OPEN ACCESS

Original research

Simplified *Helicobacter pylori* therapy for patients with penicillin allergy: a randomised controlled trial of vonoprazan-tetracycline dual therapy

Wen Gao ,[1] Jianxiang Liu,[1] Xiaolei Wang,[1] Jingwen Li,[2] Xuezhi Zhang,[3] Hui Ye,[3] Jiang Li,[1] Xinhong Dong,[1] Binbin Liu,[1] Chi Wang,[1] Ying Xu,[1] Guigen Teng ,[1] Yuling Tian,[1] Jinpei Dong ,[1] Chaoyi Ge,[1] Hong Cheng[1]

[1]GI Department, Peking University First Hospital, Beijing, Beijing, China
[2]Tsinghua University School of Medicine, Beijing, Beijing, China
[3]TCM and Integrative Medicine Department, Peking University First Hospital, Beijing, Beijing, China

Correspondence to
Dr Hong Cheng, GI Department, Peking University First Hospital, Beijing, Beijing 100034, China; chenghong1969@163.com

Received 10 April 2024
Accepted 8 June 2024
Published Online First 21 June 2024

To cite: Gao W, Liu J, Wang X, *et al*. *Gut* 2024;**73**:1414–1420.

ABSTRACT

Background and aims This study aimed to evaluate the efficacy and safety of vonoprazan and tetracycline (VT) dual therapy as first-line treatment for *Helicobacter pylori* infection in patients with penicillin allergy.

Methods In this randomised controlled trial, treatment-naïve adults with *H. pylori* infection and penicillin allergy were randomised 1:1 to receive either open-label VT dual therapy (vonoprazan 20 mg two times per day+tetracycline 500 mg three times a day) or bismuth quadruple therapy (BQT; lansoprazole 30 mg two times per day+colloidal bismuth 150 mg three times a day+tetracycline 500 mg three times a day+metronidazole 400 mg three times a day) for 14 days. The primary outcome was non-inferiority in eradication rates in the VT dual group compared with the BQT group. Secondary outcomes included assessing adverse effects.

Results 300 patients were randomised. The eradication rates in the VT group and the BQT group were: 92.0% (138/150, 95% CI 86.1% to 95.6%) and 89.3% (134/150, 95% CI 83.0% to 93.6%) in intention-to-treat analysis (difference 2.7%; 95% CI −4.6% to 10.0%; non-inferiority p=0.000); 94.5% (138/146, 95% CI 89.1% to 97.4%) and 93.1% (134/144, 95% CI 87.3% to 96.4%) in modified intention-to-treat analysis (difference 1.5%; 95% CI −4.9% to 8.0%; non-inferiority p=0.001); 95.1% (135/142, 95% CI 89.7% to 97.8%) and 97.7% (128/131, 95% CI 92.9% to 99.4%) in per-protocol analysis (difference 2.6%; 95% CI −2.9% to 8.3%; non-inferiority p=0.000). The treatment-emergent adverse events (TEAEs) were significantly lower in the VT group (14.0% vs 48.0%, p=0.000), with fewer treatment discontinuations due to TEAEs (2.0% vs 8.7%, p=0.010).

Conclusions VT dual therapy demonstrated efficacy and safety as a first-line treatment for *H. pylori* infection in the penicillin-allergic population, with comparable efficacy and a lower incidence of TEAEs compared with traditional BQT.

Trial registration number ChiCTR2300074693.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High-dose amoxicillin dual therapy is specifically effective for treating *Helicobacter pylori* infection.
⇒ So far, no dual therapy with a single antibiotic other than amoxicillin has been reported.
⇒ This therapy is unsuitable for individuals allergic to penicillin.

WHAT THIS STUDY ADDS

⇒ This study is the first randomised controlled trial using tetracycline-containing dual therapy for *H. pylori* treatment.
⇒ The results show that vonoprazan-tetracycline (VT) dual therapy is not inferior to classic bismuth quadruple therapy in efficacy and offers better safety and adherence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The VT dual regimen has been proven effective, indicating that combining a single sensitive antibiotic with potent acid suppression can potentially eradicate *H. pylori* and offers more possibilities for expanding dual therapy.

INTRODUCTION

Helicobacter pylori eradication treatment is essential for decreasing the risk of gastric cancer.[1] High-dose proton pump inhibitor (PPI) or standard-dose vonoprazan (a novel potassium-competitive acid blocker) plus amoxicillin dual therapy has been proven to be effective and safe for *H. pylori* treatment in Asia.[2 3] However, amoxicillin dual therapy may not be suitable for individuals allergic to penicillin or infected with *H. pylori* resistant to amoxicillin. Tetracycline is one of the most effective antimicrobial agents against *H. pylori*, with resistance generally <1.2%~3.3%.[4] Traditionally, tetracycline was used as a component of bismuth quadruple therapy (BQT: PPI, bismuth, metronidazole and tetracycline). In our previous retrospective study, 14-day vonoprazan and tetracycline (VT) dual therapy achieved eradication rates of 100% (18/18) as first-line treatment and 90.9% (40/44, 95% CI 78.8%~96.4%) as rescue treatment.[5]

This study aimed to prospectively evaluate the efficacy and tolerability of 14-day VT dual therapy compared with BQT as first-line treatment.

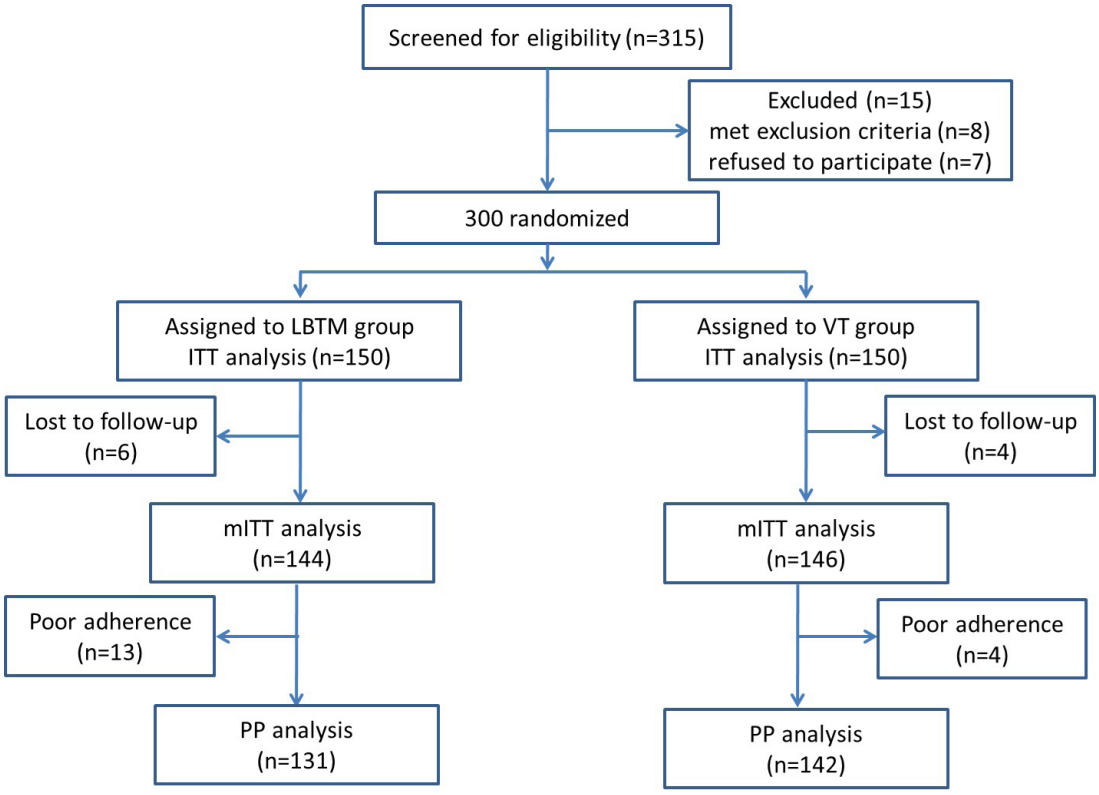

Figure 1 Flow chart of screening and recruitment of study subjects. LBTM group: (or bismuth quadruple therapy group) quadruple therapy group including lansoprazole 30 mg two times per day+colloidal bismuth 150 mg three times a day+tetracycline 500 mg three times a day+metronidazole 400 mg three times a day) for 14 days. VT group: dual therapy group including vonoprazan 20 mg two times per day+tetracycline 500 mg three times a day for 14 days. Data are n (%), or mean (SD). Cigarette smoking was defined by consumed >5 cigarettes a day or >1 cigarette pack/week consumed in the past 6 months. Alcohol drinking was defined by >50 g of alcohol/day consumed in the past 6 months. Family history of gastric cancer was defined as a family history of gastric cancer in a first-degree relative (such as parents, siblings or children), which is associated with double to triple the risk of gastric cancer.[6] The severity of AE was graded as: mild: transient and well-tolerated; moderate: discomfort noticeably interfering with daily activities; severe: considerable interference with daily activities, or requiring hospitalisation, or resulting in a study-related death. AEs, adverse effects; ITT, intention-to-treat analysis; mITT, modified intention-to-treat analysis; PP, per-protocol analysis.

MATERIALS AND METHODS

Study design and participants

This study was a prospective, single-centre, open-label, randomised controlled, non-inferiority trial conducted between August 2023 and March 2024 at Peking University First Hospital in China. Reporting adhered to the Consolidated Standards of Reporting Trials statement guidelines for randomised controlled trials. This trial was registered at chictr.org.cn (ChiCTR2300074693). The coauthors had access to the study data and have reviewed and approved the final manuscript.

Eligible patients were aged between 18 and 70 years, were treatment-naïve for *H. pylori*, and met the following criteria: they had not undergone prior treatment for *H. pylori* and were allergic to penicillin (due to an allergy to penicillin or a history of a positive penicillin skin test). Exclusion criteria included subjects who had previously received *H. pylori* treatment, pregnant or lactating women, individuals with severe systemic diseases or malignancy, those receiving antibiotics, bismuth, antisecretory drugs or with contraindications to the study drugs, or individuals deemed unsuitable for participation in the study by the researcher.

On enrolment, all subjects underwent confirmation of *H. pylori* infection with a positive ^{13}C-urea breath test (UBT, 75 mg ^{13}C-urea, Shenzhen Zhonghe Headway Bio-Sci & Tech).

Randomisation and interventions

At the start of the trial, patients were randomly assigned in a 1:1 ratio to receive either open-label VT dual therapy, consisting of vonoprazan 20 mg two times per day (20 mg/tablet, Takeda Pharmaceutical) and tetracycline 500 mg three times a day (250 mg/tablet, Guilin Pharmaceutical), or BQT therapy, consisting of lansoprazole 30 mg two times per day (30 mg/tablet, Takeda Pharmaceutical), colloidal bismuth 150 mg three times a day (North China Pharmaceutical), tetracycline 500 mg three times a day (250 mg/tablet, Guilin Pharmaceutical) and metronidazole 400 mg three times a day (Sichuan Kelun Pharmaceutical Research Institute), each administration for a duration of 14 days. Patients were instructed to take vonoprazan, lansoprazole and bismuth 30 min before meals, while tetracycline and metronidazole were to be taken immediately after meals.

Randomisation was conducted using a computer-generated random number sequence with a block size of four. The sequence was sealed in an envelope and kept by an independent research assistant until the intervention was assigned. This study was open-labelled, and both physicians and patients were aware of the treatment received. The technician responsible for performing ^{13}C-UBT was unaware of the treatment allocation. All patients were informed of the medication administration schedule, potential adverse events and the procedure for reporting them. Throughout and following the treatment

Table 1 Demographic and clinical data of all patients who were involved

	LBTM group (n=150)	VT group (n=150)	Z-score	P value
Age (mean, SD) years range	47.4 (12.8) 18–70	46.6 (12.9) 18–70	−0.475	0.635
Sex (M/F)	47/103 (1:2.2)	43/107 (1:2.5)	−0.503	0.615
Body weight (mean, SD) kg	63.5 (11.2)	64.0 (14.0)	−0.613	0.540
BMI (mean, SD) kg/m^2	23.2 (3.3)	23.2 (3.7)	−0.361	0.718
Cigarette smoking	15 (10.0%)	8 (5.3%)	−1.516	0.129
Alcohol drinking	27 (18.0%)	16	−1.622	0.105
Family history of gastric cancer	19 (12.7%)	18 (12.0%)	−0.175	0.861
Endoscopy diagnosis				
Gastritis	122 (81.3%)	131 (87.3)	−1.329	0.184
Peptic ulcers	28 (18.7%)	19 (12.7%)		
Concomitant diseases	1.00	1.61	−1.816	0.069
Diabetes mellitus	10	8	−0.485	0.627
Hypertension	22	24	−0.320	0.749
Bronchial asthma	32	32	1.284	0.199
Hepatobiliary disease	16	23	−1.200	0.230
Chronic kidney disease	3	7	−1.765	0.078
Thyroid disease	19	21	−0.876	0.381
Dermatosis	18	10	1.585	0.113
Concomitant medications	0.43	0.85	−1.858	0.063
Loss of follow-up	6 (4.0%)	4 (2.7%)	−0.642	0.521
Adherence, n/N (%)	131/150 (87.3%)	142/150 (94.7%)	−2.215	0.027

BMI, body mass index; F, female; LBTM, lansoprazole, bismuth, tetracycline, metronidazole; M, male; VT, vonoprazan and tetracycline.

period, patients were monitored for any discomforts. Patient education during consultations, combined with offline and online follow-up, was performed to enhance adherence.

Trial assessments

Demographic characteristics and relevant medical history were obtained during the screening visit. Treatment-emergent adverse events (TEAEs) and concomitant medication use were recorded. TEAEs were collected from patients who received at least one dose of medicine.

The primary end point was the eradication rate, assessed by *H. pylori* status via ^{13}C-UBT at week 8 (6 weeks after the last dose of study drugs). The secondary end point included the incidence and severity of adverse events and adherence. The severity of adverse events was graded as follows: 'none'; 'mild' (transient and well-tolerated); 'moderate' (discomfort noticeably interfering with daily activities) or 'severe' (considerable interference with daily activities, or requiring hospitalisation, or resulting in a study-related death). Adherence was considered 'poor', if the patient had taken <80% of the prescribed medications.

Sample size calculation and statistical analysis

As a positive drug parallel control with a non-inferiority hypothesis test, the sample size was determined based on the primary end point. The sample ratio of the VT dual group to the BQT group was set at 1:1, employing a unilateral test with a one-sided α error of 0.025, a power of 80% (equivalent to a β error of 0.20) and a non-inferiority threshold of 10%. Assuming an eradication rate of 90% for the control group,[6] PASS 2021 software calculated that 142 patients per treatment group would provide over 90% power to establish non-inferiority. Accounting for potential dropouts (estimated at approximately 5% of subjects), a sample size of at least 300 subjects (with 150 subjects in each group) was targeted for recruitment in this trial.

The effectiveness of treatment was assessed in three patient cohorts: (1) intention-to-treat (ITT) analysis, which encompassed all patients collected from 2023 to 2024 with a follow-up of at least 2 months. Cases lost to follow-up were considered treatment failures; (2) modified intention-to treat (mITT) analysis, which comprised patients who received at least one dose of medication and underwent reexamination of ^{13}C-UBT at least 6

Table 2 Eradication rate of each group

Analysis	LBTM group	VT group	Difference	P value for difference	P value for non-inferiority
ITT	89.3% (134/150)	92.0% (138/150)	2.7%	0.56	0.000
95% CI	83.0% to 93.6%	86.1% to 95.6%	−4.6% to 10.0%		
mITT	93.1% (134/144)	94.5% (138/146)	1.5%	0.78	0.000
95% CI	87.3% to 96.4%	89.1% to 97.4%	−4.9% to 8.0%		
PP	97.7% (128/131)	95.1% (135/142)	2.6%	0.25	0.001
95% CI	92.9% to 99.4%	89.7% to 97.8%	−2.9% to 8.3%		

ITT, intention-to treat; LBTM, lansoprazole, bismuth, tetracycline and metronidazole; mITT, modified intention-to treat; PP, per-protocol; VT, vonoprazan and tetracycline.

Table 3 Cure rates of those patients who stopped prematurely (with poor adherence) in each group

Group	No.	Sex	Age (years)	Duration of medication (days)	Successful eradication	Cure rate
LBTM group (n=13)	088	F	60	1	No	6/13 (46.2%)
	092	F	42	1	No	
	090	F	46	2	No	
	107	F	47	2	No	
	008	F	60	3	No	
	089	F	62	3.5	No	
	150	F	39	8	Yes	
	129	F	40	9	No	
	023	M	51	10	Yes	
	024	F	32	10	Yes	
	096	F	64	10	Yes	
	143	F	55	10	Yes	
	149	F	42	10	Yes	
VT group (n=4)	150	F	26	3	No	3/4 (75.0%)
	049	F	47	8	Yes	
	012	F	68	10	Yes	
	075	F	35	10	Yes	

F, female; LBTM, lansoprazole, bismuth, tetracycline, metronidazole; M, male; VT, vonoprazan and tetracycline.

weeks after the end of treatment, regardless of adherence. This analysis was designed to reflect results closest to those observed in clinical practice; (3) per-protocol (PP) analysis, which included patients who had taken at least 80% of the study drugs and completed follow-up.

Continuous variables were presented as the mean±SD, while categorical variables were expressed as numbers and percentages (%). Data analysis employed Student's t-test for continuous variables and either the χ^2 test or Fisher's exact test for categorical variables, as appropriate. All p values were two-tailed except for the test of non-inferiority, where the level of statistical significance was specified as $p<0.05$. Statistical analysis was conducted using SPSS statistical software (V.26).

RESULTS

Patients enrolled and baseline characteristics

Enrolment occurred between August 2023 and March 2024 at Peking University First Hospital. Out of 315 patients screened for eligibility, a total of 300 were randomised, with 150 subjects allocated to the VT dual therapy group and 150 subjects to the BQT group (figure 1). Final follow-up was completed in March 2024.

The demographic and clinical characteristics of the enrolled population are summarised in table 1. All patients were deemed penicillin allergy, either due to previous penicillin allergy or a positive history in previous penicillin skin test. There was no significant difference between the two groups in terms of gender, age, body weight, body mass index (BMI), smoking and drinking habits, family history of gastric cancer, diagnosis, accompanying diseases and medicines. Among the enrolled subjects, four cases in the VT dual therapy group and six cases in the BQT group were lost to follow-up without ^{13}C-UBT results. These 10 cases were considered treatment failures in the ITT analysis and were excluded in the mITT analysis. Additionally, 4 subjects in the VT dual therapy group and 13 subjects in the BQT group discontinued treatment (taken <80% of tablets) but underwent ^{13}C-UBT follow-up. In total, 27 subjects (8 in the VT dual therapy group and 19 in the BQT group) were excluded from the PP analysis (figure 1).

Eradication of *H. pylori* infection

The eradication rates in the VT dual therapy group and the BQT group were 92.0% (138/150, 95% CI 86.1% to 95.6%) and 89.3% (134/150, 95% CI 83.0% to 93.6%) in the ITT analysis (difference 2.7%; 95% CI −4.6% to 10.0%; non-inferiority p=0.000), respectively; 95.1% (135/142, 95% CI 89.7% to 97.8%) and 97.7% (128/131, 95% CI 92.9% to 99.4%) in the PP analysis (difference 2.6%; 95% CI −2.9% to 8.3%; non-inferiority p=0.000), 94.5% (138/146, 95% CI 89.1% to 97.4%) and 93.1% (134/144, 95% CI 87.3% to 96.4%) in the modified mITT analysis (difference 1.5%; 95% CI −4.9% to 8.0%; non-inferiority p=0.001), respectively.

There was no significant difference in the overall eradication rates between the two groups (p=0.56, 0.78 and 0.25 in the ITT, mITT and PP analysis, respectively). VT dual therapy met the primary end point of non-inferiority to BQT (lansoprazole, bismuth, tetracycline and metronidazole (LBTM) group) as first-line treatment, as the eradication rates did not significantly differ between two groups in the ITT, mITT and PP analyses (table 2).

A total of 17 patients (13 in the LBTM group and 4 in the VT group) discontinued the medication prematurely due to TEAEs but completed the follow-up examination. The basic information and eradication status of these patients are summarised in table 3. Although some patients did not complete the full 14-day treatment course, they still achieved successful eradication. It appears that the longer the duration of medication, the greater the likelihood of eradication.

Adverse events and adherence

The adverse event analysis set comprised 300 patients, including 10 randomised patients who were lost to follow-up. TEAEs were reported in 48.0% (72/150) of the BQT group compared with 14.0% (21/150) in the VT dual therapy group (p=0.000) (table 4). The incidence of TEAEs was higher in the BQT group than in the VT dual therapy group, whether classified as mild (p=0.000), moderate (p=0.016) or severe (p=0.005) (table 4). TEAE-related discontinuations occurred in 8.7% (13/150) of the BQT group vs 2.0% (3/150) of the VT dual therapy group (p=0.010) (table 4).

Table 4 Adverse events in each group

Variables	LBTM group	VT group	P value
Total, n/N (%)	72/150 (48.0%)	21/150 (14.0%)	0.000
AE grade			
Mild	31	6	0.000
Moderate	23	10	0.016
Severe	18	5	0.005
Moderate to severe	41	15	0.000
AEs variety			
Nausea	30	7	
Dizziness	16	2	
Bitter taste	10	2	
Abdominal discomfort	10	4	
Vomiting	7	1	
Diarrhoea	7	2	
Itchy skin	5	1	
Skin oedema	5	0	
Rash	4	4	
Headache	4	0	
Abdominal pain	4	1	
Abdominal distension	4	0	
Fatigue	4	1	
Fever	3	0	
Backache	3	0	
Palpitation	3	2	
Constipation	2	3	
Insomnia	1	0	
Loss of appetite	1	2	
Sweating	1	0	
Discontinued due to AEs	13/150 (8.7%)	3/150 (2.0%)	0.010
Lost in follow-up	6	4	0.521
Adherence, n/N (%)	131/150 (87.3%)	142/150 (94.7%)	0.027
Adherence according to AE grade			
Mild	31/31 (100.0%)	6/6 (100.0%)	–
Moderate	23/23 (100.0%)	10/10 (100.0%)	–
Severe	4/18 (22.2%)	2/5 (40.0%)	0.423

AE, adverse event; LBTM, lansoprazole, bismuth, tetracycline, metronidazole; VT, vonoprazan and tetracycline.

All TEAEs are listed in table 4, with nausea, dizziness, bitter taste, abdominal discomfort, vomiting and diarrhoea being the most common adverse events. No medical invention or hospitalisation was required, and no death occurred during treatment. Additionally, all adverse events disappeared after cessation of treatment. Adherence, defined as taking at least 80% of the prescribed drugs, was 87.3% (131/150) in the BQT group compared with 94.7% (142/150) in the VT dual therapy group (p=0.027).

In addition, three patients who initially failed treatment in our study underwent repeat penicillin skin test, two of them obtained negative results. Subsequently, they were administrated VA dual therapy (vonoprazan+amoxicillin) as rescue treatment, achieving successful eradication without allergic reactions (table 5).

DISCUSSION

In our study, the vonoprazan and tetracycline dual regimen demonstrated non-inferiority to BQT for the eradication of *H. pylori* infection as first-line treatment among patients with penicillin allergy. This randomised clinical study involving 300 patients provided the initial assessment of VT dual therapy, supporting the efficacy of tetracycline-containing dual therapy for *H. pylori* infection treatment as first-line option.

Antibiotic resistance is a significant factor contributing to the failure of *H. pylori* eradication. It has been reported that the overall prevalence of primary antibiotic resistance of *H. pylori* in the Asia-Pacific region between 1990 and 2022 was 22% (95% CI 20% to 23%) for clarithromycin, 52% (95% CI 49% to 55%) for metronidazole, 26% (95% CI 24% to 29%) for levofloxacin, 4% (95% CI 3% to 5%) for tetracycline and 4% (95% CI 3% to 5%) for amoxicillin.[7] Given that infectious disease studies are often susceptibility-based,[8] tetracycline and amoxicillin emerge as primary option for antibiotic candidates. Amoxicillin, characterised by its low resistance rate, high efficacy, safety and availability, is an essential component of *H. pylori* eradication regimens. Recently, dual therapy comprising high-dose amoxicillin has been validated as effective.[9 10] However, amoxicillin may not be the preferred choice, as approximately 10% of the population in the USA and 4%–5.6% in the Asia-Pacific region (including China) report penicillin allergy.[11] According to the Maastricht VI/Florence consensus report, BQT (PPI, bismuth, metronidazole and tetracycline) is the preferred treatment option for this population.[1] Tetracycline, at the outset of *H. pylori* treatment, has shown efficacy as a single-antibiotic regimen.[12] The efficacy of tetracycline-containing dual therapy was initially explored by Al-Assi *et al*.[13] A dual therapy comprising omeprazole 20 mg three times a day+tetracycline 500 mg four times a day and omeprazole 40 mg once daily plus tetracycline 500 mg four times a day, alongside bismuth subsalicylate 2 tablets four times a day for 14 days, was administrated to 19 and 20 patients with *H. pylori*-positive peptic ulcer disease, respectively. Successful eradication was achieved in 5/19 (26%) and 12/25 (48%) patients in tetracycline dual therapy group and the bismuth-adding group, respectively. However, the efficacy of tetracycline dual therapy was deemed inadequate for routine treatment, with low intragastric pH being considered a major barrier to effective antimicrobial therapy.

When the environmental pH increased from 5.0 to 6.0, the Minimum Inhibitory Concentration 90% (MIC90) for tetracycline decreased from 0.5 mg/L to 0.125 mg/L.[14] However, the evolution of the medicine has facilitated the updating of treatment regimens and rejuvenated the efficacy of tetracycline-containing dual therapy. Vonoprazan, a potassium-competitive acid blocker, swiftly and potently elevates intragastric pH levels and sustains them to a greater extent than PPIs. It has been

Table 5 Information of three patients who received rescue therapy following initial treatment failure in the study

Group	No.	Sex	Age (years)	Repeat penicillin skin test	Rescue therapy regimen	Successful eradication	Adverse effects
LBTM group (n=1)	146	F	31	Negative	Vonoprazan+amoxicillin	Yes	No
VT group (n=2)	025	F	65	Positive	Vonoprazan+bismuth+tetracycline+furazolidone	Yes	No
	061	F	60	Negative	Vonoprazan+amoxicillin	Yes	No

F, female; LBTM, lansoprazole, bismuth, tetracycline, metronidazole; VT, vonoprazan and tetracycline.

associated with higher *H. pylori* eradication rates in amoxicillin-containing dual therapy.[9] Inspired by the enhanced efficacy observed in AMX-containing dual therapy, it was hypothesised that tetracycline's antimicrobial effect might be more stable and exhibit better bioavailability in the gastric cavity under the higher intragastric pH value produced by vonoprazan. The results of this study demonstrated that the efficacy of VT dual therapy was non-inferior to that of classical BQT, as determined by ITT, mITT and PP analyses.

Gastric acid can reduce the absorption rate of tetracycline antibiotics, particularly in environments with higher acidity levels. Additionally, gastric acid may undergo chemical reactions with tetracycline, leading to partial degradation or inactivation. This discrepancy might explain why VT dual therapy yielded different results compared with omeprazole and tetracycline dual therapy in previous study.

Adherence and adverse events play a significant role in successful eradication. In the BQT group, 48.0% of patients reported TEAEs, with 8.7% discontinuing treatment as a result. In fact, TEAEs are frequently encountered during BQT treatment.[15 16] Gisbert[17] reported that the overall incidence of adverse events was 43% (95% CI 35% to 50%, 24 studies), leading to nearly 3% of the treatment being interrupted.[6] In our study, VT dual therapy demonstrated fewer TEAEs compared with BQT (14.0% vs 48.0%, p=0.000), while maintaining similar efficacy. This suggested that it could be a promising candidate for optimisation of regimens.

The occurrence of TEAEs was significantly lower in the VT dual therapy group compared with the BQT group (14.0% vs 48.0%, p=0.000), across all grades of severity. In theory, the use of fewer drugs leads to fewer side effects. VT dual therapy represents an optimised approach to classical BQT, offering high efficacy with low TEAE rates.

This is the first randomised trial reporting the efficacy of VT dual therapy in first-line therapy and in patients with penicillin allergy. In comparison with amoxicillin, tetracycline presents a convenient option for prescription as there is no requirement for allergy testing. Restrictions on amoxicillin use are often influenced by concerns regarding 'penicillin-allergic' status or positive penicillin skin test results. However, it is worth noting that while 10% of the population has reported penicillin allergies, only 5% of these cases were considered true allergies, meaning that 95% of reported allergies may be categorised as 'false penicillin allergy'.[18] In our study, it is likely that at least two individuals with 'false allergy' were included who were administrated VA dual therapy (vonoprazan+amoxicillin) as rescue treatment, achieving successful eradication without allergy reactions (table 5).

The VT dual therapy may also need to be optimised since the vonoprazan trial and amoxicillin dual therapy shows better effectiveness in Asian regions, while the eradication rate is relatively low in European and American countries.[19] Possible factors related to differences in eradication effectiveness include[20]: the timing of antibiotic administration, emergence of resistance, failure to achieve the intragastric pH required for effectiveness (including different prevalence of rapid metabolisers) and host factors such as body wight, for instance, the average BMI in the US/European study was 28.7 and 29.1, respectively,[19] whereas the population in our study has an average BMI of 23.2 (table 1). Optimisation could be approached through the following aspects: (1) to improve the effectiveness of vonoprazan by increasing the dosage, frequency of administration or both, or alternatively adding an H_2 receptor antagonist concurrently[20]; (2) to increase the dose of tetracycline from 1.5 g/day to 2.25 g/day, which has been confirmed to be safe in a large population study in China (750 mg three times a day)[21]; (3) to perform antibiotic resistance testing before treatment[1 8]; (4) to adjust the timing of medication of antibiotic from before meal to after meal.[20]

This study simultaneously conducted patient education when prescribing medications, including medication timing, precautions and reminded patients to contact the researchers at any time if they had questions or discomfort during medication. The medication process included maintaining telephone or online follow-ups. Therefore, there were fewer lost to follow-ups in this study, and there was not much difference in the results between ITT, mITT and PP. Previous studies have shown that adequate patient education and close follow-up during the medication process can effectively improve adherence, thereby increasing the success rate of eradication.[22]

Limitations

There were several limitations in our study. First, this trail was open-label and VT dual regimen is distinguishable from BQT, which might have influenced the incidence of adverse events or introduced other potential biases. Second, the study was conducted in a single medical centre with a limited population of patients with penicillin allergy. It needs to be verified whether the combination is applicable to a broader population. Third, there was no data available regarding *H. pylori* isolation and antimicrobial susceptibility in this study. Fourth, using vonoprazan-based BQT as comparator appears to be more favourable than using PPI. Fifth, vonoprazan is not available in many Western countries (it became available in the USA in 2022), and tetracycline may be difficult to obtain in many countries, including most tertiary hospital in China, thus limiting the use of this therapy. In the future, we could explore dual therapy regimens involving minocycline or doxycycline. Nevertheless, despite these limitations, this study still contributed to the promotion of tetracycline-containing dual therapy, especially for patients who are not suitable for amoxicillin use.[23]

CONCLUSION

VT dual therapy, consisting of vonoprazan 20 mg two times per day and tetracycline 500 mg three times a day for 14 days, proved to be effective and safe as first-line treatment for *H. pylori* infection in a population with penicillin allergy. VT dual therapy could serve as an optimised alternative to classical BQT, offering similar efficacy, fewer TEAEs and good adherence. Further studies are needed to evaluate the efficacy of VT dual therapy in the general population, both as a primary and as a rescue option.

Contributors Study concept and design: HC, WG. Case collection and data acquisition: HC, WG, JL (Jianxiang Liu), XW, XZ, HY, XD, BL, CW, YX, GT, YT, JD, CG. Performance of ^{13}C-UBT: JL(Jiang Li). Analysis and interpretation of data, statistical analysis, drafting of the manuscript: WG, HC, JL (Jingwen Li). Critical revision of the manuscript for important intellectual content: HC. Drafting of the manuscript revision: HC, WG, JL (Jiangwen Li). HC is the guarantor of this work and accepts full responsibility for the content, the conduct of the study, access to the data and the decision to publish.

Funding National High Level Hospital Clinical Research Funding (Youth Clinical Research Project of Peking University First Hospital) 2023YC27.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study received approval from the Ethics Committee Ethics Committee of Peking University First Hospital, in accordance with the principles of

the Declaration of Helsinki. Written informed consent was obtained from all patients prior to their participation in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Wen Gao http://orcid.org/0000-0003-3549-6846
Guigen Teng http://orcid.org/0000-0001-5535-4752
Jinpei Dong http://orcid.org/0000-0002-9885-261X

REFERENCES

1 Malfertheiner P, Megraud F, Rokkas T, *et al*. Management of helicobacter pylori infection: the maastricht VI/florence consensus report. *Gut* 2022;71:1724–62.
2 Gao C-P, Zhang D, Zhang T, *et al*. PPI-amoxicillin dual therapy for helicobacter pylori infection: an update based on a systematic review and meta-analysis. *Helicobacter* 2020;25:e12692.
3 Gao W, Teng G, Wang C, *et al*. 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.
4 Zhong Z, Zhang Z, Wang J, *et al*. A retrospective study of the antibiotic-resistant phenotypes and genotypes of helicobacter pylori strains in China. *Am J Cancer Res* 2021;11:5027–37.
5 Gao W, Xu Y, Liu J, *et al*. A real-world exploratory study on the feasibility of vonoprazan and tetracycline dual therapy for the treatment of helicobacter pylori infection in special populations with penicillin allergy or failed in previous amoxicillin-containing therapies. *Helicobacter* 2023;28:e12947.
6 Kim Y-I, Park B, Choi IJ, *et al*. Family history of gastric cancer and helicobacter pylori treatment. *N Engl J Med* 2020;382:2171–2.
7 Hong T-C, El-Omar EM, Kuo Y-T, *et al*. Primary antibiotic resistance of helicobacter pylori in the Asia-Pacific region between 1990 and 2022: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2024;9:56–67.
8 Graham DY. It is time for a paradigm shift in design, execution, and publishing of comparative helicobacter pylori treatment trials. *Am J Gastroenterol* 2023;118:1154–6.
9 Du R-C, Hu Y-X, Ouyang Y, *et al*. Vonoprazan and amoxicillin dual therapy as the first-line treatment of helicobacter pylori infection: a systematic review and meta-analysis. *Helicobacter* 2024;29:e13039.
10 Hsu P-I, Chen K-Y, Tai W-C, *et al*. Hybrid, high-dose dual and bismuth quadruple therapies for first-line treatment of helicobacter pylori infection in Taiwan: a multicenter, open-label. *Am J Gastroenterol* 2023;118:1184–95.
11 Mak HWF, Yeung MHY, Wong JCY, *et al*. Differences in beta-lactam and penicillin allergy: beyond the West and focusing on Asia-Pacific. *Front Allergy* 2022;3:1059321.
12 Marshall B. Gastric spirochaetes: 100 years of discovery before and after kobayashi. *Keio J Med* 2002;51 Suppl 2:33–7.
13 Al-Assi MT, Genta RM, Graham DY. Short report: omeprazole-tetracycline combinations are inadequate as therapy for helicobacter pylori infection. *Aliment Pharmacol Ther* 1994;8:259–62.
14 Cheng A, Sheng W-H, Liou J-M, *et al*. Comparative in vitro antimicrobial susceptibility and synergistic activity of antimicrobial combinations against helicobacter pylori isolates in Taiwan. *J Microbiol Immunol Infect* 2015;48:72–9.
15 Huang Y, Chen J, Ding Z, *et al*. Minocycline vs. tetracycline in bismuth-containing quadruple therapy for helicobacter pylori rescue treatment: a multicentre, randomized controlled trial. *J Gastroenterol* 2023;58:633–41.
16 Alsamman MA, Vecchio EC, Shawwa K, *et al*. Retrospective analysis CONFIRMS tetracycline quadruple as best helicobacter pylori regimen in the USA. *Dig Dis Sci* 2019;64:2893–8.
17 Nyssen OP, McNicholl AG, Gisbert JP. Meta-analysis of three-in-one single capsule bismuth-containing quadruple therapy for the eradication of helicobacter pylori. *Helicobacter* 2019;24:e12570.
18 Sacco KA, Bates A, Brigham TJ, *et al*. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* 2017;72:1288–96.
19 Chey WD, Mégraud F, Laine L, *et al*. Vonoprazan triple and dual therapy for helicobacter pylori infection in the United States and Europe: randomized clinical trial. *Gastroenterology* 2022;163:608–19.
20 Graham DY. Why the vonoprazan helicobacter pylori therapies in the US-European trial produced unacceptable cure rates. *Dig Dis Sci* 2023;68:1691–7.
21 Pan K, Zhang L, Gerhard M, *et al*. A large randomised controlled intervention trial to prevent gastric cancer by eradication of helicobacter pylori in Linqu County, China: baseline results and factors affecting the eradication. *Gut* 2016;65:9–18.
22 Zha J, Li Y-Y, Qu J-Y, *et al*. Effects of enhanced education for patients with the helicobacter pylori infection: a systematic review and meta-analysis. *Helicobacter* 2022;27:e12880.
23 Liu L, Nahata MC. Treatment of helicobacter pylori infection in patients with penicillin allergy. *Antibiotics (Basel)* 2023;12:737.