Received: 29 May 2021 | Revised: 19 February 2022 | Accepted: 21 February 2022

DOI: 10.1002/hsr2.780

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Comparison of eradication rates of moxifloxacin–rifabutin triple therapy and bismuth quadruple therapy as second-line regimens in patients with peptic ulcers

Chang Min Lee[1,2] | Seong Je Kim[1] | Se In Hah[1] | Ji Yoon Kwak[1] | Jung Woo Choi[1] | Hyun Chin Cho[1,2] | Chang Yoon Ha[1,2] | Ok Jae Lee[1,2] | Woon Tae Jung[1,2]

[1]Department of Internal Medicine, Gyeongsang National University College of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea

[2]Gyeongsang National University Institute of Health Sciences, Jinju, Republic of Korea

Correspondence

Woon Tae Jung, Department of Internal Medicine, Gyeongsang National University College of Medicine and Gyeongsang National University Hospital, Gyeongsang National University Institute of Health Sciences, Jinju, Republic of Korea.
Email: wtjung@gnu.ac.kr

Abstract

Background: Bismuth quadruple (BQ) therapy is known to have poor patient compliance and a complex dosing method, and no appropriate third-line regimen exists if second-line BQ therapy fails. In Korea, some alternative regimens have shown unsatisfactory eradication rates. Therefore, we investigated the success rates of the second-line moxifloxacin–rifabutin triple (MRT) regimen and compared it with BQ regimen in subgroup analysis of peptic ulcer patients.

Materials and Methods: This study was a retrospective study of 71 patients who underwent a second-line MRT for *Helicobacter pylori* after failing to clarithromycin triple regimen. To compare the eradication rate in gastric ulcer patients, 51 patients in the MRT group and 132 patients in BQ group were included. After age and sex propensity matching, 45 patients were included in each group (the alpha value and power were set at 0.05% and 77%, respectively).

Results: The eradication rate in the MRT group was 69.0% (49/71) in the intention-to-treat (ITT) analysis and 77.8% (49/63) in the per-protocol (PP) analysis. These were significantly lower than the eradication rate in the BQ group (82.5%, $p = 0.019$ in the ITT analysis; 89.3%, $p = 0.022$ in the PP analysis). In subgroup analysis of peptic ulcer patients, the success rate of BQ group was significantly higher than that of MRT group in both ITT and PP populations (81.8% (108/132) vs. 60.8% (31/51) in the ITT populations, $p = 0.004$; and 90.0% (108/120) vs. 72.1% (31/43) in the PP populations, $p = 0.010$). Among the 14 patients with MRT therapy failure, 10 were eradicated with BQ as the third-line regimen. The eradication rate of the third-line BQ after the second-line MRT failure was 90.0% (9/10).

Conclusion: Second-line MRT therapy was not as effective as BQ therapy, so it should be considered for limited use only when BQ is not available.

Abbreviations: BQ, bismuth quadruple therapy; MRT, moxifloxacin-rifabutin triple therapy.

KEYWORDS
bismuth quadruple, eradication, *Helicobacter pylori*, moxifloxacin, rifabutin

1 | INTRODUCTION

As clarithromycin resistance in *Helicobacter pylori* infections is increasing worldwide, the need for an appropriate second-line regimen is increasing.[1] The recommended regimen after clarithromycin triple therapy failure differs with regions. In areas with low metronidazole resistance, such as Japan, metronidazole triple therapy is the recommended second-line regimen.[2] European Maastricht V Consensus recommends bismuth quadruple (BQ) or fluoroquinolone triple/quadruple regimen as a second-line.[3] Korean guidelines still allow clarithromycin triple therapy as a first-line therapy.[1,4–6]

To date, BQ therapy is the best option in terms of eradication rates. However, the BQ regimen is rather complicated, and patients show poor compliance. In addition, the third-line regimens after the second-line BQ regimen failure are not effective enough in Korea. In particular, quinolone–amoxicillin triple therapy has shown unsatisfactory success rates.[7,8] This may be because of the high resistance to fluoroquinolone[9,10] and exposure to amoxicillin during the first-line therapy. Despite the unsatisfactory eradication rate of rifabutin triple therapy, the resistance rate of rifabutin in Korea has been reported to be very low (less than 3%[10]). The possible cause of this may be due to the repeated use of amoxicillin in rifabutin triple regimen.

Apart from metronidazole and tetracycline as antibiotics for third-line BQ therapy, the available antibiotic options for second-line therapy are limited. Moxifloxacin and rifabutin are the available antibiotics; however, the effect of moxifloxacin–rifabutin triple (MRT) regimen have been rarely reported. In a German study, the only randomized clinical trial for MRT regimen, it was reported that the eradication rate of MRT was 77.7% in intention-to-treat (ITT) and 83.3% in the per-protocol (PP) analyses as the second to fourth-line eradication.

Therefore, the purpose of this study is to investigate the success rates of the second-line moxifloxacin–rifabutin triple regimen in comparison with bismuth quadruple regimen after the failure of the first-line clarithromycin therapy in patients with peptic ulcers in Korea.

2 | PATIENTS AND METHODS

2.1 | Patients

In this retrospective study, 665 patients who had failed the first-line clarithromycin therapy and underwent the second-line therapy for *H. pylori* eradication were consecutively included at the Gyeongsang National University Hospital between January 2013 and December 2019.

Of the 665 patients, 71 were treated with MRT and 252 were treated with BQ. The remaining 342 patients, who were treated with regimens other than the two intended regimens, were excluded (Figure 1). Among the qualified 323 patients, 51 from the MRT group and 132 from the BQ group were included for subgroup analysis of peptic ulcer patients. Finally, 45 patients in each group were analyzed after propensity matching according to age and sex.

This study was conducted in accordance with the Declaration of Helsinki guidelines, and the study protocol was reviewed and approved by the Institutional Review Board of the Gyeongsang National University Hospital (approval no. 2020-03-037).

2.2 | Diagnosis for *H. pylori* infection

Initially, rapid urease tests and endoscopic biopsies with/without Giemsa staining were conducted to identify *H. pylori* infection. One or more follow-up tests (endoscopic biopsies with/without Giemsa staining, rapid urease tests, and urea breath tests) were conducted to evaluate eradication success.

2.3 | Regimens

MRT therapy comprised 400 mg/24 h moxifloxacin, 300 mg/24 h rifabutin, and 40 mg/12 h pantoprazole for 7 days. BQ therapy comprised 300 mg/6 h bismuth, 500 mg/6 h tetracycline, 500 mg/8 h metronidazole, and full dose of proton pump inhibitors (PPIs) b.i.d. for 14 days.

2.4 | Propensity score matching and sample size estimation

To compare the eradication rate of the MRT regimen with the BQ regimen, the MRT group and the BQ group were 1:1 matched with propensity scores for age and sex using the Matchit package in R program (R version 4.0.3). We calculated that the sample size in each treatment group should be 49 at an alpha of 0.05 and a power of 0.80 in a one-side test when the eradiation rate of the BQ regimen is set to an ideal 90% and MRT regimen differs by more than 20% from BQ regimen.

2.5 | Statistical analysis

For two-group comparisons, the Fisher's exact test (for small frequencies) was used to determine categorical variables, while Mann–Whitney test was used for continuous variables. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS 21.0 (SPSS Inc.).

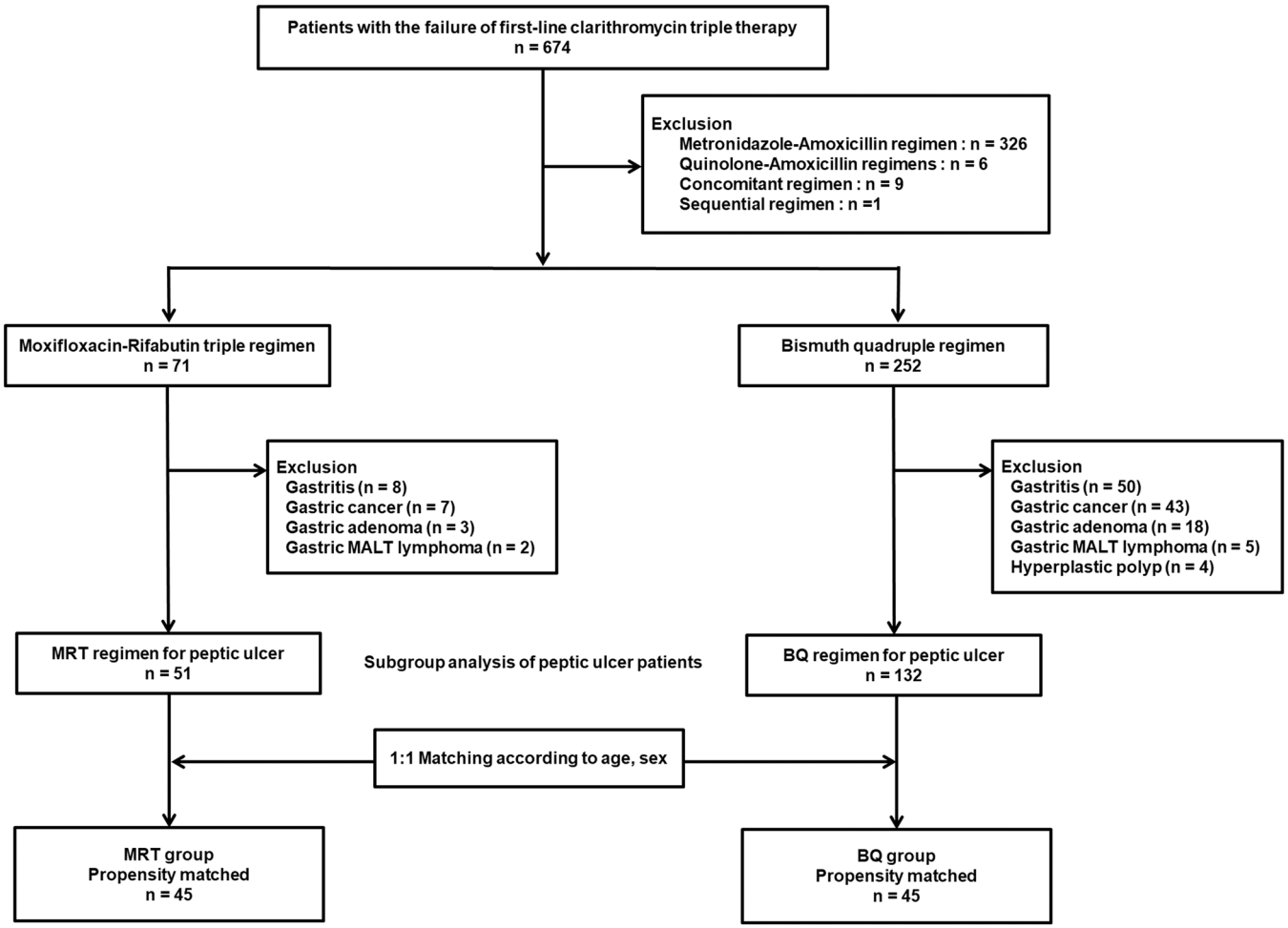

FIGURE 1 Flowchart for the enrollment. BQ, bismuth quadruple therapy; MALT, mucosa-associated lymphoid tissue; MRT, moxifloxacin–rifabutin triple therapy

3 | RESULTS

3.1 | Demographic clinical characteristics

In total 323 patients, the mean age of MRT group was significantly higher by 3.7 years than that of the BQ group (Table 1). There was also a significant difference in the distribution of the main reasons for *H. pylori* eradication therapy. However, peptic ulcer was the most common reason in both groups. The other variables, including sex, did not significantly differ between the two groups.

After the propensity score matching, there were no variables with a significant difference between both groups (Table 2).

3.2 | Predictive factors for the successful eradication with second-line regimen

In univariate logistic regression analysis, the regimen used for second-line eradication was the only factor influencing a successful eradication ($p = 0.019$). Other factors, including age and peptic ulcer history, did not affect the success of eradication (Table 3).

3.3 | The second-line eradication rates of MRT and BQ therapy

In total of 323 patients, the eradication rate of the MRT group was significantly lower than that of the BQ group, with a difference of about 13.5% in the ITT population and 11.5% in the PP population ($p = 0.019$ in the ITT; $p = 0.022$ in the PP; Figure 2A).

In a subgroup analysis of 183 peptic ulcer patients, there was a significantly higher difference between the both groups. Compared with the BQ group, the MRT group showed a lower eradication rate by 21% in the ITT population and 17.2% in the PP population ($p = 0.004$ in the ITT; $p = 0.010$ in the PP; Figure 2B).

In the 90 propensity score-matched patients with peptic ulcer, the eradication rate of the MRT group was lower than that of the BQ group by 15.6% in the ITT analysis and 11.5% in the PP analysis.

TABLE 1 Demographic clinical characteristics of total 323 patients receiving moxifloxacin–rifabutin triple (MRT) and bismuth quadruple (BQ) therapies.

Variable	MRT group ($n = 71$)	BQ group ($n = 252$)	p-value
Age, years	61.7 ± 12.6	58.0 ± 12.1	0.019
Sex, male	43 (60.6%)	151 (59.9%)	1.000
Familial history of gastric cancer	2/47 (4.3%)	11/144 (7.6%)	0.526
Smoking history	19/60 (31.7%)	44/184 (23.9%)	0.239
Alcohol consumption history	28/59 (47.5%)	69/179 (38.5%)	0.285
Main reason for eradiation			0.040
Peptic ulcer	51 (71.8%)	132 (52.4%)	
Gastritis	8 (11.3%)	50 (19.8%)	
Gastric cancer	7 (9.9%)	43 (17.1%)	
Gastric adenoma	3 (4.2%)	18 (7.1%)	
MALT lymphoma	2 (2.8%)	5 (2.0%)	
Hyperplastic polyp	0 (0.0%)	4 (1.6%)	

Abbreviations: BQ, bismuth quadruple therapy; MALT, mucosa-associated lymphoid tissue; MRT, moxifloxacin–rifabutin triple therapy.

TABLE 2 Clinical characteristics of the 90 propensity score-matched patients with peptic ulcer

Variable	MRT group ($n = 45$)	BQ group ($n = 45$)	p-value
Age, years	60.8 ± 11.0	60.8 ± 11.8	0.846
Sex, male	28 (62.2%)	35 (75.6%)	0.255
Familial history of gastric cancer	0/28 (0.0%)	1/20 (5.0%)	0.417
Smoking history	14/38 (36.8%)	10/29 (34.5%)	1.000
Alcohol consumption history	25/39 (64.1%)	12/27 (44.4%)	0.136

Abbreviations: BQ, bismuth quadruple therapy; MRT, moxifloxacin–rifabutin triple therapy.

However, they were not statistically significant ($p = 0.167$ in the ITT; $p = 0.286$ in the PP; Figure 2C).

3.4 | The third-line eradication rates after failures of the second-line MRT therapy

Of the 14 patients who showed unsuccessful eradication with MRT regimen, 10 were treated with BQ therapy as the third-line regimen. Nine of 10 patients showed successful eradication of *H. pylori*. Of the 71 patients who underwent the second MRT regimen, 12 were not followed up, 49 were eradicated by the second-line MRT regimen, and 9 were eradicated by the third-line BQ regimen. Only one patient was not eradicated despite the second-line MRT and third-line BQ regimen.

TABLE 3 Predictive factors for the success of eradication in patients who underwent second-line regimen for *Helicobacter pylori* in univariate logistic regression analyses

Variable	Univariate	
	Odds ratio (95% CI)	p-value
Age (years)	1.00 (0.97–1.03)	0.952
Sex (male)	1.09 (0.55–2.17)	0.812
Familial history of gastric cancer	0.41 (0.12–1.43)	0.160
Smoking history	0.68 (0.30–1.55)	0.362
Alcohol consumption history	1.31 (0.61–2.80)	0.491
Peptic ulcer history	0.74 (0.37–1.47)	0.385
MRT regimen (vs. BQ)	0.42 (0.20–0.87)	0.019

Abbreviations: BQ, bismuth quadruple regimen; CI, confidence interval; MRT, moxifloxacin–rifabutin triple regimen.

4 | DISCUSSION

The purpose of this study was to compare the success rates of the second-line eradication between the MRT group and BQ group in peptic ulcer patients following failure of the first-line clarithromycin regimen, and it was found that the second-line MRT therapy was not as effective as BQ therapy.

Few studies have focused on MRT therapy for *H. pylori* infection, and no study has been conducted in Asia. In a 2008 German study,[11] 1 week of once-daily moxifloxacin–rifabutin therapy resulted in success rates of 77.7% in ITT and 83.3% in the PP analyses, which were a higher success rate than 69.0% in ITT and 77.8% in the PP analyses in our study. This may be related to the high proportion of elderly and males in subjects of this study. This study also showed different success rates depending on the main reason for eradication in the MRT group (Table S1); however, it is unclear what causes this difference in success rates. The number of patients with disorders other than peptic ulcers in this study is small; thus, research with a large number of patients is required to evaluate the different eradication rates.

In this study, the success rate of the second-line MRT with peptic ulcers was not satisfactory (60.8% in ITT analysis; 72.1% in PP analysis). It is presumed that the low eradication rates were attributed to the high resistance rate to moxifloxacin demographically. In a Korean study based on the susceptibility test through culture of *Helicobacter pylori*, the resistance rates to moxifloxacin were reported to be 39.2%.[9] In previous studies in Korea,[7,8] the success rates of the moxifloxacin–amoxicillin triple regimen were low (approximately 73.8%–73.9% in PP analysis), which is similar to the success rate in our study. Prior studies showed that the success rate of eradication may be increased by extending the period of

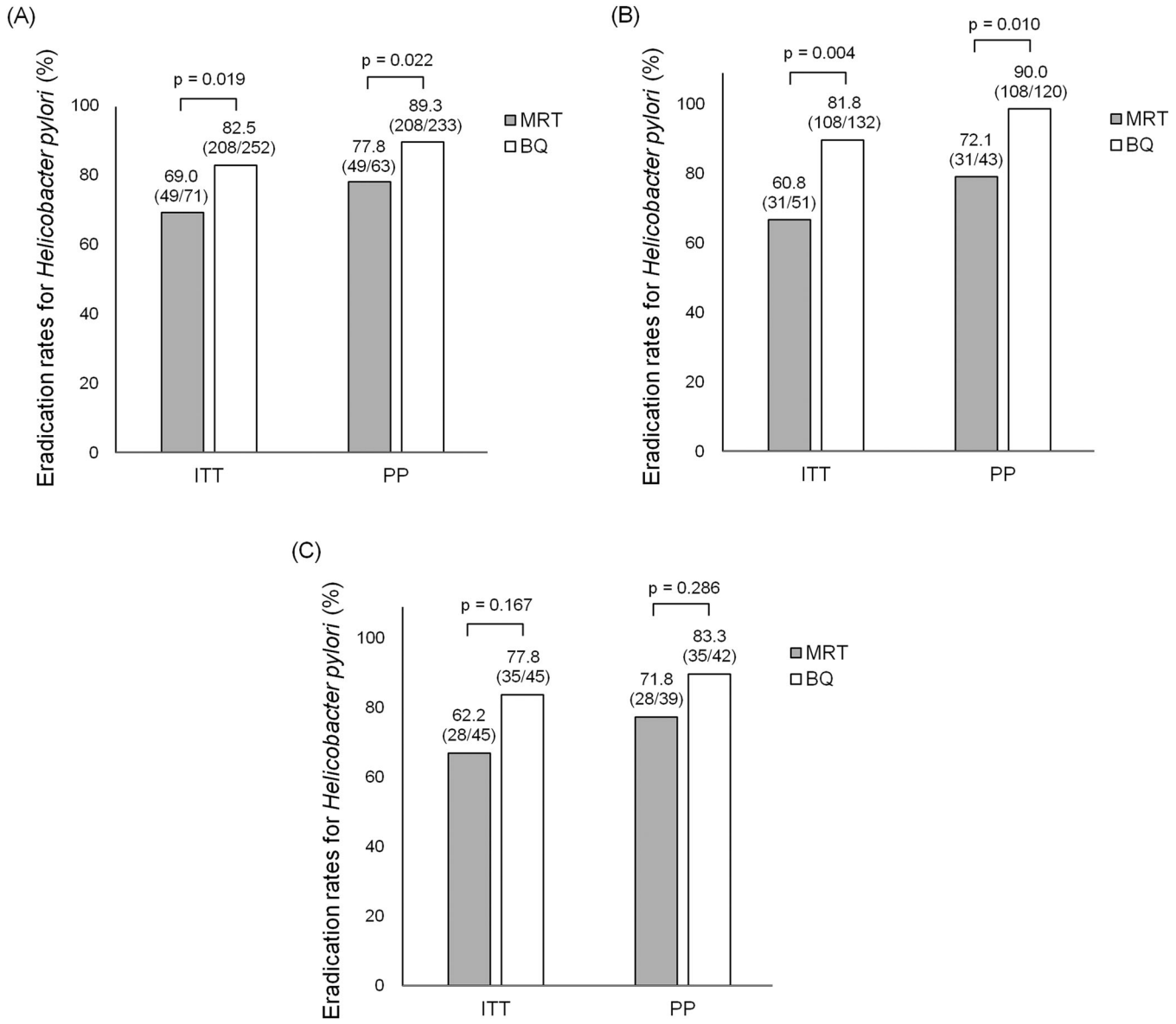

FIGURE 2 Comparison of secondary-line eradication rates between the MRT and BQ groups in ITT and PP populations. (A) total 323 patients; (B) subgroup analysis of 183 patients with peptic ulcer; (C) the 90 propensity score-matched patients with peptic ulcer. BQ, bismuth quadruple regimen; ITT, intent-to-treat; MRT, moxifloxacin-rifabutin triple regimen; PP, per protocol

moxifloxacin[7] and rifabutin[12] therapy from 7 to 14 days or by using high-dose PPIs.[13]

The present study showed that the success rates of the third-line BQ regimen after failure of the second-line MRT regimen was 90% (9/10), which is similar to the success rates of the second-line BQ regimen. Though the number of patients who underwent with third-line BQ after second-line MRT therapy was as small as 10, this may imply that second-line MRT therapy did not affect the success rates of third-line BQ therapy. This is theoretically possible because there are no overlapping antibiotics between the MRT and BQ regimen.

There are certain limitations to this study. First, because it was a single retrospective study, the number of patients was insufficient to conduct adequate randomization for efficacy comparison. The number of patients included in the sub-analysis was 45 in each group, and the power of this analysis was 0.77, which was lower than the appropriate 0.80 when an alpha of 0.05 was applied in a one-sided test. Second, this was a retrospective study, so the side effects were not sufficiently investigated. In addition, no patient underwent a *H. pylori* culture test to identify the susceptibility of antibiotics. And the 7-day regimen in this study was shorter than the recently recommended 10- or 14-day eradication. A clinical trial in which these limitations are adjusted is needed in the future. These limitations may be corrected through additional clinical trials.

In conclusion, the efficacy of the second-line MRT regimen was not as effective as BQ regimen, so it should be considered for limited use only in patients for whom the BQ regimen is not available.

AUTHOR CONTRIBUTIONS

Chang Min Lee: Conceptualization; data curation; formal analysis; investigation; writing—original draft; writing—review & editing. **Seong Je Kim**: Supervision. **Se In Hah**: Supervision; writing—review & editing. **Ji Yoon Kwak**: Supervision. **Jung Woo Choi**: Supervision. **Hyun Chin Cho**: Supervision. **Chang Yoon Ha**: Supervision. **Ok Jae Lee**: Supervision. **Woon Tae Jung**: Conceptualization; resources; writing—review & editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

DISCLOSURE STATEMENT

The corresponding author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported, no important aspects of the study have been omitted, and any discrepancies from the study as planned have been explained.

TRANSPARENCY STATEMENT

The lead author (Woon Tae Jung) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

GUARANTOR OF THE ARTICLE

Dr. Woon Tae Jung.

ORCID

Chang Min Lee https://orcid.org/0000-0001-5587-2023

REFERENCES

1. Lee JY, Kim N, Kim MS, et al. Factors affecting first-line triple therapy of *Helicobacter pylori* including CYP2C19 genotype and antibiotic resistance. *Dig Dis Sci*. 2014;59(6):1235-1243.
2. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter*. 2010;15(1):1-20.
3. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the maastricht V/Florence consensus report. *Gut*. 2017;66(1):6-30.
4. Kim JJ. Analysis of metronidazole, clarithromycin and tetracycline resistance of *Helicobacter pylori* isolates from Korea. *J Antimicrob Chemother*. 2001;47(4):459-461.
5. Kim JM, Kim JS, Jung HC, Kim N, Kim YJ, Song IS. Distribution of antibiotic MICs for *Helicobacter pylori* strains over a 16-year period in patients from Seoul, South Korea. *Antimicrob Agents Chemother*. 2004;48(12):4843-4847.
6. Kim JY, Kim N, Kim SJ, et al. Regional difference of antibiotic resistance of helicobacter pylori strains in Korea. *Korean J Gastroenterol*. 2011;57(4):221-229.
7. Kang KK. Helicobacter pylori eradication with moxifloxacin-containing therapy following failed first-line therapies in South Korea. *World J Gastroenterol*. 2014;20(22):6932-6938.
8. Kim SE, Roh JH, Park MI, et al. Effect of 7-day bismuth quadruple therapy versus 14-day moxifloxacin triple therapy for second-line helicobacter pylori eradication therapy. *Korean J Gastroenterol*. 2019;73(1):26-34.
9. 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(2):e12561.
10. Lee JY, Kim N, Nam RH, In choi S, lee JW, lee DH. Primary and secondary antibiotic resistance of *Helicobacter pylori* in korea from 2003 to 2018. *Helicobacter*. 2019;24(6):e12660.
11. Miehlke S, Schneider-Brachert W, Kirsch C, et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter*. 2008;13(1):69-74.
12. Sung J, Kim N, Park YH, et al. Rifabutin-based fourth and fifth-line rescue therapy in patients with for *Helicobacter pylori* eradication failure. *Korean J Gastroenterol*. 2017;69(2):109-118.
13. Lim HC, Lee YJ, An B, Lee SW, Lee YC, Moon BS. Rifabutin-based high-dose proton-pump inhibitor and amoxicillin triple regimen as the rescue treatment for *Helicobacter pylori*. *Helicobacter*. 2014;19(6):455-461.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee CM, Kim SJ, Hah SI, et al. Comparison of eradication rates of moxifloxacin–rifabutin triple therapy and bismuth quadruple therapy as second-line regimens in patients with peptic ulcers. *Health Sci Rep*. 2022;5:e780. doi:10.1002/hsr2.780