **Wu DC**, Kuo CH, Tsay FW, Hsu WH, Chen A, Hsu PI. A Pilot Randomized Controlled Study of Dexlansoprazole MR-Based Triple Therapy for Helicobacter Pylori Infection. *Medicine (Baltimore)* 2016; **95**: e2698 [PMID: 26986096 DOI: 10.1097/MD.0000000000002698]

14 **Park F**. Phathom Pharmaceuticals Provides Update on New Drug Application Review of Vonoprazan for Erosive Esophagitis. [cited 20 June 2024]. Available from: https://investors.phathompharma.com/news-releases/news-release-details/phathom-pharmaceuticals-provides-update-new-drug-application#:~:text=FLORHAM%20PARK%2C%20N.J.%2C%20Jan.%2003%2C%202023%20%28GLOBE%20NEWSWIRE%29,%28PDUFA%29%20target%20action%20date%20of%20January%2011%2C%202023

15 **Scott D**, Weeks D, Melchers K, Sachs G. The life and death of Helicobacter pylori. *Gut* 1998; **43** Suppl 1: S56-S60 [PMID: 9764042 DOI: 10.1136/gut.43.2008.s56]

16 **Yang J**, Zhang Y, Fan L, Zhu YJ, Wang TY, Wang XW, Chen DF, Lan CH. Eradication Efficacy of Modified Dual Therapy Compared with Bismuth-Containing Quadruple Therapy as a First-Line Treatment of Helicobacter pylori. *Am J Gastroenterol* 2019; **114**: 437-445 [PMID: 30807294 DOI: 10.14309/ajg.0000000000000132]

17 **Yu L**, Luo L, Long X, Liang X, Ji Y, Graham DY, Lu H. High-dose PPI-amoxicillin dual therapy with or without bismuth for first-line Helicobacter pylori therapy: A randomized trial. *Helicobacter* 2019; **24**: e12596 [PMID: 31111580 DOI: 10.1111/hel.12596]

18 **Furuta T**, Yamade M, Kagami T, Uotani T, Suzuki T, Higuchi T, Tani S, Hamaya Y, Iwaizumi M, Miyajima H, Umemura K, Osawa S, Sugimoto K. Dual Therapy with Vonoprazan and Amoxicillin Is as Effective as Triple Therapy with Vonoprazan, Amoxicillin and Clarithromycin for Eradication of Helicobacter pylori. *Digestion* 2020; **101**: 743-751 [PMID: 31434101 DOI: 10.1159/000502287]

19 **Hu Y**, Xu X, Ouyang YB, He C, Li NS, Xie C, Peng C, Zhu ZH, Xie Y, Shu X, Lu NH, Zhu Y. Optimization of vonoprazan-amoxicillin dual therapy for eradicating Helicobacter pyloriinfection in China: A prospective, randomized clinical pilot study. *Helicobacter* 2022; **27**: e12896 [PMID: 35466521 DOI: 10.1111/hel.12896]

20 **Lin Y**, Xu H, Yun J, Yu X, Shi Y, Zhang D. The efficacy of vonoprazan combined with different dose amoxicillin on eradication of Helicobacter pylori: an open, multicenter, randomized clinical study. *Ann Transl Med* 2022; **10**: 987 [PMID: 36267745 DOI: 10.21037/atm-22-4133]

21 **Hu Y**, Xu X, Liu XS, He C, Ouyang YB, Li NS, Xie C, Peng C, Zhu ZH, Xie Y, Shu X, Zhu Y, Graham DY, Lu NH. Fourteen-day vonoprazan and low- or high-dose amoxicillin dual therapy for eradicating Helicobacter pylori infection: A prospective, open-labeled, randomized non-inferiority clinical study. *Front Immunol* 2022; **13**: 1049908 [PMID: 36726990 DOI: 10.3389/fimmu.2022.1049908]

22 **Gao W**, Teng G, Wang C, Xu Y, Li Y, Cheng H. Eradication rate and safety of a "simplified rescue therapy": 14-day vonoprazan and amoxicillin dual regimen as rescue therapy on treatment of Helicobacter pylori infection previously failed in eradication: A real-world, retrospective clinical study in China. *Helicobacter* 2022; **27**: e12918 [PMID: 35877765 DOI: 10.1111/hel.12918]

23 **Gao CP**, Zhang D, Zhang T, Wang JX, Han SX, Graham DY, Lu H. PPI-amoxicillin dual therapy for Helicobacter pylori infection: An update based on a systematic review and meta-analysis. *Helicobacter* 2020; **25**: e12692 [PMID: 32314468 DOI: 10.1111/hel.12692]

24 **Huang X**, Liu Y, Lin Z, Wu B, Nong G, Chen Y, Lu Y, Ji X, Zhou X, Suo B, Chen Q, Wei J. Minimum inhibitory concentrations of commonly used antibiotics against Helicobacter Pylori: A multicenter study in South China. *PLoS One* 2021; **16**: e0256225 [PMID: 34473713 DOI: 10.1371/journal.pone.0256225]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com