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Original Article

Comparative Efficacy of Potassium-Competitive Acid Blocker-Based Triple Therapy with Tegoprazan versus Vonoprazan for *Helicobacter pylori* Eradication: A Randomized, Double-Blind, Active-Controlled Pilot Study

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Background/Aims: Triple therapy with vonoprazan, a potassium-competitive acid blocker, has shown an acceptable eradication rate. The aim of this study was to evaluate the efficacy and safety of tegoprazan-based triple therapy compared with those of vonoprazan-based triple therapy for *Helicobacter pylori* eradication.

Methods: This randomized, double-blind, active-controlled, multicenter pilot study included treatment-naive adults with *H. pylori* infection. Participants were randomized 1:1:1 to receive tegoprazan 50 mg (TAC 1), tegoprazan 100 mg (TAC 2), or vonoprazan 20 mg (VAC) with amoxicillin 1,000 mg plus clarithromycin 500 mg twice daily for 10 days. The primary outcome was the eradication rate.

Results: Of the 102 enrolled participants, 97 completed the study. The eradication rates in the full analysis set were 60.61% (95% confidence interval [CI], 43.93% to 77.28%), 78.79% (95% CI, 64.84% to 92.74%), and 84.85% (95% CI, 72.62% to 97.08%) in TAC 1, TAC 2, and VAC, respectively. The eradication rates in the per-protocol set were 66.67% (95% CI, 49.80% to 83.54%), 86.67% (95% CI, 74.50% to 98.83%), and 87.50% (95% CI, 76.04% to 98.96%) in TAC 1, TAC 2, and VAC, respectively. In the full analysis set, the eradication rate differences were –6.06% (95% CI, –24.61% to 12.49%) between TAC 2 and VAC and –24.24% (95% CI, –44.92% to –3.56%) between TAC 1 and VAC. In the per-protocol set, the eradication rate differences were –0.83% (95% CI, –19.97% to 17.37%) between TAC 2 and VAC and –20.83% (95% CI, –41.23% to –0.44%) between TAC 1 and VAC. All therapies were well tolerated with no notable safety differences.

Conclusions: After 10 days, tegoprazan 100 mg showed eradication rates comparable to those of vonoprazan 20 mg, while 50 mg may be insufficient. These findings support future research to optimize tegoprazan dosing in clinical practice (ClinicalTrials.gov; NCT04128917). **(Gut Liver, 2025;19:696-705)**

Key Words: *Helicobacter pylori*; Antibiotics; Clinical trials, randomized

INTRODUCTION

Helicobacter pylori is a well-known pathogen associated with various upper gastrointestinal tract diseases, including gastric malignancies.[1,2] Eradication of *H. pylori* is strongly recommended for the treatment, prevention, and reduction of recurrence of these conditions.[3-5] However, despite the widespread use of standard triple therapy (STT), which

includes a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, eradication rates for this regimen have been declining in many regions.[6-8] This decline is primarily attributed to increasing antibiotic resistance, particularly to clarithromycin, which varies significantly by geographic location.[8,9]

To achieve optimal therapeutic outcomes with antibiotics, it is essential to maintain a stable gastric pH and ensure sufficient antibiotic effect in the acidic environment of the stomach.[10] The stability of clarithromycin and amoxicillin is reduced in acidic conditions, making effective acid suppression crucial for maximizing antimicrobial activity.[11] Similarly, for amoxicillin, increasing the gastric pH significantly enhances its effectiveness.[11] This understanding has led to the consideration of more potent acid suppressants, such as potassium-competitive acid blockers (P-CABs), as alternatives to PPIs in eradication regimens.

P-CABs are thought to provide more potent, rapid-onset and sustained inhibition of gastric acid secretion than PPIs.[12,13] Tegoprazan, a P-CAB recently developed in Korea, has now been approved for the treatment of *H. pylori* infection and other acid-related diseases in several countries. Notably, triple therapy including vonoprazan, another P-CAB developed in Japan, has shown promising results in improving eradication rates, suggesting that P-CABs may help overcome the challenges posed by antibiotic resistance.[14-16] It is thought that the enhanced acid suppression provided by P-CABs could potentially improve the efficacy of eradication therapy by creating a more favorable environment for antibiotic stability and activity.

However, there have been very limited data from well-designed, prospective randomized controlled trials (RCTs) specifically evaluating the efficacy of tegoprazan-based triple therapy. Therefore, the objective of this pilot study was to explore, in an exploratory manner, the efficacy and safety of tegoprazan-based triple therapy compared to vonoprazan-based triple therapy after 10 days of twice-daily oral administration for *H. pylori* eradication.

MATERIALS AND METHODS

1. Study design

This study was designed as a randomized, double-blind, active-controlled, multicenter pilot study to evaluate the efficacy and safety of tegoprazan-based triple therapy, using variable doses of tegoprazan (50 mg or 100 mg), compared to vonoprazan-based triple therapy in *H. pylori*-positive patients. It was conducted at six centers in Korea (National Cancer Center, Pusan National University Hospital, Soonchunhyang University Bucheon Hospital, Severance Hospital, Chung-Ang University Hospital, and Kyungpook National University Chilgok Hospital) between January 21, 2020 and January 29, 2021. The study was conducted in compliance with the protocol approved by the Ministry of Food and Drug Safety and the Institutional Review Boards of each hospital (Chung-Ang University Hospital; IRB number 1912-019-398), as well as applicable regulations, including the Declaration of Helsinki and Good Clinical Practice of Rules on Safety of Medicinal Products, etc. The study protocol was registered at ClinicalTrials.gov (Identifier: NCT04128917). Results obtained from the study were collected in electronic case report forms. All subjects provided written informed consent before participating in the study.

2. Study subjects

Eligible patients were *H. pylori*-positive, aged 19 to 75 years, and had at least one of the following clinical conditions at screening: a diagnosis of gastric or duodenal ulcer or presence of peptic ulcer scars; a diagnosis of low-grade gastric mucosa-associated lymphoid tissue lymphoma; requirement for eradication therapy after endoscopic resection of early gastric cancer or gastric adenoma; or the presence of chronic atrophic gastritis. They were treatment-naive, and *H. pylori* infection was confirmed with a positive ^{13}C-urea breath test (UBT).

The main exclusion criteria included inability to undergo upper gastrointestinal endoscopy, prior treatment for *H. pylori* eradication, prior or planned surgery that might affect gastric acid secretion (e.g., upper gastrointestinal resection, vagotomy), Zollinger-Ellison syndrome or other gastric acid hypersecretion disorders, administration of P-CABs, PPIs, or histamine H_2 receptor antagonists within 14 days, or antibiotics with confirmed effect of *H. pylori* eradication or bismuth-containing drugs within 28 days, clinically significant laboratory or electrocardiogram (ECG) abnormalities at the screening test, history of malignant tumors within the past 3 years (except for gastric neoplasms completely removed by endoscopic resection), clinically significant systemic disorders, hypersensitivity to any of the active ingredients or excipients of study drugs, planned surgery, and pregnant or lactating women. Any sexually active female of childbearing potential was required to use medically acceptable methods of contraception during the study. Individuals with other clinically significant findings, based on the investigator's medical judgment, were also excluded.

3. Randomization and interventions

Included subjects were centrally randomized using block randomization in a 1:1:1 ratio to receive one of the

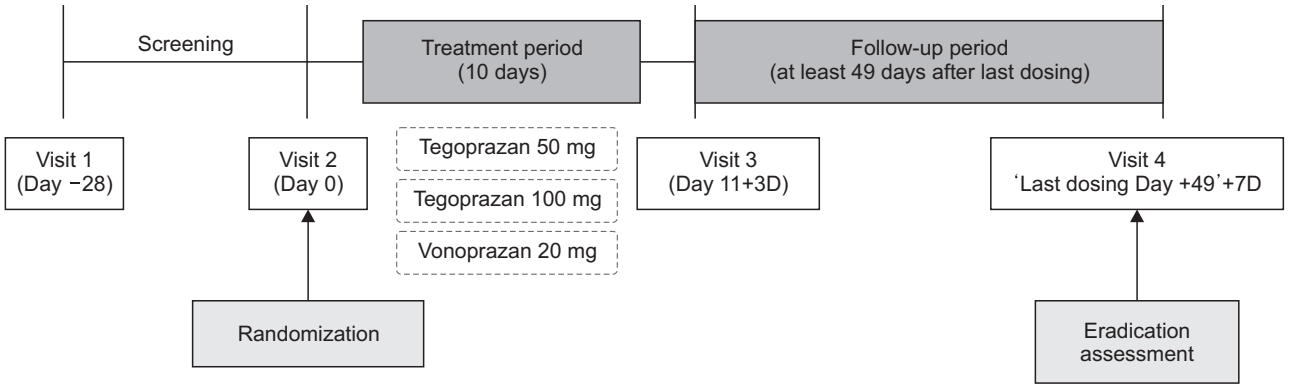

Fig. 1. Flow diagram showing the study protocol.

following treatments: triple therapy with tegoprazan 50 mg twice daily (TAC 1, test group), triple therapy with tegoprazan 100 mg twice daily (TAC 2, test group), or triple therapy with vonoprazan 20 mg twice daily (VAC, comparator group). Each therapy was administered orally with amoxicillin 1,000 mg plus clarithromycin 500 mg, taken twice daily after meals for 10 days. Randomization was performed using the Interactive Web Response System. Subjects were assigned to each treatment group according to allocation codes provided by the randomization program, and a seed was allocated to randomization codes for reproducibility. Independent personnel responsible for maintaining blinding managed the randomization codes and study drug numbers. To maintain double-blind conditions and avoid potential bias, a double-dummy method using matched placebo tablets for tegoprazan and vonoprazan was implemented. The subjects were then followed up and evaluated for *H. pylori* status between 7 and 8 weeks after the end of the treatment (Fig. 1). A detailed explanation of the rationale for dose selection and treatment duration is provided in the Supplementary Material.

4. Procedures and trial assessments

Demographic characteristics, relevant medical history, prior medication use, vital signs, physical examinations, clinical laboratory tests (hematology, blood chemistry, blood coagulation, and urinalysis), pregnancy tests, ECGs, upper gastrointestinal endoscopy results, and *H. pylori* test results were obtained at the screening visit. At the end of treatment, data on vital signs, physical examinations, clinical laboratory tests, pregnancy tests, and ECGs were collected.

The primary endpoint for the study was *H. pylori* eradication rate. *H. pylori* status was assessed by ^{13}C-UBT at Visit 4, which was performed between 7 and 8 weeks (49 to 56 days) after the last study drug dose. Eradication was defined as successful if the ^{13}C-UBT performed strictly during the aforementioned period was negative. For the full analysis set (FAS), eradication was also considered successful if a negative ^{13}C-UBT result was obtained within 28 to 56 days after the last dose. Eradication was considered a failure if the ^{13}C-UBT result at Visit 4 was positive, Visit 4 was not performed within 28 to 56 days after the last dose (in accordance with the Food and Drug Administration guidance for *H. pylori* studies), the test was unassessable, or Visit 4 was not performed. Medication compliance was assessed by reviewing the study drugs and medication diary, calculated as the actual doses administered out of the total doses to be administered within the 14-day treatment window. Taking only part of the study drugs each time was considered a skipped dose.

Adverse events (AEs) and concomitant medications were monitored throughout the study. The safety of the study drug was assessed based on AEs, clinical laboratory tests, vital signs, ECG, and physical examination. All AEs, including their severity, causality, those leading to study drug discontinuation, adverse drug events (ADRs), and serious AEs (SAEs), were summarized and presented by treatment group in the safety analysis set (SAS; all subjects who received at least one dose of the study drug and had safety information collected at least once). Prior and concomitant medications were coded using Anatomical Therapeutic Chemical code 2021, and medical history and AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v.23.1 System Organ Class and Preferred Term and the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

5. Sample size calculation

Given the exploratory nature of the study, statistical analysis was not used for sample size calculation. Instead, sample size was determined as appropriate to meet the study objective. Based on a report by Browne[17] suggesting 30 subjects per group as an appropriate sample size to meet

study objectives in exploratory studies, the present study aimed to include 30 subjects per group, with 34 subjects per group to account for a 10% dropout rate, bringing the total number of subjects to 102.

6. Statistical analysis

For continuous data, the number of subjects, mean, and standard deviation were presented, while categorical data were summarized with frequency and percentage. Point estimates and two-sided 95% confidence intervals (CIs) were presented by treatment group for the exploratory comparisons of efficacy between the test groups and the comparator group. The differences in *H. pylori* eradication rates between these respective groups were also presented in the same manner. For AEs, ADRs, and SAEs, the number of events and the number and percentage of subjects in each category were presented by treatment group.

Efficacy was primarily analyzed in the FAS, which included all randomized subjects who did not violate the inclusion/exclusion criteria and received at least one dose of the study drug. The efficacy evaluation was repeated in the per-protocol set (PPS), defined as all subjects in the FAS except those who were prematurely withdrawn from the study, did not complete all major endpoints, were not treated with the randomized study drugs, received prohibited drugs prior to the primary efficacy endpoint assessment (Visit 4), exhibited noncompliance (medication compliance <80% within a treatment window of "Day 11+3" based on the assessment conducted at Visit 3, or had other major protocol deviations/violations. A subject whose efficacy endpoint data (assessment of *H. pylori* eradication) was missing was handled as a failure in the FAS analyses. In the SAS analyses, missing data were handled as missing. All statistical analyses were performed using SAS 9.4 (SAS

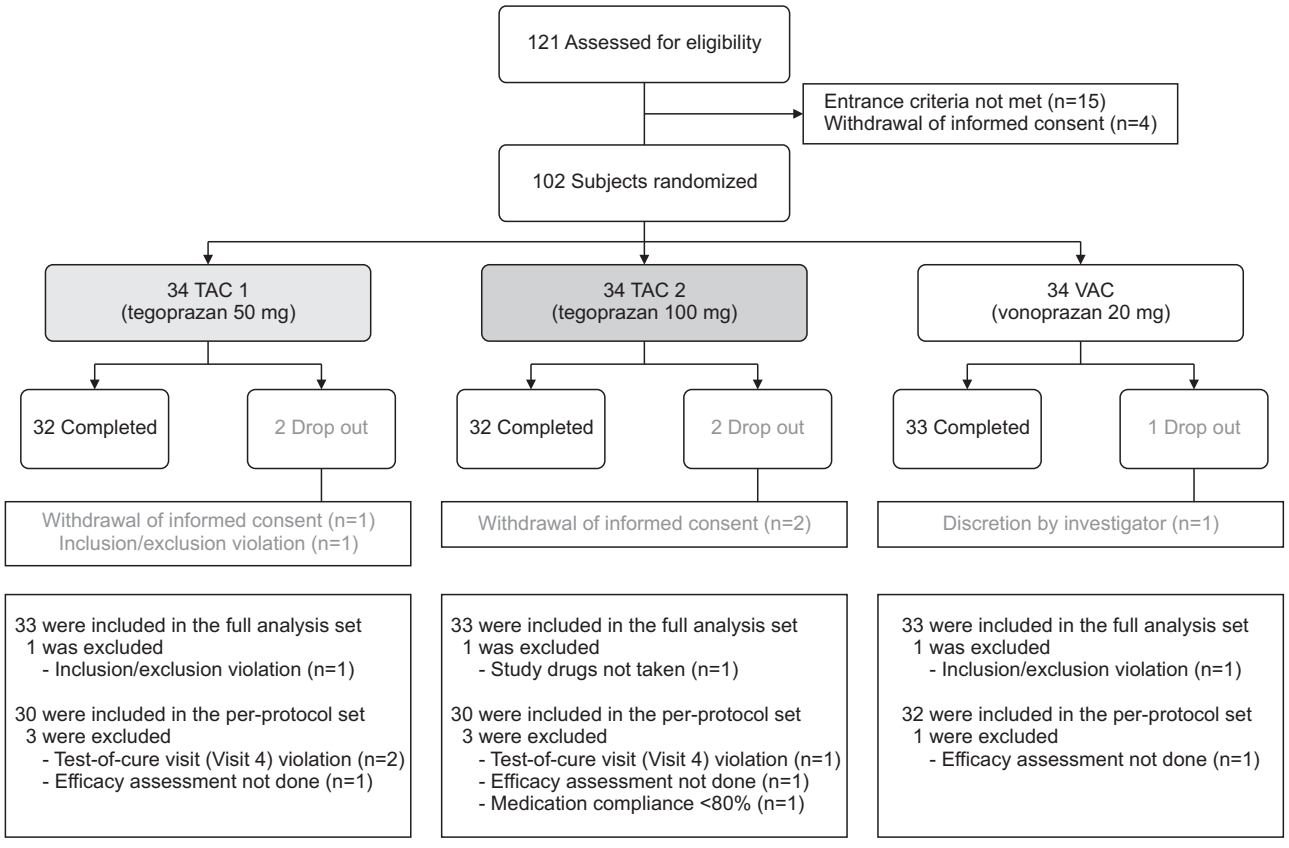

Fig. 2. Study enrollment and treatment allocation after randomization. TAC 1 refers to triple therapy with tegoprazan 50 mg twice daily, TAC 2 to triple therapy with tegoprazan 100 mg twice daily, and VAC to triple therapy with vonoprazan 20 mg twice daily. Each regimen was administered with amoxicillin 1,000 mg and clarithromycin 500 mg, both taken orally twice daily after meals for 10 days. The full analysis set included all randomized participants who did not violate the inclusion/exclusion criteria and received at least one dose of the study drug. Participants were considered noncompliant and excluded from the per-protocol set if the medication compliance rate was <80% within a treatment window of "Day 11+3" based on the assessment conducted at Visit 3. The per-protocol set was defined as all participants in the full analysis set (FAS) except those who were prematurely withdrawn from the study, did not complete all major endpoints, were not treated with the randomized study drugs, received prohibited drugs prior to the primary efficacy endpoint assessment (Visit 4), exhibited noncompliance (<80% within a treatment window of "Day 11+3" based on the assessment conducted at Visit 3), or had other major protocol deviations/violations. A participant whose efficacy endpoint data (assessment of *Helicobacter pylori* eradication) was missing was handled as an eradication failure in the FAS analyses.

Institute, Cary, NC, USA).

RESULTS

1. Patient disposition and baseline characteristics

Among 121 subjects screened, 102 eligible subjects were randomly allocated to the TAC 1 (n=34), TAC 2 (n=34), or VAC (n=34) groups (Fig. 2). A total of 97 subjects completed the study. Safety was assessed in the SAS (n=101). Two subjects with inclusion/exclusion criteria violations were excluded from the final efficacy analysis, leaving 99 subjects—33 per group—in the FAS. Reasons for exclusion from the PPS were test-of-cure visit violations (n=3), efficacy assessments not completed (n=3), and medication compliance <80% (n=1), leaving 92 subjects in the PPS (Fig. 2). The efficacy endpoint was then analyzed in both the FAS and PPS.

Baseline characteristics of patients in the FAS were comparable among the groups (Table 1). Mean age was 53.66±11.65 years old, and male subjects were 61.62% (61/99 subjects) in the FAS. The baseline characteristics of patients in the PPS are shown in Supplementary Table 1. Treatment compliance was high, with 97.07% in the FAS and 99.24% in the PPS populations.

2. Efficacy analysis

In the FAS, *H. pylori* eradication rate was 60.61% (20/33 subjects), 78.79% (26/33 subjects), and 84.85% (28/33 subjects) in the TAC 1, TAC 2, and VAC groups, respectively (Fig. 3). The difference in eradication rates between the TAC 1 group and the VAC group was –24.24% (95% CI, –44.92% to –3.56%), while the difference between the TAC 2 group and the VAC group was –6.06% (95% CI, –24.61% to 12.49%).

Similar trends were observed in the PPS, with *H. pylori* eradication rates of 66.67% (20/30 subjects), 86.67% (26/30 subjects), and 87.50% (28/32 subjects) in the TAC 1, TAC 2, and VAC groups, respectively (Fig. 3). The difference in eradication rate between the TAC 1 group and the VAC group was –20.83% (95% CI, –41.23% to –0.44%), while the difference between the TAC 2 group and the VAC group was –0.83% (95% CI, –19.97% to 17.37%).

For the primary endpoint in the FAS, approximately 3% of patients had missing data imputed, including one patient from each of the three groups with missing ^{13}C-UBT results, who were classified as "eradication failure" in the analysis.

3. Safety analysis

Among 101 subjects treated with the study drugs (SAS), 46 subjects experienced 79 AEs. The overall incidence of AEs was 38.24% (13/34 subjects, 23 events), 54.55% (18/33 subjects, 30 events), and 44.12% (15/34 subjects, 26 events) in the TAC 1, TAC 2, and VAC groups, respectively (Table 2). The incidence of AEs, ADRs, AEs leading to study drug dis-

Table 1. Demographic and Baseline Characteristics (Full Analysis Set)

Characteristic	Tegoprazan 50 mg (n=33)	Tegoprazan 100 mg (n=33)	Vonoprazan 20 mg (n=33)	Total (n=99)
Age, yr	55.70±11.38	49.73±12.30	55.55±10.54	53.66±11.65
Sex				
Male	22 (66.67)	19 (57.58)	20 (60.61)	61 (61.62)
Female	11 (33.33)	14 (42.42)	13 (39.39)	38 (38.38)
Height, cm	166.97±9.69	166.95±8.39	165.10±9.33	166.34±9.10
Weight, kg	69.64±11.69	66.81±14.01	69.03±12.60	68.49±12.73
Smoking				
Yes	5 (15.15)	8 (24.24)	4 (12.12)	17 (17.17)
No	28 (84.85)	25 (75.76)	29 (87.88)	82 (82.83)
Drinking				
Yes	14 (42.42)	11 (33.33)	13 (39.39)	38 (38.38)
No	19 (57.58)	22 (66.67)	20 (60.61)	61 (61.62)
Upper gastrointestinal disease*				
Gastric ulcer (including ulcer scars)	3 (9.09)	6 (18.18)	8 (24.24)	17 (17.17)
Duodenal ulcer (including ulcer scars)	5 (15.15)	5 (15.15)	4 (12.12)	14 (14.14)
Low-grade gastric MALT lymphoma	0	1 (3.03)	1 (3.03)	2 (2.02)
Endoscopic resection of EGC	6 (18.18)	5 (15.15)	3 (9.09)	14 (14.14)
Endoscopic resection of gastric adenoma	7 (21.21)	2 (6.06)	4 (12.12)	13 (13.13)
Chronic atrophic gastritis	28 (84.85)	26 (78.79)	27 (81.82)	81 (81.82)

Data are presented as mean±SD or number (%).
MALT, mucosa-associated lymphoid tissue; EGC, early gastric cancer.
*Duplicate counting.

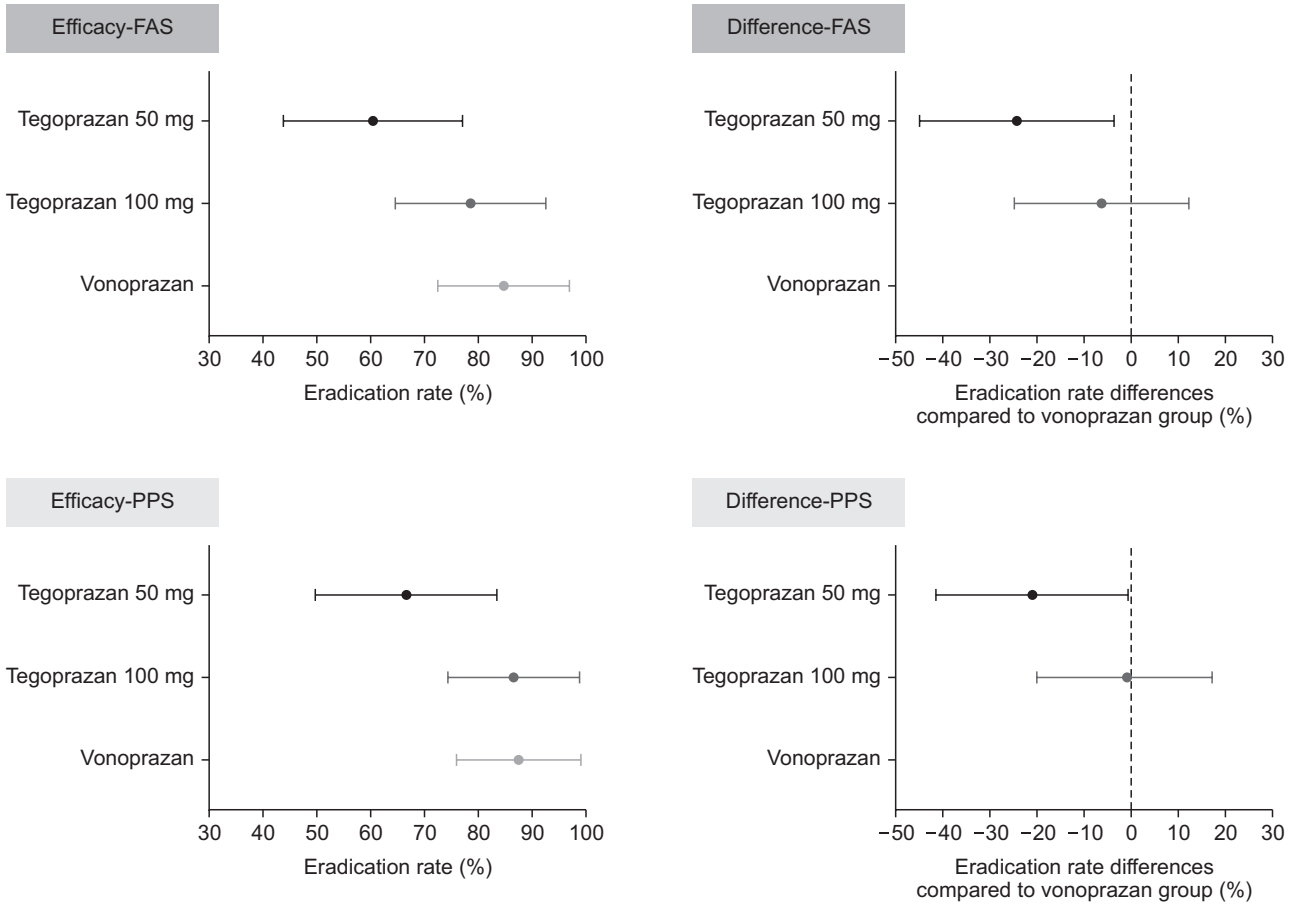

Fig. 3. Efficacy assessment. *Helicobacter pylori* eradication rates for each regimen in both the FAS and PPS are shown on the left. The differences in eradication rates between the tegoprazan groups (50 mg and 100 mg) and the vonoprazan 20 mg group are displayed on the right. Error bars denote 95% confidence intervals. FAS, full analysis set; PPS, per-protocol set.

continuation and SAEs were comparable between the treatment groups.

The most common AE was diarrhea in 17.65% (6/34 subjects) in the TAC1 group and 23.53% (8/34 subjects) in the VAC group; and taste disorder/dysgeusia in 17.65% (6/34 subjects) in the TAC1 group and 30.30% (10/33 subjects, 10 events) in the TAC2 group (Table 2). By severity, none of the AEs were classified as "severe." The incidence of SAEs was 2.94% (1/34 subjects, 1 event), occurring only in the VAC group, and was deemed unrelated to the study drugs. Neither the TAC1 group nor the TAC2 group reported any SAEs.

DISCUSSION

This randomized, double-blind, active-controlled, multicenter pilot study explored the efficacy and safety of tegoprazan-based triple therapy, using variable doses of tegoprazan, compared to vonoprazan-based triple therapy for *H. pylori* eradication. The study demonstrated that the *H. pylori* eradication rate with tegoprazan 100 mg-based triple therapy was comparable to vonoprazan-based therapy, with differences of –6.06% in the FAS and –0.83% in the PPS. However, tegoprazan 50 mg-based triple therapy showed lower eradication rates, with a difference of –24.24% in the FAS. Importantly, no concerning AEs were observed, supporting the safety of both tegoprazan and vonoprazan therapies.

STT has been the most commonly used regimen for *H. pylori* eradication in many regions worldwide, including South Korea.[3,18,19] However, the eradication rates of STT have declined due to the increasing prevalence of antibiotic resistance associated with rising antibiotic use.[6-8] In the past two decades, the widespread use of clarithromycin for respiratory infections has led to a significant increase in *H. pylori* resistance to this antibiotic, which has emerged as a major cause of eradication failure globally.[8,9,20,21] Recent studies in South Korea have reported clarithromycin resistance rates ranging from 17.8% to 31.0%.[20,22,23]

Various strategies are implemented to address resistance issues, with P-CABs gaining particular attention as

Table 2. Overall Summary of Adverse Events

Adverse events	Tegoprazan 50 mg (n=34)		Tegoprazan 100 mg (n=33)		Vonoprazan 20 mg (n=34)	
	Events	Subjects	Events	Subjects	Events	Subjects
SAEs	0	0	0	0	1*	1 (2.94)
Adverse events leading to treatment discontinuation†	1	1 (2.94)	2	2 (6.06)	0	0
ADRs	9	7 (20.59)	9	6 (18.18)	15	10 (29.41)
Adverse events	23	13 (38.24)	30	18 (54.55)	26	15 (44.12)
Most common (occurring in >1 patient)‡						
Taste disorder/dysgeusia		6 (17.65)		10 (30.30)		5 (14.71)
Diarrhea		6 (17.65)		3 (9.09)		8 (23.53)
Nausea		2 (5.88)		3 (9.09)		1 (2.94)
Headache		2 (5.88)		1 (3.03)		2 (5.88)
Dizziness		1 (2.94)		2 (6.06)		1 (2.94)
Dyspepsia		0		2 (6.06)		1 (2.94)
Aspartate aminotransferase increased		1 (2.94)		1 (3.03)		1 (2.94)
Alanine aminotransferase increased		1 (2.94)		1 (3.03)		1 (2.94)
Blood creatine phosphokinase increased		0		1 (3.03)		1 (2.94)
Severe		0		0		0

Data are presented as number (%).

SAE, serious adverse event; ADR, adverse drug reaction; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

*The adverse event (AE) was classified as an SAE due to hospitalization but deemed unrelated to the study drugs, as the participant was hospitalized for COVID-19 and later recovered following two negative PCR tests; †Concerning individual AE leading to treatment discontinuation, one AE was reported in the tegoprazan 50 mg group (diarrhea), and two AEs were reported in the tegoprazan 100 mg group (diarrhea and taste disorder/dysgeusia), while no AEs were reported in the vonoprazan 20 mg group; ‡Only AEs (reported using MedDRA (V.23.1) Preferred Terms) occurring in more than one patient in the safety analysis set are shown. All other individual AEs were reported only once each in the tegoprazan 50 mg group (abdominal pain, hemorrhoids, increased γ-glutamyltransferase, and foot fracture), the tegoprazan 100 mg group (decreased neutrophil count, paresthesia, bursitis, myalgia, and oropharyngeal pain), and the vonoprazan 20 mg group (large intestine polyp/colon adenoma, decreased blood potassium, COVID-19, and insomnia).

a replacement for PPIs. Unlike PPIs, P-CABs allow meal-independent dosing, provide prolonged and potent acid suppression, and are less affected by CYP2C19 polymorphisms.[24] Emerging data from recent studies have demonstrated that vonoprazan-based triple therapy achieves better eradication rates than PPI-based regimens, suggesting that P-CABs may effectively overcome the limitations of traditional therapies.[14,15] Tegoprazan, a P-CAB developed in South Korea, has recently been introduced in several countries and is gaining wider clinical use globally. However, data on tegoprazan-based triple therapy, particularly with the currently approved 50 mg twice-daily dosing, has been limited and less promising, with earlier studies reporting eradication rates comparable to those of PPI-based STT.[25,26] To address this gap, our study included a tegoprazan 100 mg twice-daily group, hypothesizing that 50 mg dose may have been insufficient for achieving optimal eradication rates.

In our study, the *H. pylori* eradication rate was 78.79% in the tegoprazan 100 mg group and 84.85% in the vonoprazan 20 mg group in the FAS, and 86.67% and 87.50% in the PPS, respectively, showing comparable results. However, the eradication rates in the tegoprazan 50 mg group were 60.61% in the FAS and 66.67% in the PPS, demonstrating suboptimal efficacy. Our findings align with those of the RCT conducted in the United States and Europe, which reported eradication rates of 80.8% (modified intention-to-treat) and 85.7% (PPS) for 14-day vonoprazan-based triple therapy, comparable to our 10-day results.[16] In addition, the eradication rates observed in a prior South Korean RCT of 7-day tegoprazan 50 mg-based triple therapy (62.9% in the intention-to-treat and 69.3% in the PPS) closely resemble the outcomes of our tegoprazan 50 mg group, reinforcing concerns about the inadequacy of this dosage for effective treatment.[25]

The higher eradication rate of vonoprazan compared to tegoprazan 50 mg and its comparability with tegoprazan 100 mg might be explained by pharmacodynamic and pharmacokinetic differences. Maintaining a higher median gastric pH and longer duration of elevated pH are critical for the effectiveness of antibiotics in eradicating *H. pylori*.[27] Studies have shown that tegoprazan 100 mg twice daily maintains a median pH of 7.4 and a median time percentage of 99.4% >pH 6 over 7 days, compared to 6.9% and 88.1%, respectively, for the 50 mg dose, when co-administered with amoxicillin and clarithromycin.[27] Vonoprazan 40 mg once daily achieved similarly high pH maintenance (a mean time percentage of 98.6% >pH 5) supporting its efficacy.[28]

From a pharmacokinetic perspective, existing data

provide insights into the high eradication rates observed with vonoprazan-based therapy. When administered, it shows a strong synergistic drug-drug interaction potential, particularly in increasing the exposure of clarithromycin, a potent inhibitor of CYP3A. Compared with vonoprazan monotherapy, the combination therapy increased the area under the curve from time 0 to 12 hours (AUC_{0-12}) and maximum plasma concentration (C_{max}) of clarithromycin by 1.450- and 1.635-fold, respectively.[29] Furthermore, co-administration also raised the AUC_{0-12} and C_{max} of vonoprazan itself by 1.846- and 1.868-fold. This increased exposure of both clarithromycin and vonoprazan may be attributed to the dual role of vonoprazan as a CYP3A substrate and time-dependent inhibitor.[30,31] Similarly, tegoprazan is also a substrate of CYP3A, leading to potential drug-drug interaction with clarithromycin. When administered as triple therapy, plasma concentrations of tegoprazan and its primary metabolite increased under steady-state conditions.[27] Additionally, the level of 14-OH-clarithromycin, the primary metabolite of clarithromycin, increased, while the plasma level of clarithromycin remained unchanged. A possible explanation for this observation is that tegoprazan competitively inhibits CYP3A, thereby preventing further degradation of 14-OH-clarithromycin into secondary metabolites through oxidative mechanisms. Although the reasons for the differing interactions of clarithromycin with tegoprazan and vonoprazan remain unclear, they may be attributed to their distinct CYP3A inhibition effects. The 10-day regimen with tegoprazan 50 mg may have been insufficient to maintain an adequate pH compared to vonoprazan, and potential differences in drug interactions among P-CABs might also have influenced the results.

In summary, two key implications arise: first, maintaining a high and stable gastric pH is essential for antibiotic efficacy; second, drug-drug interactions via CYP3A4 can elevate the plasma concentrations of antibiotics themselves or their active metabolites, thereby enhancing overall effectiveness. These factors may explain the increased eradication rates observed with tegoprazan and vonoprazan, particularly the correlation between higher doses of tegoprazan and improved outcomes.

From a safety perspective, all therapies were well tolerated, consistent with findings from previous studies.[14,16,25,27,32] No clinically significant differences were observed in AEs, ADRs, or AEs leading to study drug discontinuation across the groups, and no severe AEs or SAEs associated with study drug administration were reported.

To the best of our knowledge, this is the first double-blind RCT evaluating the efficacy of *H. pylori* eradication through a triple therapy regimen incorporating varying doses of tegoprazan. Finding a regimen with over 90% efficacy is challenging, and bismuth-based quadruple therapy is associated with a high incidence of side effects.[5] In this context, we present a regimen that enhances acid suppression, providing an effective solution for overcoming antibiotic resistance while ensuring high compliance and tolerability. Notably, this study is the first to suggest that a 100 mg dose of tegoprazan, administered for 10 days, would be more appropriate than the previously tested 50 mg dosage for *H. pylori* eradication.

This study has some limitations. First, the relatively small sample size, inherent to pilot studies, limits the generalizability of the findings. Cautious interpretation is required, particularly given the potential variability in *H. pylori* eradication rates due to regional differences in clarithromycin resistance and racial variations. Second, the impact of extended treatment duration was not investigated, leaving data on a 14-day regimen unavailable. When this study was designed, the recommended duration for STT in the Korean guidelines was 7 to 14 days.[33] However, given the recent trend emphasizing the extension of treatment duration for STT, supported by data on 14-day vonoprazan regimens, further research with extended duration is needed to address this issue. Furthermore, clarithromycin resistance was not assessed, which could have provided more detailed insights into efficacy outcomes. Future studies should incorporate resistance testing and evaluate extended treatment durations to identify optimal therapeutic strategies.

In conclusion, this pilot study provides valuable insights into the efficacy and safety of tegoprazan-based triple therapy for *H. pylori* eradication. While the 50 mg dose of tegoprazan may be insufficient, the 100 mg dose shows promise, yielding results comparable to vonoprazan 20 mg. These findings offer a basis for determining appropriate dosing in future clinical research and practice involving tegoprazan-based regimens. Further studies with larger sample sizes, prolonged treatment durations, and comprehensive resistance profiling are necessary to validate and expand upon these findings, as well as to refine dosage recommendations.

CONFLICTS OF INTEREST

This study was funded in full by HK inno.N Corp., Seoul, Republic of Korea. HK inno.N Corp. contributed to the study design, data management, statistical analysis, and approval of publication in co-operation with all the authors. No other potential conflicts of interest relevant to this article were reported.

J.G.K. is the president of the society that publishes Gut

and Liver. However, he was not involved in the peer review process or decision-making regarding publication. Otherwise, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.G.K. Data acquisition: I.J.C., G.H.K., S.J.H., S.K.S., S.W.J., J.G.K. Data analysis and interpretation: J.Y.P., J.G.K. Drafting of the manuscript: J.Y.P. Critical revision of the manuscript for important intellectual content: I.J.C., G.H.K., S.J.H., S.K.S., S.W.J., J.G.K. Statistical analysis: J.Y.P. Obtained funding: J.G.K. Administrative, technical, or material support; study supervision: J.G.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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