Original Article

Bismuth-Based Quadruple Therapy versus Metronidazole-Intensified Triple Therapy as a First-Line Treatment for Clarithromycin-Resistant *Helicobacter pylori* Infection: A Multicenter Randomized Controlled Trial

Seung In Seo[1,2], Hyun Lim[2,3], Chang Seok Bang[2,4], Young Joo Yang[2,4], Gwang Ho Baik[2,4], Sang Pyo Lee[2,5], Hyun Joo Jang[2,5], Sea Hyub Kae[2,5], Jinseob Kim[6], Hak Yang Kim[1,2], and Woon Geon Shin[1,2]

[1]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, [2]Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, [3]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, [4]Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, [5]Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, and [6]Department of Epidemiology, Graduate School of Public Health, Seoul National University, Seoul, Korea

Corresponding Author

Woon Geon Shin
ORCID https://orcid.org/0000-0002-9851-5576
E-mail sgun9139@gmail.com

Hyun Lim
ORCID https://orcid.org/0000-0001-6581-6420
E-mail hlim77@hallym.or.kr

Background/Aims: Clarithromycin resistance is a main factor for treatment failure in the context of *Helicobacter pylori* infection. However, the treatment regimen for clarithromycin-resistant *H. pylori* infection has not yet been determined. We aimed to compare the efficacy and cost-effectiveness of 14-day bismuth-based quadruple therapy versus 14-day metronidazole-intensified triple therapy for clarithromycin-resistant *H. pylori* infection with genotypic resistance.

Methods: This was a multicenter, randomized, controlled trial. A total of 782 patients with *H. pylori* infection examined using sequencing-based clarithromycin resistance point mutation tests were recruited between December 2018 and October 2020 in four institutions in Korea. Patients with significant point mutations (A2142G, A2142C, A2143G, A2143C, and A2144G) were randomly assigned to receive either 14-day bismuth-based quadruple therapy (n=102) or 14-day metronidazole-intensified triple therapy (n=99).

Results: The overall genotypic clarithromycin resistance rate was 25.7% according to the sequencing method. The eradication rate of 14-day bismuth-based quadruple therapy was not significantly different in the intention-to-treat analysis (80.4% vs 69.7%, p=0.079), but was significantly higher than that of 14-day metronidazole-intensified triple therapy in the per-protocol analysis (95.1% vs 76.4%, p=0.001). There were no significant differences in the incidence of side effects. In addition, the 14-day bismuth-based quadruple therapy was more cost-effective than the 14-day metronidazole-intensified triple therapy.

Conclusions: Fourteen-day bismuth-based quadruple therapy showed comparable efficacy with 14-day metronidazole-intensified triple therapy, and it was more cost-effective in the context of clarithromycin-resistant *H. pylori* infection. **(Gut Liver 2022;16:697-705)**

Key Words: *Helicobacter pylori*; Clarithromycin; Drug resistance; Point mutation; Therapy

INTRODUCTION

Helicobacter pylori infection remains one of the most common chronic bacterial infections in humans in the world.[1] The first-line therapy for *H. pylori* infection is a combination of a proton pump inhibitor (PPI), amoxicil-lin, and clarithromycin. However, the efficacy of empirical clarithromycin-based triple therapy (CTT) has decreased gradually, owing to antibiotic resistance.[2] According to a nationwide study of antibiotic resistance mapping in Korea, the resistance rates against clarithromycin, metronidazole, amoxicillin were 17.8%, 29.5%, and 9.5%, respectively,

differing geographically.[3]

The eradication rate of empirical CTT over the past decade in Korea was 71.6% (95% confidence interval, 69.9% to 73.3%); therefore, the revised Korean guidelines suggested the use of CTT for 14 days when a clarithromycin resistance test was not performed.[4] Clarithromycin resistance is known to be a primary factor for treatment failure in *H. pylori* infections; hence, there have been numerous studies about tailored therapies according to a clarithromycin resistance test.[5-11] The overall eradication rates of tailored therapy were higher than that of empirical CTT; however, until now, the treatment regimen for *H. pylori* infection with point mutations with clarithromycin resistance has not yet been determined.

We recently reported that a 7-day metronidazole-based triple therapy for *H. pylori* infection with significant point mutations according to sequencing-based clarithromycin resistance test showed significantly lower eradication rates (55.4%) after an intention-to-treat (ITT) analysis.[8] Therefore, in this study, we increased the duration from 7 days to 14 days because metronidazole resistance is generally known to be partially overcome by increasing the dosage or expanding treatment duration.[1]

We aimed to compare the efficacy of a 14-day bismuth-based quadruple therapy (BQT) versus a 14-day metronidazole-intensified triple therapy (MIT) as a first-line treatment for *H. pylori* infection with genotypic clarithromycin resistance. The secondary aim was to investigate the cost-effectiveness of a tailored therapy based on a sequencing-based clarithromycin resistance test compared with empirical CTT.

MATERIALS AND METHODS

1. Subjects and study design

This study was a multicenter, open-label, randomized controlled trial. Patients who underwent esophagogastroduodenoscopy with diagnosis of *H. pylori* infection and underwent the clarithromycin resistance point mutation test were recruited from four institutions located in Seoul, Gyeonggi-do, and Gangwon-do in Korea between December 2018 and October 2020.

Patients were eligible if they were aged 19 to 85 years and had confirmed *H. pylori* infection using a rapid urease test (CLOtest, Pronto Dry New; Medical Instruments Corp., Herford, Germany). All subjects underwent a clarithromycin resistance point mutation test using two gastric biopsy samples, from the antrum and the corpus. Patients were excluded as following criteria: history of *H. pylori* eradication therapy, allergy to the study drugs, history

of gastric surgery, use of PPIs and/or antibiotics within 4 weeks of study enrollment, severe organ dysfunction such as liver cirrhosis or end-stage renal disease, malignant tumors other than gastric cancer within 5 years, hematologic disease, organic neurologic disease, infectious mononucleosis, central nervous system infection, pregnancy or breastfeeding, or lack of informed consent.

The study was approved by the ethics committee of four institutions, and was approved by the ethical guidelines of the Declaration of Helsinki (IRB numbers: 2018-01-015 for Kangdong Sacred Heart Hospital, 2018-04-007 for Hallym University Sacred Heart Hospital, 2018-04-043 for Chuncheon Sacred Heart Hospital, and 2018-11-009 for Dongtan Sacred Heart Hospital). This study was registered with the Clinical Trials Registry (NCT03431688). Informed consent was obtained from all subjects at the time of enrollment.

2. Detection of clarithromycin resistance point mutation by sequencing

The distribution of 23S rRNA point mutations associated with clarithromycin resistance was detected via sequencing. The detailed method for this was described in our previous study.[8] *H. pylori* genomic DNA was isolated from a frozen gastric biopsy specimen that was stored at a temperature of less than −20℃ using the MagNA Pure 96 system (Roche Diagnostics Inc., Rotkreuz, Switzerland) and Viral NA SV Kit (Roche Diagnostics Inc., Indianapolis, IN, USA) according to the manufacturer's instructions. Polymerase chain reaction (PCR) was conducted in a final reaction volume of 20 μL containing 4 μg of DNA, 2 μL of primer mixture, and 8 μL of 2×Master Mix (Samkwang Medical Laboratories, Seoul, Korea). After an initial incubation step at 95℃ for 10 minutes, 45 amplification cycles were performed in AB SimpliAMP PCR (Applied Biosystems Inc., Foster City, CA, USA), using the following amplification parameters: 95℃ for 20 seconds, 55℃ for 30 seconds, and 72℃ for 30 seconds. The final extension was performed at 72℃ for 5 minutes.

Nucleotide sequencing of the amplified DNA was performed using ABI 3730 DNA analyzer (Applied Biosystems Inc.) with BigDye® Terminator V3.1 (Applied Biosystems Inc.) according to the manufacturer's instructions. All endpoint PCR reactions, agarose gel electrophoresis, and sequencing work were performed by Samkwang Medical Laboratories. This method can identify mutations in the nucleotide sequence of domain V in the 23S rRNA gene of *H. pylori* by amplifying the first 300 bp of the gene in seven *H. pylori* strains using PCR primers 23S F (50-CGT AAC TAT AAC GGT CCT AAG-30, corresponding to *H. pylori* 23S rRNA gene positions 2007–2027) and 23S R (50-TTA

GCT AAC AGA AAC ATC AAG-30, positions 2281–2301) to detect the mutations at positions 2115, 2141, 2142, 2143, 2144, 2147, 2182, 2190, 2195, and 2223.

In the sequencing-based method, point mutations such as A2142G, A2142C, A2143G, A2143C, and A2144G were defined as clinically significant point mutations, whereas other mutations such as T2182C, T2190C, A2166G, A2144T, and A2223G were defined as clinically insignificant point mutations according to previous studies.[12-14]

3. Randomization and trial intervention

All study patients received tailored therapy. The *H. pylori* eradication regimen was determined according to the results of the sequencing-based clarithromycin resistance test. If clinically significant point mutations related to clarithromycin resistance were detected, patients were randomly assigned to receive either a 14-day BQT versus a 14-day MIT. The MIT consisted of pantoprazole 40 mg twice a day, amoxicillin 1,000 mg twice a day, and metronidazole 500 mg three times a day for 14 days. The BQT consisted of pantoprazole 40 mg twice a day, bismuth 300 mg four times a day, metronidazole 500 mg three times a day, and tetracycline 500 mg four times a day for 14 days. If the presumed insignificant mutations or no mutations were detected, patients were assigned to receive the 14-day CTT. The CTT consisted of pantoprazole 40 mg twice a day, amoxicillin 1,000 mg twice a day, and clarithromycin 500 mg twice a day for 14 days. A flowchart of the study is shown in Fig. 1. The method of randomization was simple randomization according to a random number table, and treatment groups were randomly assigned by the random number table. The patients and investigators were not blinded to the allocated treatment groups. All subjects were asked to report adverse reactions and monitor their compliance.

4. Outcome assessment and safety profile

To confirm *H. pylori* eradication, the ^{13}C-urease breath test (^{13}C-UBT; UBiT-IR 300, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was performed at least 6 to 8 weeks after treatment. The compliance was assessed at this time. Treatment success was defined as a negative ^{13}C-UBT result of <2.5%. Noncompliance was defined as the intake of <80% of the prescribed pills. To analyze the safety profile, all patients reported baseline symptoms and side effects after treatment. The side effects were documented as mild, moderate, and severe grades. Treatment-related side effects included nausea, diarrhea, headache, dyspepsia, dizziness, bitter taste, bloating, fatigue, soreness, and skin rash. The ITT analysis was defined to include all randomized patients. Patients who did not examine the ^{13}C-UBT test after treatment and showed noncompliance were excluded from
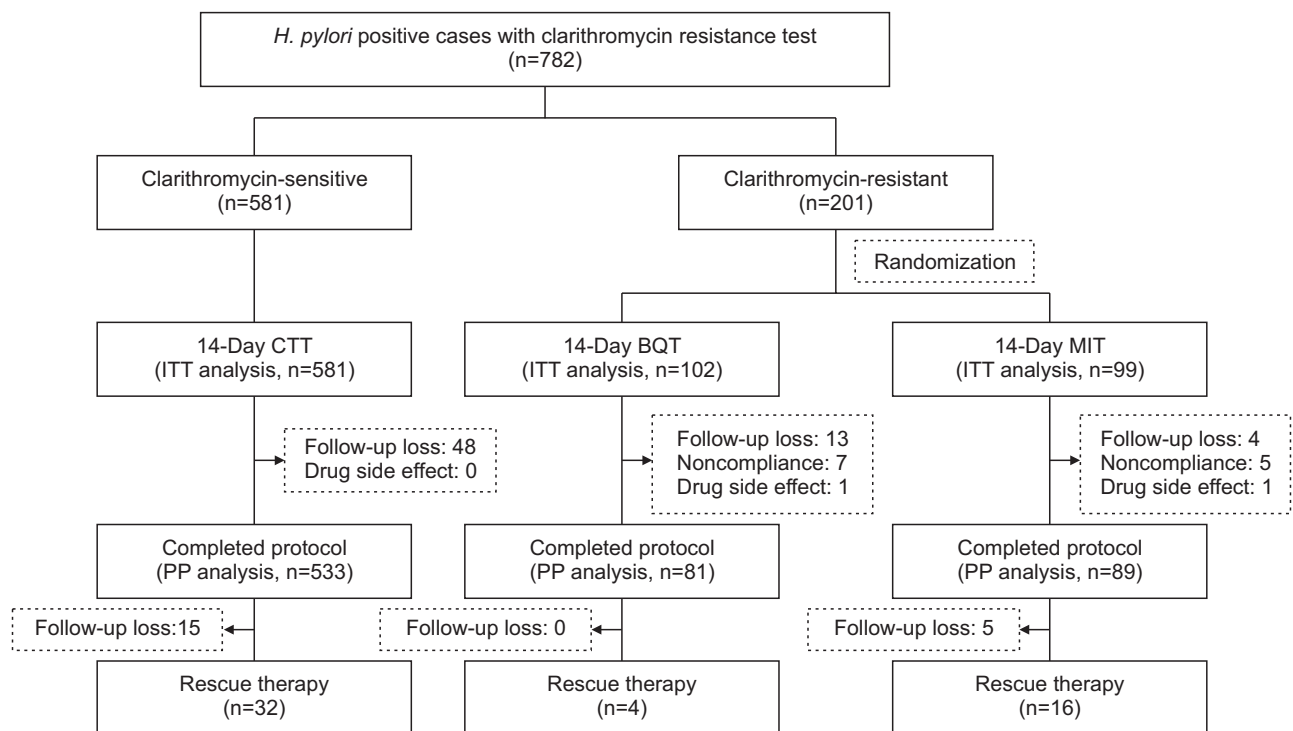

Fig. 1. Study flowchart.
H. pylori, *Helicobacter pylori*; CTT, clarithromycin-based triple therapy; BQT, bismuth-based quadruple therapy; MIT, metronidazole-intensified triple therapy; ITT, intention-to-treat; PP, per-protocol.

the per-protocol (PP) analysis.

The primary endpoint was the comparison of *H. pylori* eradication rates between the 14-day BQT and the 14-day MIT in patients with clarithromycin resistance point mutations. The secondary endpoint was the cost-effectiveness analysis of tailored therapy compared with empirical CTT.

5. Cost-effectiveness analysis

The cost-effectiveness analysis was performed according to economic modeling analysis in reference to previous study.[15] The incremental cost-effectiveness ratio (ICER) was calculated to evaluate the cost-effectiveness of the tailored therapy according to the sequencing-based clarithromycin resistance test. The ICER is defined as the difference in the average cost per patient between the two *H. pylori* eradication regimens, divided by the difference in *H. pylori* eradication rates, according to the equation:

$$ICER = (\text{average cost}_{regimen1} - \text{average cost}_{regimen2})/100 \times$$
$$(H.\ pylori\ \text{eradication rate}_{regimen1} - H.\ pylori\ \text{eradication rate}_{regimen2}).$$

The cost of *H. pylori* eradication included *H. pylori* eradication regimen costs (CTT: 63.8 USD, MIT: 29.9 USD, and BQT: 43.8 USD), diagnostic costs (^{13}C-UBT: 33.7 USD, sequencing-based clarithromycin resistance test: 57.5 USD), and outpatient clinic registration costs (19.6 USD). The costs were calculated using an exchange rate of 1,130 Korean won to 1 USD. The average cost was estimated as:

$$\text{Average cost} = \text{eradication rate} \times (H.\ pylori\ \text{eradication regimen cost}_{first-line} + {}^{13}\text{C-UBT cost} + \text{outpatient clinic registration cost}) + (1 - \text{eradication rate}) \times (H.\ pylori\ \text{eradication regimen cost}_{first-line} + H.\ pylori\ \text{eradication regimen cost}_{second-line} + 2 \times {}^{13}\text{C-UBT cost} + 2 \times \text{outpatient clinic registration cost}) + \text{sequencing-based clarithromycin resistance test cost}.$$

The *H. pylori* eradication rate of the tailored therapy was defined as the sum of the eradication rate of the CTT and MIT or BQT according to the group assigned. The *H. pylori* eradication rate of the tailored therapy was estimated as:

$$H.\ pylori\ \text{eradication rate of tailored therapy} = (1 - \text{clarithromycin resistance rate}) \times \text{eradication rate of CTT} + \text{clarithromycin resistance rate} \times \text{eradication rate of MIT or BQT}.$$

6. Statistical analysis

We assumed the eradication rate of MIT to be 82%,[11] and the eradication rate of BQT to be 95%,[1] with a statistical power of 80%, a significance level of 0.05, and a two-sided α=0.05. We anticipated a dropout rate of 15%, and the final calculated sample size included in the randomization of patients with clarithromycin resistance was 100 patients per group. In addition, we assumed a clarithromycin resistance rate of 30%; therefore, the minimum sample size of the CTT was calculated to be 460.

Table 1. Baseline Characteristics of the Patients

Variable	14-Day BQT (n=102)	14-Day MIT (n=99)	p-value*	14-Day CTT (n=581)
Age, yr	56.6±11.1	56.7±11.3	0.905	55.3±12.6
Male sex	41 (40.2)	42 (42.9)	0.703	332 (57.1)
Mean BMI, kg/m²	24.3	24.6	0.263	25.4
Diabetes	18/97 (18.6)	18/97 (18.6)	>0.999	79/563 (14.0)
Hypertension	18/99 (18.2)	14/97 (14.4)	0.478	168/563 (29.8)
History of peptic ulcer	12 (11.7)	13 (13.1)	0.809	118/563 (20.9)
Smoking	11/89 (12.4)	17/89 (19.1)	0.051	153/479 (31.9)
Alcohol	17/76 (22.4)	26/82 (31.7)	0.247	230/479 (48.0)
Diagnosis			0.429	
Gastritis	51 (50.0)	41 (41.4)		244 (42.0)
Peptic ulcer	46 (45.1)	53 (53.5)		302 (52.0)
Gastric cancer	2 (2.0)	1 (1.0)		17 (2.9)
Gastric adenoma	2 (2.0)	4 (4.1)		15 (2.6)
MALT lymphoma	1 (0.9)	0		3 (0.5)
Significant point mutation†				
A2142G	3 (2.9)	3 (3.0)	>0.999	
A2143G	95 (93.1)	93 (93.9)	0.290	
A2142C	2 (2.1)	1 (1.0)	0.619	
A2143C	2 (2.1)	1 (1.0)	0.621	
A2144G	34 (35.1)	36 (37.9)	0.795	

Data are presented as mean±SD, number (%), or number/number (%).
BQT, bismuth-based quadruple therapy; MIT, metronidazole-intensified triple therapy; CTT, clarithromycin-based triple therapy; BMI, body mass index; MALT, mucosa-associated lymphoid tissue.
*p-value indicates comparison between the BQT and MIT; †The sum of proportion is not 100% because of overlapping among point mutations.

Continuous variables and categorical variables were compared between BQT and MIT groups using the t-tests and chi-square tests or Fisher exact test, respectively. *H. pylori* eradication rates were analyzed based on the ITT and PP analyses. The eradication rates were compared between BQT and MIT groups using the chi-square test. A two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 19.0; IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient characteristics

A total of 782 patients were included in the tailored therapy group according to the sequencing-based clarithromycin resistance test. Of these, 201 patients were randomly assigned to the 14-day BQT group (n=102) or the 14-day MIT group (n=99). Of these 201 patients, 21 (follow-up loss: 13, noncompliance: seven, drug side effect: one) and 10 patients (follow-up loss: four, noncompliance: five, drug side effect: one) in the BQT and MIT groups, respectively, were excluded from the PP analysis. Another 581 patients with clarithromycin-sensitive results received the 14-day CTT (Fig. 1). The baseline characteristics of the BQT, MIT, and CTT groups are presented in Table 1. There were no significant differences between the BQT and MIT groups (Table 1).

2. *H. pylori* eradication rates

The *H. pylori* eradication rate of all patients was 81.5% in the ITT analysis and 89.7% in the PP analysis. The eradication rate of the 14-day CTT in clarithromycin-sensitive patients was 83.6% in the ITT analysis and 91.2% in the PP analysis. The eradication rate of the 14-day BQT was not significantly different from that of 14-day MIT in the ITT analysis, but it was significantly higher in the PP analysis (ITT analysis: BQT 82/102 [80.4%] vs MIT 69/99 [69.7%], p=0.079 and PP analysis: BQT 77/81 [95.1%] vs MIT 68/89 [76.4%], p=0.001) (Table 2).

In patients with clarithromycin-sensitive strain, 15 patients were lost to follow-up. The 32 patients received rescue therapy with 14-day BQT, and the overall eradication rate including rescue therapy was 97.7% in CTT group. Of the four patients with eradication failure in the BQT group, the three patients were repeatedly treated with 14-day BQT, and the one patient was treated with a PPI, amoxicillin, and levofloxacin for 14 days. The overall eradication rate including the rescue therapy was 98.8% in the BQT group. Meanwhile, of the 21 patients with eradication failure in the MIT group, 5 patients were lost to follow-up. The 13 patients received the 14-day BQT, and the other three patients were treated with PPI, levofloxacin, and rifaximin. The overall eradication rate including rescue therapy was 94% in the MIT group. There was no significant difference of eradication rates in the overall rescue therapy between BQT and MIT group (Table 2).

3. Sequencing-based clarithromycin resistance point mutation

The overall clarithromycin resistance rate was 25.7% (201/782), and the resistance rates differed among regions (Seoul: 19.3%, Gyeonggi-do: 31.3%, Gangwon-do: 24.5%). The A2143G point mutation was the most common in the clinically significant point mutations, as previously noted. The distribution of point mutations and eradication rates for each point mutation are shown in Table 3. The overall eradication rate in the patients with significant point mutations was 75.1%. In the CTT group, the eradication rate in patients with clinically insignificant point mutations was 82.8%, and that of those who had no point mutations was 91.0%. Of the patients with A2143G point mutations (n=188), 68 patients also had T2182C point mutations, and 65 patients had A2144G point mutations. There were six patients with A2142G, three with A2142C, three with A2143C, and 70 with A2144G point mutations. Of those that had A2144G point mutations, 65 patients also had

Table 2. *Helicobacter pylori* Eradication Rates for Tailored Therapy

| Analysis | Eradication rates of tailored therapy by genotypic clarithromoycin resistance test | | | |
| | Clarithromycin-sensitive | Clarithromycin-resistant | | |
	14-Day CTT	14-Day BQT	14-Day MIT	p-value*
ITT analysis	486/581 (83.6)	82/102 (80.4)	69/99 (69.7)	0.079
PP analysis	486/533 (91.2)	77/81 (95.1)	68/89 (76.4)	0.001
Including rescue therapy	506/518 (97.7)	80/81 (98.8)	79/84 (94.0)	0.064

Data are presented as the number/number (%).

CTT, clarithromycin-based triple therapy; BQT, bismuth-based quadruple therapy; MIT, metronidazole-intensified triple therapy; ITT, intention-to-treat; PP, per-protocol.

*p-value indicates comparison between the BQT and MIT groups.

Table 3. Distribution of Point Mutations Associated with Clarithromycin Resistance Detected by Sequencing and *Helicobacter pylori* Eradication Rates Associated with Point Mutations (n= 782)

Point mutation	No.	Eradication rates, No. (%)*
Clinically significant mutation	201	151 (75.1)
A2142G	4	2 (50.0)
A2142C	1	1 (100)
A2143G	53	41 (77.4)
A2143C	3	3 (100)
A2144G	3	3 (100)
A2142G+A2143G	2	2 (100)
A2142C+A2144G	2	2 (100)
A2143G+A2144G	65	48 (73.8)
A2143G+T2182C	68	49 (72.1)
Clinically insignificant mutation	525	435 (82.8)
T2182C	483	396 (81.9)
T2190C, A2166G, A2144T, A2223G	42	39 (92.8)
No point mutation	56	51 (91.0)

*The eradication rate was calculated using an intention-to-treat analysis.

Table 4. Comparison of Adverse Effects

Variable	14-Day BQT (n=81)	14-Day MIT (n=89)	p-value
Any side effects	47 (58.0)	54 (60.7)	0.725
Nausea	8 (9.9)	8 (9.0)	0.507
Diarrhea	6 (7.4)	9 (10.1)	0.381
Headache	9 (11.1)	8 (9.0)	0.645
Dyspepsia	16 (19.8)	21 (23.5)	0.377
Dizziness	7 (8.6)	6 (6.7)	0.641
Bitter taste	9 (11.1)	10 (11.2)	0.622
Bloating	13 (16.0)	12 (13.5)	0.509
Fatigue	27 (33.4)	28 (31.4)	0.794
Soreness	16 (19.7)	20 (22.4)	0.899
Skin rash	2 (2.5)	4 (4.5)	0.684
Moderate side effects	7 (8.6)	7 (7.8)	0.898

Data are presented as the number (%).
BQT, bismuth-based quadruple therapy; MIT, metronidazole-intensified triple therapy.

A2143G point mutations, and two patients had A2142C point mutations. Only three patients had A2144G mutations alone. In the clarithromycin-sensitive group (n=581), 483 patients had T2182C mutations, and 42 patients had other mutations (T2190C, A2166G, A2144T, and A2223G). Only 56 patients (7.2%) had no point mutations (Table 3).

4. Compliance and adverse events

The proportion of noncompliance was 8% in the BQT group and 5.3% in the MIT group (BQT 7/88 [8%] vs MIT 5/94 [5.3%], p=0.558). One patient in each group was withdrawn from the study owing to severe side effects. No significant difference was observed in the prevalence of side effects between the two groups (BQT 47/81 [58%] vs MIT 54/89 [60.7%], p=0.725) (Table 4). The number of patients with moderate side effects was 8.6% in the BQT group and 7.8% in the MIT group. The detailed information is provided in Table 4.

5. Cost-effectiveness analysis of tailored therapy according to a sequencing-based clarithromycin resistance test

Table 5 shows the cost-effectiveness analysis of the tailored therapy using a sequencing-based clarithromycin resistance test compared with empirical CTT. Based on the PP analysis of the first-line therapies, the average cost of tailored BQT and MIT per person were 169.5 USD and 166 USD, respectively. Compared with empirical CTT, the ICER of the tailored BQT and MIT were 3.5 USD and 4.9 USD per patient for first-line therapy, respectively. The estimated ICER of the tailored BQT and MIT was 14.1

USD and 14.8 USD per patient after second-line therapy, respectively, assuming all patients with first-line CTT or MIT failure were treated with 14-day BQT as the second-line rescue therapy.

DISCUSSION

This study was the first multicenter randomized controlled trial that compared a 14-day BQT and a 14-day MIT in the *H. pylori* infection with genotypic clarithromycin resistance. In the PP analysis, BQT showed significantly higher eradication rates than MIT, with comparable adverse event rates, though BQT showed similar efficacy compared with MIT in the ITT analysis. The present study also analyzed the cost-effectiveness of tailored therapy based on a sequencing-based clarithromycin resistance test compared with empirical CTT, and the results suggested that BQT was more cost-effective than MIT. To date, no study has compared the two regimens in *H. pylori* infection with point mutations related to clarithromycin resistance; therefore, our study provides important evidence for clarithromycin resistance-based tailored therapy in the era of increasing antibiotic resistance worldwide.

Several studies have compared tailored therapy and empirical therapy as a first-line treatment for *H. pylori* infection, and reported that tailored therapy had a better efficacy.[5-7,9-11,16-20] Further, recent cost-effectiveness studies showed that tailored therapy was more cost-effective than standard triple therapy.[15,21,22] In previous studies of tailored therapy, however, the treatment regimens for clarithromycin-resistant *H. pylori* infection were different among studies. Ong *et al.*[9] and Lee *et al.*[11] performed a multicenter randomized controlled trial using a tailored therapy accord-

Table 5. Incremental Cost-Effectiveness Ratio Analysis of the Tailored Therapies According to the Sequencing-Based Clarithromycin Resistance Test

Therapy	Tailored BQT*	Tailored MIT*	Empirical CTT
First-line therapy			
Average cost, USD	169.5	166.0	117.1
Overall eradication rate, %	92.2	87.5	77.4[†]
Incremental cost-effectiveness ratio, USD	3.5	4.9	-
Second-line therapy			
Average cost, USD[‡]	175.9	178.2	139.0
Overall eradication rate, %[‡]	97.1	96.8	94.5
Incremental cost-effectiveness ratio, USD	14.1	14.8	-

BQT, bismuth-based triple therapy; MIT, metronidazole-intensified triple therapy; CTT, clarithromycin-based triple therapy.
*In the tailored therapy group, patients received the eradication regimen based on the results of the sequencing-based clarithromycin resistance test. CTT was prescribed as the first-line eradication regimen in patients without clarithromycin resistance. For those who showed clarithromycin resistance, BQT or MIT was prescribed as the first-line eradication regimen according to the group assignment; [†]The first-line eradication rate of empirical CTT was assumed to be 77.4%[4]; [‡]In the cost-effectiveness analysis after second-line therapy, it was assumed that BQT was administered as the second-line rescue therapy in all patients with CTT or MIT failure, and the second-line eradication rate of the BQT was assumed to be 75.5%.[4]

ing to the results of a dual-priming oligonucleotide (DPO)-based multiplex PCR test, and the eradication rate of the tailored therapy was approximately 80% according to the ITT analysis. The regimen used against the clarithromycin-resistant strain was metronidazole-based triple therapy for 7 to 14 days.[9,11] Our previous single-center retrospective study also concluded that a 7-day metronidazole-based triple therapy showed a significantly lower eradication rate.[8] A prospective study by Choi *et al.*[10] reported a higher overall eradication rate of 96% after ITT analysis when BQT was applied to the clarithromycin-resistant strains according to the results of a DPO-PCR test, although the study only included 13 patients.

In our study, genotypic clarithromycin resistance was 25.7%, which was consistent with previous report based on point mutations with clarithromycin resistance (25.9%),[9] and higher than the results reported by the Korean nationwide antibiotic resistance mapping study according to agar dilution method (17.8%).[3] The regions included in our study were Seoul, Gyeonggi-do, and Gangwon-do, and the resistance rate in Gyeonggi-do was higher than that of Seoul, which is consistent with a previous nationwide study.[3] Approximately 45% of the total patients were from Gyeonggi-do; thus, it may have resulted in a higher resistance rate. In addition, we applied a sequencing-based PCR method and detected more point mutations associated with clarithromycin resistance than the conventional DPO-PCR method for detecting A2142G and A2143G. Although all strains with eradication failure had either A2142G or A2143G mutation, the sequencing-based PCR method detected a small number of additional point mutations other than A2142G and A2143G, therefore, overcame the limitations of the conventional DPO-PCR method to some degree. In addition, in our study, the eradication

rates in patients with both A2143G and T2182C point mutations were lower than those with the A2143G point mutation only, and the eradication rate of the CTT in patients with T2182C point mutations was slightly lower than that in patients with insignificant point mutations or no point mutations. To date, it has been controversial topic whether T2182C is associated with clarithromycin resistance.[13,23] Notably, the T2182C mutation was the most common point muation in our study; therefore, it may be considered to apply a triple-priming PCR method to include the T2182C point mutation compared to that of the conventional DPO-PCR method. Given our results, further large-scale studies are needed to identify the usefulness of tailored therapy based on the sequencing-based clarithromycin resistance test.

The overall eradication rates were 81.5% (ITT analysis) and 89.7% (PP analysis), which are comparable with the results of a recent study by Ong *et al.*[9] that included a 14-day metronidazole-based triple therapy in patients infected with clarithromycin-resistant strains. The resistance rate of metronidazole was reported to be 29.5% in a nationwide Korean study,[3] and Ong *et al.*[9] reported that 25% of cases positive for point mutation tests and 17.6% of cases resistant to clarithromycin were also resistant to metronidazole. Thus, the dual resistance to clarithromycin and metronidazole may be the main factor contributing to the lower eradication rates. In addition, the eradication rates obtained in this study were lower than those reported in previous studies of tailored therapies as first-line regimens from a culture-based susceptibility testing.[17,19] In our study, the eradication rate of CTT in patients with no point mutations (91%) was less than 100%, which reflects the possibility of amoxicillin resistance. Indeed, amoxicillin resistance has been reported to be 9.5% in Korea.[3] Taken together,

the best method is tailored therapy based on the results of a culture-based susceptibility test; however, culture-based methods are costly and time-consuming, thus its application is rather difficult in clinical practice.

Another strength of our study is the addition of the cost-effectiveness analysis. The introduction of new treatments should consider cost-effectiveness as well as treatment outcomes. In this study, the tailored therapy according to a sequencing-based clarithromycin resistance test showed a high eradication rate, especially in BQT, and this result is consistent with other studies.[5-11] However, although BQT was more cost-effective than MIT, the cost-effectiveness analysis showed an increased cost in our tailored therapy compared with empirical CTT. In previous studies, it was demonstrated that the cost-effectiveness of tailored therapy according to the DPO-based multiplex PCR assay could improve as the eradication rate of empirical CTT decreased.[15,21] In Korea, the eradication rate of empirical CTT has decreased to 77.4% due to increased clarithromycin resistance.[4] In this study, BQT decreased the cost of second-line rescue therapy compared to empirical CTT, but the ICER was evaluated as 14.1 USD, which was not economical, owing to the high cost of the sequencing-based clarithromycin resistance test. However, the potential benefits of tailored therapies should be considered. Its acceptance will likely be due to the assessment of societal costs, globally increasing antibiotic resistance, as well as savings resulting from *H. pylori* eradication compared to treatment-based medical costs alone.

Despite its strengths, our study has some limitations. First, we were unable to perform *H. pylori* culture and antimicrobial susceptibility testing; thus, we could not assess resistance to metronidazole, amoxicillin, or dual resistance to both antibiotics. Second, the rescue regimen was determined by clinician's experience and decision; therefore, it was different among patients and we could not assess the actual cost-effectiveness after second-line therapy. Additionally, the incidence of adverse events associated with BQT is generally known to be higher than those of other therapies,[9] which is inconsistent with the results obtained in this study. Indeed, our study revealed many more patients lost to follow-up from those that received the BQT; thus, the results of the ITT and PP analyses were statistically different. Third, we did not consider factors affecting eradication rates, such as the presence of the CYP2C19 polymorphism. The efficacy of potassium-competitive acid blockers in tailored therapy is also warranted.

In conclusion, the 14-day BQT showed a comparable eradication rate and incidence of side effects to 14-day MIT; however, it might be more cost-effective than 14-day MIT considering the PP analysis. The sequencing-based clarithromycin resistance test showed a small number of other significant point mutations compared with the DPO-PCR method; however, the clinical usefulness of other point mutations needs to be clarified through antimicrobial susceptibility testing. Tailored therapy may be applied as a first-line treatment for *H. pylori* infection in the future, and the BQT might be appropriate regimen in the clarithromycin-resistant *H. pylori* infection.

CONFLICTS OF INTEREST

ACKNOWLEDGEMENTS

AUTHOR CONTRIBUTIONS

Study concept and design: S.I.S., H.L., W.G.S. Acquisition of data, analysis and interpretation of data: S.I.S., H.L., C.S.B., Y.J.Y., G.H.B., S.P.L., H.J.J., S.H.K. Statistical analysis, technical, or material support: J.K. Drafting of the manuscript: S.I.S., H.L. Critical revision of the manuscript for important intellectual content: H.Y.K. Study supervision: W.G.S. All authors read and approved the final manuscript.

ORCID

Seung In Seo https://orcid.org/0000-0003-4417-0135
Hyun Lim https://orcid.org/0000-0001-6581-6420
Chang Seok Bang https://orcid.org/0000-0003-4908-5431
Young Joo Yang https://orcid.org/0000-0001-6325-1104
Gwang Ho Baik https://orcid.org/0000-0003-1419-7484
Sang Pyo Lee https://orcid.org/0000-0002-4495-3714
Hyun Joo Jang https://orcid.org/0000-0003-4424-1968
Sea Hyub Kae https://orcid.org/0000-0003-3101-1135
Jinseob Kim https://orcid.org/0000-0002-9403-605X
Hak Yang Kim https://orcid.org/0000-0002-7459-3473
Woon Geon Shin https://orcid.org/0000-0002-9851-5576

REFERENCES

1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.

2. Shin WG, Lee SW, Baik GH, et al. Eradication rates of Helicobacter pylori in Korea over the past 10 years and correlation of the amount of antibiotics use: nationwide survey. Helicobacter 2016;21:266-278.

3. Lee JH, Ahn JY, Choi KD, et al. Nationwide antibiotic resistance mapping of Helicobacter pylori in Korea: a prospective multicenter study. Helicobacter 2019;24:e12592.

4. Jung HK, Kang SJ, Lee YC, et al. Evidence-based guidelines for the treatment of Helicobacter pylori infection in Korea: 2020 revised edition. Korean J Helicobacter Up Gastrointest Res 2020;20:261-287.

5. Pan J, Shi Z, Lin D, et al. Is tailored therapy based on antibiotic susceptibility effective? A multicenter, open-label, randomized trial. Front Med 2020;14:43-50.

6. Horie R, Handa O, Ando T, et al. Helicobacter pylori eradication therapy outcome according to clarithromycin susceptibility testing in Japan. Helicobacter 2020;25:e12698.

7. Delchier JC, Bastuji-Garin S, Raymond J, et al. Efficacy of a tailored PCR-guided triple therapy in the treatment of Helicobacter pylori infection. Med Mal Infect 2020;50:492-499.

8. Seo SI, Do BJ, Kang JG, et al. Helicobacter pylori eradication according to sequencing-based 23S ribosomal RNA point mutation associated with clarithromycin resistance. J Clin Med 2019;9:54.

9. Ong S, Kim SE, Kim JH, et al. Helicobacter pylori eradication rates with concomitant and tailored therapy based on 23S rRNA point mutation: a multicenter randomized controlled trial. Helicobacter 2019;24:e12654.

10. Choi YI, Chung JW, Park DK, et al. Tailored eradication *vs* empirical bismuth-containing quadruple therapy for first-line Helicobacter pylori eradication: a comparative, open trial. World J Gastroenterol 2019;25:6743-6751.

11. Lee HJ, Kim JI, Cheung DY, et al. Eradication of Helicobacter pylori according to 23S ribosomal RNA point mutations associated with clarithromycin resistance. J Infect Dis 2013;208:1123-1130.

12. De Francesco V, Zullo A, Ierardi E, et al. Phenotypic and genotypic Helicobacter pylori clarithromycin resistance and therapeutic outcome: benefits and limits. J Antimicrob Chemother 2010;65:327-332.

13. Kim JM, Kim JS, Kim N, et al. Gene mutations of 23S rRNA associated with clarithromycin resistance in Helicobacter pylori strains isolated from Korean patients. J Microbiol Biotechnol 2008;18:1584-1589.

14. Umegaki N, Shimoyama T, Nishiya D, Suto T, Fukuda S, Munakata A. Clarithromycin-resistance and point mutations in the 23S rRNA gene in Helicobacter pylori isolates from Japan. J Gastroenterol Hepatol 2000;15:906-909.

15. Gweon TG, Kim JS, Kim BW. An economic modeling study of Helicobacter pylori eradication: comparison of dual priming oligonucleotide-based multiplex polymerase chain reaction and empirical treatment. Gut Liver 2018;12:648-654.

16. Kim JL, Cho SJ, Chung SJ, et al. Empiric versus clarithromycin resistance-guided therapy for Helicobacter pylori based on polymerase chain reaction results in patients with gastric neoplasms or gastric mucosa-associated lymphoid tissue lymphoma: a randomized controlled trial. Clin Transl Gastroenterol 2020;11:e00194.

17. Lee JW, Kim N, Nam RH, et al. Favorable outcomes of culture-based Helicobacter pylori eradication therapy in a region with high antimicrobial resistance. Helicobacter 2019;24:e12561.

18. López-Góngora S, Puig I, Calvet X, et al. Systematic review and meta-analysis: susceptibility-guided versus empirical antibiotic treatment for Helicobacter pylori infection. J Antimicrob Chemother 2015;70:2447-2455.

19. Park CS, Lee SM, Park CH, et al. Pretreatment antimicrobial susceptibility-guided vs. clarithromycin-based triple therapy for Helicobacter pylori eradication in a region with high rates of multiple drug resistance. Am J Gastroenterol 2014;109:1595-1602.

20. Zhou L, Zhang J, Song Z, et al. Tailored versus triple plus bismuth or concomitant therapy as initial Helicobacter pylori treatment: a randomized trial. Helicobacter 2016;21:91-99.

21. Cho JH, Jeon SR, Kim HG, Jin SY, Park S. Cost-effectiveness of a tailored Helicobacter pylori eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes clarithromycin resistance in Korean patients. J Gastroenterol Hepatol 2019;34:700-706.

22. Papaefthymiou A, Liatsos C, Georgopoulos SD, et al. Helicobacter pylori eradication regimens in an antibiotic high-resistance European area: a cost-effectiveness analysis. Helicobacter 2020;25:e12666.

23. Hwang TJ, Kim N, Kim HB, et al. Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of H. pylori in a single center of Korea. J Clin Gastroenterol 2010;44:536-543.