Efficacy of Seven-Day Potassium-Competitive Acid Blocker-Based First-Line *Helicobacter Pylori* Eradication Therapy Administered with Bismuth

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Purpose: To determine the efficacy of a potassium-competitive acid blocker (P-CAB)-based first-line eradication therapy with bismuth compared with that of proton pump inhibitor-based first-line therapy with bismuth.

Materials and Methods: Eradication-naive *H. pylori*-infected patients were consecutively enrolled from January to November 2020. Before approval of the P-CAB-based eradication therapy, twice daily administration of a regimen containing lansoprazole 30 mg, amoxicillin 1 g, clarithromycin 500 mg, and bismuth potassium citrate 300 mg was prescribed for 7 days. After approval, lansoprazole was replaced with tegoprazan (50 mg). Clarithromycin resistance was examined in patients who underwent gastroscopic biopsy at our center. Efficacy was assessed via the ^{13}C-urea breath test.

Results: Of the 381 eradication-naive patients, eradication was successful in 88.3% (151/171) treated with tegoprazan and 82.8% (140/169) treated with lansoprazole in per-protocol analysis (*p*=0.151). In intention-to-treat analysis, eradication rates were 78.8% (152/193) in the tegoprazan and 74.5% (140/188) in the lansoprazole group (*p*=0.323). Clarithromycin resistance was observed in 30 (20.1%) of the 148 patients (74 from each group), and only four of the 16 clarithromycin-resistant patients in the tegoprazan group achieved successful eradication. Clarithromycin resistance [odds ratio (OR)=42.1, 95% confidence intervals (CIs)=12.6–141.0] and poor patient compliance (OR=17.1, 95% CIs=1.6–189.1) were independent risk factors for eradication failure.

Conclusion: In eradication-naive patients, eradication success rates for 7-day first-line triple therapy regimen exceeded 82% with bismuth administration. In clarithromycin-resistant patients, neither tegoprazan 50 mg nor lansoprazole 30 mg achieved acceptable eradication rates when administered twice daily for 7 days.

Key Words: *Helicobacter pylori*, eradication, bismuth, proton pump inhibitor

INTRODUCTION

Acid suppressants are administered along with antibiotics during *Helicobacter pylori* eradication therapy because antibiotics degrade rapidly in gastric acid.[1] *H. pylori* eradication

success rates are higher in therapies using potassium-competitive acid blockers (P-CABs) than those using proton pump inhibitors (PPIs), owing to the stronger acid suppression capability of P-CABs;[2] however, no data in support thereof are available outside Japan. Meanwhile, research has shown eradication success rates in clarithromycin-resistant strains of 76.1% and 40.2% after 7 days of P-CAB-based and PPI-based therapy, respectively.[3] Others have shown that the efficacy of P-CAB-based eradication therapy reduces with aging,[4] and that an acceptable eradication success rate is not achieved against clarithromycin-resistant strains.[5] Therefore, the efficacy of P-CAB-based eradication therapy needs to be further evaluated, especially in a population with high clarithromycin resistance.

Clarithromycin and amoxicillin resistance rates among *H. pylori* infections are 18% and 9% in South Korea.[6] In a recent multicenter study, the eradication success rate of 7-day con-

ventional triple therapy was only 71.7%.[7] To enhance the eradication rate, administrating bismuth along with acid suppressants has been recommended.[8] Bismuth is used as an additive not only for second-line eradication therapy, but also for first-line eradication therapy.[9] Administration of conventional triple therapy for 10 days achieved an eradication rate of 93.1% in per-protocol analysis when bismuth was added in an eradication therapy regimen.[10] Furthermore, an eradication rate of 94.0% was achieved after 14 days administration of bismuth-added triple therapy.[11] Nevertheless, no data are available on the efficacy of administration of a 7-day triple therapy regimen administered with bismuth. Moreover, there are no studies on the comparison of efficacy between bismuth-administered P-CAB-based triple therapy and bismuth-administered PPI-based triple therapy.

The present study aimed to compare the efficacy and safety of 7-day bismuth-administered conventional triple therapy using P-CAB and that using PPI. We also attempted to determine the eradication success rates of 7-day bismuth-administered triple therapy according to clarithromycin resistance: previous studies have only achieved acceptable eradication rates using longer durations (10 or 14 days).[9-12]

MATERIALS AND METHODS

Patient selection and ethical statement

The study was conducted as a retrospective study of *H. pylori* eradication-naive patients who were referred to a gastroenterologist (Dr. S.-Y. Lee) with a positive *H. pylori* test finding after gastroscopy between January and November 2020. Patients with past eradication therapy, penicillin allergy, age above 75 or below 20 years, renal failure, hepatic failure, pregnancy, or breast-feeding were excluded. Tegoprazan was available for *H. pylori* eradication therapy from late June at our center; hence, all eradication-naive patients who visited thereafter were administered a regimen containing tegoprazan 50 mg, amoxicillin 1 g, clarithromycin 500 mg, and bismuth tripotassium dicitrate (Denol®) 300 mg twice daily for 7 days (tegoprazan group). Among patients who visited before the approval of P-CAB use, lansoprazole 30 mg was administered instead of tegoprazan (lansoprazole group). The present research was approved by the Institutional Review Board (IRB) of Konkuk University Medical Center (KUMC 2020-09-045). The study was conducted in accordance with the Declaration of Helsinki.

Findings before the eradication therapy

Endoscopic findings along with histology, Giemsa staining, and/or rapid urease test findings were collected. For the serology test, the Chorus *H. pylori* IgG assay (DIESSE, Siena, Italy) which shows a clinically acceptable accuracy in the Korean population, was used (sensitivity: 100%, specificity: 75.4%).[13] Serum pepsinogen assay was performed using the latex-en-

hanced turbidimetric immunoassay (HBi Co., Anyang, Korea) as previously described.[14] Gastrointestinal symptoms before first-line eradication therapy and comorbidities requiring management were recorded.

The degree of chronic atrophic gastritis were graded as closed-type (C)-O, C-1, C-2, C-3; open-type (O)-1, O-2, O-3; and pangastritis (Op) using GIF-H290 or GIF-H260 (Olympus, Tokyo, Japan) based on modified Kimura-Takemoto classification.[15] Furthermore, it was classified into score 0 (C-O or C-1), score 1 (C-2 or C-3), and score 2 (O) based on the Kyoto classification scoring system for gastritis.[16] Representative cases are summarized in Supplementary Figs. 1-8 (only online).

Pyrosequencing analysis for *H. pylori* clarithromycin resistance

Clarithromycin resistance was examined using the gastric biopsy specimens taken during *H. pylori* infection diagnosis. DNA extraction and PCR amplification were performed only in patients who were biopsied at our center. *H. pylori*-infected patients who were diagnosed by a positive rapid urease test or endoscopic biopsy performed at other hospitals were not tested for clarithromycin resistance.

For DNA extraction, tissues were obtained from paraffin sections, after which 50–100 μL of DNA extraction buffer solution consisting of 50 mM Tris buffer (pH 8.3), 1 mM EDTA (pH 8.0), 5% Tween 20, 100 μg/mL proteinase K, and 10% resin were added to the tissue. After incubation at 56°C for more than an hour, the tubes were heated to 100°C for 10 min. After centrifuging the solution, 5 μL of supernatant was used for PCR amplification. For identification, forward primer 5′-AGGTAGCGAAATTCCTT-GTC-3′ and reverse primer 5′-biotin-GCATGATATTCCCATTAG-CA-3′ were used to amplify 184-bp DNA fragments from the 23S rRNA region of *H. pylori*. Five microliters of DNA were added to make 50 μL of PCR solution mix containing 20 pmol of each primer, 0.2 mmol of dNTP, 1.5 mmol/l of $MgCl_2$, 1.5 U of Immolase DNA Taq Polymerase (Bioline, London, UK), and 1× PCR buffer. PCR amplification was performed using the Pro-Flex PCR System (Thermo Fisher Scientific, Waltham, CA, USA) for 5 min at 95°C, 50 cycles (30 s at 95°C, 30 s at 52°C, and 30 s at 72°C), and 10 min at 72°C. The final products were electrophoresed using the Qsep100 (Bioptic, New Taipei City, Taiwan).

Biotinylated PCR products were immobilized on Streptavidin-Sepharose™ High Performance (GE Healthcare, Uppsala, Sweden) based on the standard protocol provided with Pyro-Mark® Gold 24 reagents sample preparation kit (Qiagen, Valencia, CA, USA). Two microliters of beads were diluted with a binding buffer and biotinylated PCR products. The beads were incubated at 1400 rpm at room temperature (15–25°C) for 20 min. After transferring the beads to filter probes, the liquid was removed by vacuum filtration. DNA was separated in denaturation solution for 10 s. The templates were washed using a washing buffer and transferred to a PyroMark Q24 plate (Qiagen). The templates were then annealed with a sequencing

primer reverse 5'-GCGGCAAGACGG-3' in an annealing buffer at room temperature. The Q24 plate was warmed for 2 min using a pre-heated PyroMark Q24 plate holder (Qiagen) at 80°C. Thereafter, the PyroMark Q24 plate was removed. It was placed on a second PyroMark Q24 plate holder, which was kept at room temperature for 10–15 min. Sequence analysis was conducted using PyroMark Q24 software (Qiagen).

Study outcomes

The primary outcome of this study was *H. pylori* eradication success rate. This was assessed via the ^{13}C-urea breath test (UBT) using POCone® (Otsuka Electronics Co. Ltd., Osaka, Japan) at the fifth week after the eradication therapy. Eradication success was defined as a cut-off value below 2.5% as previously described.[17]

The secondary study outcome was any adverse drug effects that occurred with first-line eradication therapy. The severity of adverse effects was graded as mild (transient symptoms that improved spontaneously), moderate (symptoms that required management), and severe (symptoms that led to an emergency visit).

Statistical analysis

A sample size of 72 patients in each group achieved 90% power to detect an effect size of 0.3823 using one degree of freedom based on a recent meta-analysis study.[18] In that study, eradication rates of first-line triple therapy using PPI and P-CAB were 74.8% and 91.4%, respectively. The chi-square test was used with a significance level (alpha) of 0.0500 for sample size calculation.

Differences between the tegoprazan and lansoprazole groups were analyzed using the chi-square and t-tests for categorical and continuous variables, respectively. For continuous variables with symmetrical distribution, data are presented as a mean±standard deviation (SD). For continuous variables with asymmetrical distribution, data are presented as a median with ranges using the Kruskal-Wallis test. For categorical variables, data are presented as a number and proportion (%) of the patients. For categorical variables with asymmetrical distribution, Fisher's exact test was used instead of the chi-square test. Logistic regression analysis was used to identify significant risk factors for eradication failure. Data are presented as odds ratio (OR) with 95% confidence intervals (CIs). The PASW statistics version 24.0 (IBM Corp., Armonk, NY, USA) was used, and a *p* value of <0.05 was considered significant.

RESULTS

Baseline characteristics of eradication-naive patients with *H. pylori* infection

During first-line eradication therapy, 193 and 188 eradication-naive patients were administered tegoprazan and lansoprazole, respectively. There were no significant differences between the tegoprazan and lansoprazole groups with respect to age, sex, comorbidities, and gastrointestinal symptoms before first-line eradication therapy (Table 1). Initial gastrointestinal symptoms, serum assay and endoscopic findings did not significantly differ between the two groups.

Efficacy and safety of bismuth-administered first-line eradication therapies

Among the 381 patients, 171 (88.6%) of the 193 patients in the tegoprazan group and 169 (89.9%) of the 188 patients in the lansoprazole group followed given instructions. Eradication was successful in 88.3% (151/171) of the tegoprazan group and 82.8% (140/169) of the lansoprazole group according to per-protocol analysis (*p*=0.151) (Fig. 1). In intention-to-treat analysis, eradication rates were 78.8% (152/193) in the tegoprazan group and 74.5% (140/188) in the lansoprazole group (*p*=0.323).

Adverse effects were reported in 58 (15.2%) of the 381 patients. Most (53/58, 91.4%) of the patients showed mild adverse effects that did not interrupt the eradication therapy. Five (8.6%) patients showed moderate adverse effects, and none suffered from severe adverse effects. The incidence, number, type, and degree of adverse effects did not significantly differ between the two groups (Table 2).

Eradication success rate in clarithromycin-resistant patients

Clarithromycin resistance was examined in 148 patients (74 from each group), and resistance was observed in isolates from 30 (20.1%) patients. Point mutations were found at positions 2142 and 2143 in 16 (21.6%) of 74 patients tested from the tegoprazan group and 14 (18.9%) of 74 patients tested from the lansoprazole group (*p*=0.683). Four of the 16 clarithromycin-resistant patients in the tegoprazan group achieved successful eradication, whereas none of the 14 clarithromycin-resistant patients in the lansoprazole group did (*p*=0.103) (Fig. 2).

Independent risk factors for eradication failure

The presence of clarithromycin resistance (*p*<0.001), poor patient compliance (*p*<0.001), and moderate degree of adverse effects (*p*<0.001) differed between 292 patients with successful eradication and 89 patients with eradication failure (Table 3). On logistic regression analysis, clarithromycin resistance (OR=42.1) and poor compliance (OR=17.1) were independent risk factors for eradication failure (Table 4).

Follow-up management in eradication failure patients

Second-line eradication regimen (bismuth subcitrate 300 mg, metronidazole 750 mg, tetracycline 1 g, and pantoprazole 20 mg twice a day for 1 week) was provided to all 89 eradication failure patients based on our recent study.[17] Among 41 patients in the tegoprazan group and 48 patients in the lansoprazole group, 38 and 46 patients underwent ^{13}C-UBT after 5 weeks at our center, respectively. The remaining five patients wanted to

Table 1. Baseline Characteristics of Eradication-Naive Patients with *H. pylori* Infection

Variables	Total (n=381)	Tegoprazan group (n = 193)	Lansoprazole group (n = 188)	*p* value
Age (yr)	55.5±11.1	55.3±11.1	55.7±11.2	0.750
Female sex	204 (53.5)	102 (52.8)	102 (54.3)	0.783
Comorbidities	156 (40.9)	78 (40.4)	78 (41.5)	0.831
Serum anti-*H. pylori* IgG (AU/mL)	153.9±62.5	164.6±57.5	146.3±65.0	0.051
Serum pepsinogen I (ng/mL)	81.4±35.1	84.1±37.3	79.5±33.5	0.424
Serum pepsinogen II (ng/mL)	25.9±12.4	27.2±13.6	25.0±11.4	0.279
Serum pepsinogen I/II ratio	3.5±1.4	3.4±1.2	3.5±1.4	0.725
Gastrointestinal symptoms	142 (37.3)	69 (35.8)	73 (38.8)	0.534
Initial symptoms that required management before eradication				
Epigastric pain or soreness	54 (14.2)	30 (15.5)	24 (12.8)	0.437
Indigestion, postprandial discomfort or early satiety	46 (12.1)	21 (10.9)	25 (13.3)	0.469
Esophageal symptoms (globus sensation, acid reflux, etc.)	17 (4.5)	7 (3.6)	10 (5.3)	0.424
Anorexia, nausea or vomiting	7 (1.8)	2 (1.0)	5 (2.7)	0.279*
Bloating or retching	8 (2.1)	3 (1.6)	5 (2.7)	0.498*
Others (halitosis, melena, etc.)	10 (2.6)	6 (3.2)	4 (2.0)	0.751*
Initial endoscopic findings				
Nodular gastritis	22 (5.8)	13 (6.7)	9 (4.8)	0.415
Gastric polyp larger than 5 mm	18 (4.7)	10 (5.2)	8 (4.2)	0.670
Gastric ulcer (excluding scar)	12 (3.1)	4 (2.1)	8 (4.2)	0.223
Duodenal ulcer (excluding scar)	12 (3.1)	7 (3.6)	5 (2.7)	0.589
Gastric adenoma or adenocarcinoma	8 (2.1)	4 (2.1)	4 (2.1)	>0.999*
Gastric subepithelial lesion larger than 5 mm	4 (1.1)	1 (0.5)	3 (1.6)	0.367*
Gastric erosion larger than 5 mm	7 (1.8)	2 (1.0)	5 (2.7)	0.279*
Gastritis without focal lesion	298 (78.3)	152 (78.8)	146 (77.7)	0.795
Degree of atrophy based on modified Kimura-Takemoto classification (C-0:C-1:C-2:C-3:O-1:O-2:O-3:Op)	68:70:97:70:43:27:4:2	30:42:48:38:25:8:1:1	38:28:49:32:18:19:3:1	0.147
Atrophy score based on Kyoto classification scoring system (score 0:score 1:score 2)	138:167:76	72:86:35	66:81:41	0.664

C, closed-type; O, open-type; Op, pangastritis.
Atrophy score 0 indicates C-O or C-1. Score 1 indicates C-2 or C-3. Score 2 indicates O-1, O-2, O-3, or Op. Data are presented as a mean±standard deviation using the t-test or a number with proportion (%) of the patients using the chi-square test.
*Fisher's exact test was used for categorical variables with asymmetrical distribution.

undergo confirmation tests at other centers. Negative ¹³C-UBT findings were found in all 38 (100%) of the 38 tegoprazan group patients and 42 (91.3%) of the 46 lansoprazole group patients (*p*=0.123). In the four lansoprazole group patients who failed second-line eradication therapy, third-line eradication therapy (amoxicillin 1 g, levofloxacin 500 mg, bismuth subcitrate 300 mg, and lansoprazole 30 mg twice a day for 10 days) was administered. All four patients showed negative ¹³C-UBT findings after 5 weeks at our center.

DISCUSSION

In the present study, the efficacy of tegoprazan- and lansoprazole-based first-line eradication therapy was 88.3% and 82.8%, respectively, when administered with bismuth for 7 days. Adverse effects were reported in 15.2% of 381 patients, and most (91.4%) were mild symptoms that resolved spontaneously. There were no severe adverse effects. In clarithromycin-resistant patients, only 25% of patients in the tegoprazan group achieved eradication success with tegoprazan 50 mg twice daily for 7 days.

Incomplete neutralization of intragastric pH seems to be the most important reason for eradication failure in clarithromycin-resistant strains, because P-CAB-based triple therapy is effective, regardless of clarithromycin resistance, presuming that amoxicillin is susceptible.[19] Compared to the dose of vonoprazan used during eradication therapy (20 mg administered twice daily, which is a four times higher dose than used for gastroesophageal reflux disease, 10 mg per day),[20] only tegoprazan 50 mg twice daily is approved by the Korean government for eradication therapy. Although tegoprazan improves susceptibility against antimicrobial-resistant strains,[21] the efficacy of tegoprazan 100 mg per day seems to be limited because the same
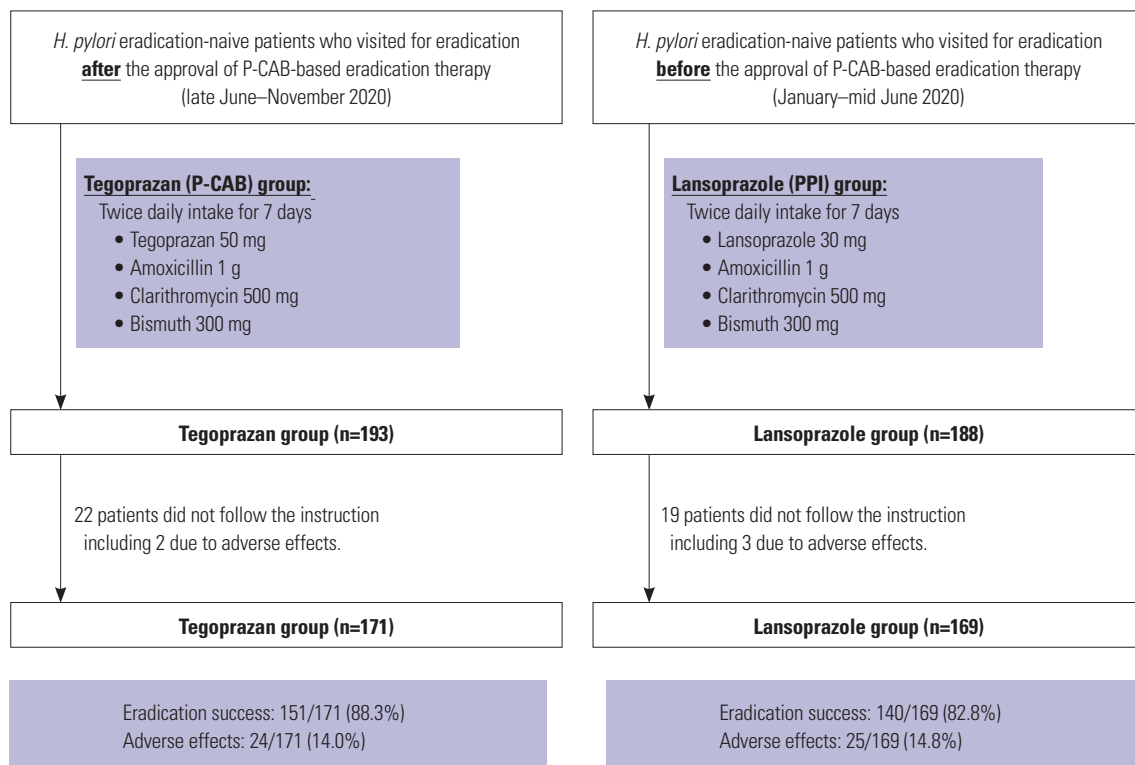
Fig. 1. Flow of 7-day bismuth-administered first-line eradication therapy. Patients who underwent ^{13}C-UBT after completing first-line eradication therapy were included in the per-protocol analysis after excluding the patients who did not follow instructions. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; ^{13}C-UBT, ^{13}C-urea breath test.

**Table 2.** Findings after 7-Day Bismuth-Administered First-Line Eradication Therapy

Variables	Tegoprazan group (n=193)	Lansoprazole group (n=188)	*p* value
Poor compliance of the patients	22 (11.4)	19 (10.1)	0.684
Negative ^{13}C-UBT findings	152 (78.8)	140 (74.5)	0.323
Adverse drug effects	30 (15.5)	28 (14.9)	0.860
Number of adverse drug effects	0.16 (0–2)	0.15 (0–2)	0.616
Severity of adverse drug effects (mild:moderate:severe)	28:2:0	25:3:0	0.650*
Types of adverse drug effects			
General weakness	6 (3.1)	2 (1.1)	0.284*
Insomnia, dizziness, or headache	4 (2.1)	0	0.123*
Skin rash	0	1 (0.5)	0.493*
Flu-like symptoms	2 (1.0)	1 (0.5)	>0.999*
Bitter taste	6 (3.1)	6 (3.2)	0.963
Anorexia, nausea, or vomiting	6 (3.1)	5 (2.7)	0.793
Acid reflux	1 (0.5)	1 (0.5)	>0.999*
Epigastric pain or soreness	3 (1.6)	3 (1.6)	>0.999*
Indigestion	3 (1.6)	1 (0.5)	0.623*
Abdominal gaseous distention	1 (0.5)	4 (2.1)	0.210*
Loose stool	2 (1.0)	5 (2.7)	0.279*
Constipation	2 (1.0)	0	0.499*
Others (urinary symptom)	0	1 (0.5)	0.493*

^{13}C-UBT, ^{13}C-urea breath test.
The severity of adverse effects was graded as mild (transient symptoms that improved spontaneously), moderate (symptoms that required management), or severe (symptoms that led to an emergency visit). Data are presented as the number of patients (%) using the chi-square test for categorical variables with symmetrical distribution.
*Fisher's exact test was used for categorical variables with asymmetrical distribution.

dose is used for gastroesophageal reflux disease.[22] Tegoprazan increases gastric pH to the neutral range after being administered at 1−3 mg/kg in a dose-dependent manner;[23] therefore, an acceptable eradication success rate might be achieved by administering tegoprazan 200 mg or 400 mg per day during eradication therapy. Further studies involving longer durations and higher doses of tegoprazan are warranted to achieve acceptable eradication rates in clarithromycin-resistant patients.
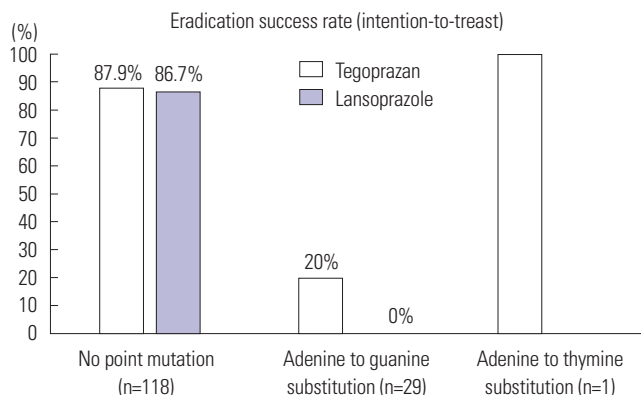
Fig. 2. Eradication success rates according to 23S rRNA gene mutations conferring *H. pylori* clarithromycin resistance. Point mutations in 23S rRNA nucleotides 2142 and 2143 were reported in isolates from 30 of 148 patients who were tested for clarithromycin resistance. Among these clarithromycin-resistant isolates, an adenine (A) to guanine (G) substitution was found in isolates from 29 patients. An A to thymine (T) substitution was found in an isolate from one patient. Eradication was successful in only three (20%) of the 15 tegoprazan group patients with A to G substitution and in one (100%) tegoprazan group patient with A to T substitution.

Clarithromycin resistance and poor compliance were independent risk factors for eradication failure in this study. On the other hand, the degree of gastric atrophy measured by serum pepsinogen assay and endoscopic findings did not affect the eradication rate. During the study period, some refused to follow instructions for revisitation or follow up due to fear of coronavirus disease 2019 (COVID-19). As such, patient adherence rates were below 90% in both groups; nevertheless, eradication rates were higher than those reported in a recent Korean study (per-protocol: 78.5%, intention-to-treat: 64.0%).[24] Adding bismuth and including only eradication-naive patients under the age of 75 years might have been helpful in increasing the successful eradication rates in our study, because previous exposure to macrolides leads to eradication failure.[25]

In this study, we did not prescribe a 2-week eradication regimen because recent multicenter studies have shown that administering P-CAB for 1 week increased *H. pylori* eradication rates.[26,27] Moreover, 2-week therapy using bismuth decreased patient adherence in Koreans,[28,29] and increased subsequent adverse drug effects.[30] Therefore, rather than prolonging treatment duration or increasing the number of antibiotics, using stronger acid suppressants for 1 week is recommended nowadays.[31]

The low eradication rate of 78.8% in the tegoprazan group in intention-to-treat analysis and the high eradication rate of 82.8% observed in the lansoprazole group in per-protocol analysis seem to be the main reason for the lack of significant differences between the groups in our study. The former might be due to insufficient acid suppression from tegoprazan 50 mg

Table 3. Comparisons between Patients with Successful Eradication and Those with Eradication Failure

Variables	Eradication success (n=292)	Eradication failure (n=89)	*p* value
Tegoprazan group:Lansoprazole group	152:140	41:48	0.323
Age (yr)	55.6±11.3	54.9±10.5	0.577
Female sex	152 (52.1)	52 (58.4)	0.291
Comorbidities requiring medication	119 (40.8)	37 (41.6)	0.891
Clarithromycin resistance	4/107 (3.7)	26/41 (63.4)	<0.001
Poor compliance of the patients	1 (0.3)	40 (44.9)	<0.001
Adverse drug effects	48 (16.4)	10 (11.2)	0.232
Number of adverse drug effects	0.17 (0–2)	0.11 (0–1)	0.138
Severity of adverse drug effects (mild:moderate:severe)	48:0:0	5:5:0	<0.001*
Findings before the eradication therapy			
Gastrointestinal symptoms	104 (47.9)	38 (42.7)	0.227
Serum anti-*H. pylori* IgG (AU/mL)	154.8±61.8	151.0±65.2	0.726
Serum pepsinogen I (ng/mL)	79.8±32.9	86.8±41.5	0.285
Serum pepsinogen II (ng/mL)	25.0±11.8	28.9±13.8	0.092
Serum pepsinogen I/II ratio	3.5±1.4	3.3±1.1	0.452
Degree of atrophy based on modified Kimura-Takemoto classification (C-0:C-1:C-2:C-3:O-1:O-2:O-3:Op)	50:53:76:55:36:18:3:1	18:17:21:15:7:9:1:1	0.755
Atrophy score based on Kyoto classification scoring system (0:1:2)	103:131:58	35:36:18	0.735

C, closed-type; O, open-type; Op, pangastritis.
Atrophy score 0 indicates C-0 or C-1. Score 1 indicates C-2 or C-3. Score 2 indicates O-1, O-2, O-3, or Op. The severity of adverse effects was graded as mild (transient symptoms that improved spontaneously), moderate (symptoms that required management), or severe (symptoms that led to an emergency visit). Data are presented as a mean±standard deviation or number of patients with proportion (%) using the t-test and chi-square test for continuous and categorical variables.
*Fisher's exact test was used for categorical variables with asymmetrical distribution.

Table 4. Logistic Regression Analysis for the Risk of Eradication Failure

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Tegoprazan	0.787 (0.489–1.266)	0.323		
Lansoprazole	1 (reference)			
Age (yr)	1.006 (0.985–1.028)	0.576		
Female sex	1.294 (0.801–2.092)	0.292		
Comorbidities requiring medication	1.034 (0.639–1.675)	0.891		
Clarithromycin resistance	44.633 (13.662–145.814)	<0.001	42.063 (12.552–140.952)	<0.001
Poor compliance of the patients	237.551 (31.916–1768.067)	<0.001	17.120 (1.550–189.103)	0.020
Adverse drug effects	0.634 (0.311–1.331)	0.235		
Number of adverse drug effects	1.643 (0.846–3.190)	0.142		
Severity of adverse drug effects	0.825 (0.476–1.429)	0.493		
Gastrointestinal symptoms before eradication	1.347 (0.831–2.184)	0.227		
Serum anti-*H. pylori* IgG titer (AU/mL)	1.001 (0.996–1.006)	0.724		
Serum pepsinogen I level (ng/mL)	0.994 (0.984–1.005)	0.285		
Serum pepsinogen II level (ng/mL)	0.977 (0.950–1.004)	0.097		
Serum pepsinogen I/II ratio	1.120 (0.834–1.505)	0.450		

Data are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

twice daily for 7 days, and the latter might be due to the enhanced efficacy observed with bismuth administration.[32] Bismuth seems to increase eradication rates and patient compliance in first-line eradication therapy by preventing diarrhea due to its antidiarrheal, anti-inflammatory, and antibacterial properties that prevent colonization of pathogens.[33] Another reason for the lack of superiority of P-CAB group might be the genomic diversity of *H. pylori* showing antibiotic heteroresistance and/or coexistence of amoxicillin-resistant *H. pylori*. There might be other strains present with different antibiotic resistance characteristics: *H. pylori* obtained from biopsy does not represent all strains inside the stomach, as observed in our previous study.[34] In that study, we observed that 23.8% of the patients showed different clarithromycin susceptibility test findings between the antrum and corpus.

There are limitations to this study. First, clarithromycin resistance test was not performed in all patients, because most of them were referred from other hospitals after endoscopic biopsy. Nevertheless, we could draw a conclusion based on a larger group involving more than 72 patients in each group based on sample size calculation in the present study. Second, culture was not performed in this study. Clarithromycin resistance mutations were detected using culture-free PCR assays as recommended in a recent study.[35] In that study, PCR assays were useful for detecting clarithromycin resistance. Third, the patients were not randomized owing to the fact that tegoprazan was only available for eradication therapy from late June 2020 at our center. Nonetheless, there were no obvious variations between the two groups, and all patients were evaluated using the same methods.

In conclusion, the eradication success rates of tegoprazan- and lansoprazole-based first-line eradication therapy exceed-ed 82% with acceptable tolerability when administered with bismuth in *H. pylori* eradication-naive patients. Nevertheless, efficacy was limited in clarithromycin-resistant strains. Studies with longer durations and higher doses of tegoprazan are needed to determine the efficacy of bismuth-administered first-line conventional therapy for clarithromycin-resistant strains.

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AUTHOR CONTRIBUTIONS

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