



Efficacy of S-pantoprazole 10 mg in the Symptom Control of Non-erosive Reflux Disease: A Phase III Placebo-controlled Trial

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Background/Aims

S-isomer (S) pantoprazole is more bioavailable and less dependent on cytochrome 2C19 than is racemic pantoprazole. We aim to evaluate the efficacy and safety of 10 mg S-pantoprazole for treatment of non-erosive reflux disease (NERD).

Methods

In this phase 3, double-blind, randomized placebo controlled, multicenter study, 174 NERD patients were randomized to one of both treatment groups: 10 mg S-pantoprazole, or placebo once daily for 4 weeks. Symptoms and safety were assessed. The efficacy endpoints were complete relief of symptoms, > 50% improvement of all reflux symptoms and recurrence.

Results

Eighty-eight patients were assigned to the S-pantoprazole group (25 males, mean 43.7 years old) and 86 to the placebo group (32 males, mean 43.0 years old), and 163 patients were subjected to full Analysis Set. A higher proportion of patients in the S-pantoprazole group had complete symptom relief (42.0% [34/81] vs 17.1% [14/82], $P < 0.001$) and > 50% symptom responses (66.0% vs 50.0%, $P = 0.010$ for heartburn; 64.2% vs 28.0%, $P = 0.010$ for acid regurgitation; and 51.9% vs 30.5%, $P = 0.03$ for epigastric discomfort) compared to the placebo group. The factors associated with poor responsiveness to PPI were older age, female, greater body mass index, and severe baseline symptoms.

Conclusions

Low dose of S-pantoprazole (10 mg) for 4 weeks was more efficacious than placebo in providing reflux symptom relief in patients with NERD, especially acid regurgitation. More doses or longer periods of treatment with S-pantoprazole would be needed to completely eliminate symptoms.

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Key Words

Double-blind method; Gastroesophageal reflux; Heartburn; Pantoprazole

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Introduction

All proton pump inhibitors (PPIs) are chiral compounds. Chirality can introduce selectivity and specificity in terms of interactions with receptors or enzyme-binding sites. This may lead to variations in pharmacokinetic and pharmacodynamic properties, as well as differences in safety and toxicity profiles.^{1,2} The use of a single isomer offers predictable pharmacokinetics and increased potency.^{3,4} Esomeprazole, the S-enantiomer of omeprazole, dexrabeprazole, and dexlansoprazole are good examples of racemic PPI switches, which have the clinical advantages of increasing the homogeneity of the treatment response and providing better efficacy with comparable safety compared with racemic compounds.⁵⁻⁷

Pantoprazole is a selective and long-acting PPI. S-pantoprazole, the optical S-isomer of pantoprazole, was developed for the treatment of acid-related disorders. This agent displays a similar mechanism of action to that of racemic pantoprazole and is a highly effective inhibitor of gastric acid secretion.^{8,9} S-pantoprazole is subject to less extensive first-pass metabolism than is pantoprazole, resulting in higher systemic bioavailability.¹⁰

A reduction of the therapeutic dosage by chiral purification decreases the metabolic load on the body. Animal studies have shown that S-pantoprazole is more potent (1.5-1.9 fold) and effective (3-4 fold) than racemate in inhibiting gastric lesions in several preclinical models.⁹ S-pantoprazole is associated with less pronounced inter-individual variation of intragastric pH and more effective and longer-lasting inhibition of gastric acid secretion in a human study¹¹; therefore, it may be expected to produce a more consistent clinical response. S-pantoprazole (20 mg) was more effective than racemic pantoprazole (40 mg) in improving the symptoms of heartburn, acid regurgitation, and bloating and was equally effective in healing esophagitis.¹¹ The relative risk reduction was 15-33%. Another study showed 20 mg S-pantoprazole was effective in healing reflux esophagitis compared to placebo.¹² There has been no study on the efficacy of low-dose (10 mg) S-pantoprazole for the treatment of gastroesophageal reflux disease (GERD).

We performed a multi-center, double-blind, randomized, placebo-controlled phase III trial to evaluate the effect and safety of 10 mg S-pantoprazole in NERD patients and assessed the rate of recurrence after cessation of medication.

Materials and Methods

Patients

Patients who met all of the following criteria were eligible to enter the study: men or women aged 19-75 years living in South Korea and being an outpatient who had been diagnosed with NERD. Patients had heartburn and/or acid regurgitation for at least 3 months occurring on at least 2 days per week. The absence of endoscopic erosive esophagitis was proven during the previous 7 days at the time of screening. Patients who had experienced at least 1 symptom of heartburn or acid regurgitation above moderate intensity for at least 2 days during the previous 7 days at the time of screening were included. Baseline symptoms were assessed by reflux disease questionnaire (RDQ). The RDQ assesses the degree of upper gastrointestinal symptoms over the previous 7 days using a set of 6 items (2 items per symptom) relating to symptom frequency (0-5 point) and severity (0-5 point) on a 6-point Likert scale. If a person has experienced at least 1 symptom of heartburn or acid regurgitation above moderate intensity for at least 2 days during the previous 7 days, the frequency score and intensity score on RDQ are more than 3 points both.

Patients with any one of the following conditions were ineligible to enter the study: Zollinger-Ellison syndrome; GI bleeding; esophageal stricture; ulcer stenosis; pyloric stenosis; esophageal gastric varices; Barrett's esophagus measuring > 3 cm; intractable ulcer; digestive ulcer perforation or malignancy on upper gastrointestinal endoscopy; clinically significant hepatic, renal, cardiovascular, respiratory, endocrine, or central nervous system disorder; history of malignancy or psychiatric disorder; pregnant or nursing mother; history of allergy to any of the study drugs or their related compounds; clinically significant liver disease or renal disease; using antipsychotics, antidepressants, or anxiolytics; using a PPI, histamine H₂-blocker, prokinetic agent, or antacid within 14 days before screening; or persistent daily use of non-steroidal anti-inflammatory drugs or aspirin during the study period.

Study Design

Randomization, treatment, and follow-up

This phase III multicenter study was involving 6 tertiary university hospitals in South Korea. This was a multicenter, prospective, randomized, double-blind, placebo-controlled trial to assess effect and safety of 10 mg S-pantoprazole once daily for 4 weeks

compared to placebo in patients with NERD. The protocol for this study was approved by the institutional review boards at each institute according to the Declaration of Helsinki and the International Congress on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice guidelines (Approval No. KC14MDMT0431). All patients provided written informed consent. This study was performed with the approval of the Korean Food and Drug Administration (Approval No. LTP10_KR_1301). The study was registered with ClinicalTrials.gov under the number NCT02274961 (Study title: S-pantoprazole 10 mg Phase III Clinical Study).

Ahn-Gook Pharmaceuticals Co, Ltd, Seoul, Korea, carried out centralized randomization and allocation to 10 mg S-pantoprazole or placebo group at a 1:1 ratio. All randomization information was securely stored and could be accessed by authorized personnel only. A double-dummy method, using matching 10 mg S-pantoprazole and placebo tablets, was employed to ensure that the study was double blinded with key codes kept off site by an external data manager. All medications were provided in sealed boxes and supplied by the medication supervisor to ensure blinded allocation. Study patients were instructed to take 2 tablets, 10 mg S-pantoprazole and 1 placebo once daily before eating breakfast. Patients returned for a study visit after 4 weeks of treatment and underwent reflux symptom assessment (heartburn and/or acid regurgitation). Physical examination including assessment of vital signs, laboratory evaluation of safety (including a serum pregnancy test for all females), collection and/or dispensing of the study drug, and assessment of concomitant medications and adverse events (AEs). In patients whose reflux symptoms had resolved after 4 weeks, the rate of reflux symptom recurrence was reassessed at 4 weeks after cessation of the medication. Medication compliance was monitored by counting the number of tablets remaining in the packet.

Outcome parameters used to assess efficacy

The primary efficacy endpoint was complete relief of reflux symptoms (heartburn and/or acid regurgitation). Complete relief of reflux symptoms was defined as the absence of any reflux symptoms (heartburn or acid regurgitation) within the past 7 days at the 4-week time point, as assessed by reflux disease questionnaire (RDQ) score. The RDQ is a self-administered questionnaire designed to assess the frequency and severity of upper gastrointestinal symptoms over the previous week and to facilitate the diagnosis of GERD in primary care.¹³ The RDQ assesses the presence of these symptoms over the previous 7 days using a set of 6 items (2 items per symptom) relating to symptom frequency and severity (12 items

total). RDQ are scored between 0 and 5 for each item of frequency and intensity. RDQ was validated in Korean GERD patients.¹⁴

Secondary efficacy endpoints were improvement of reflux symptoms and rate of reflux symptom recurrence at 4 weeks after cessation of the medication in patients whose symptoms were resolved at 4 weeks. For evaluation of symptom improvement, we assessed the mean RDQ scores of each reflux symptom (heartburn and acid regurgitation) and the sum of the mean RDQ scores of these 2 symptoms at baseline and at 4 weeks. Improvement of symptoms was defined as a decrease in the RDQ score from baseline. The symptom responses were compared both within a group and between groups. Each group compared Δ symptom scores between baseline and 4 weeks (intragroup analysis). The degree of symptom responses was compared between the placebo group and the s-pantoprazole group (intergroup analysis).

Safety Assessment

Safety was evaluated based on laboratory evaluations, physical examinations, and vital signs. Patients were also monitored for AEs from the day of signing the informed consent form until 30 days after the last day of study drug administration; the severity of each AE and its causal relationship to the study medication were evaluated. All AEs that occurred after the patient signed the informed consent form were recorded (treatment-emergent AEs). The investigator rated the severity of each AE and assessed its relationship to the study drug.

Sample Size Calculation

To determine the number of test subjects required to carry out this clinical trial, it was decided that: (1) superiority test; (2) level of significance, $\alpha = 0.025$; (3) the error (β) of Class II was 0.2 and the power of the test was remained at 80%; (4) the proportion of S-pantoprazole group and placebo group = 1:1; and (5) the rate of loss of reflux symptoms was assumed as 33.9% in the S-pantoprazole group and 13.7% in the placebo group, and the reference value for the loss rate was based on the Full Analysis Set (FAS) group's response rate for the medical review of NDA 21-153 (nexium).¹⁵ The required number of subjects was calculated to be 69 per group. Considering a 20% of dropout rate, 87 people per group were finally set as the target number of test subjects.

Data Analysis

The data were analyzed in 3 main forms: Safety Analysis, FAS Analysis, and Per Protocol Set (PPS) Analysis. The Safety Analysis included all subjects who were administered the study drugs at least

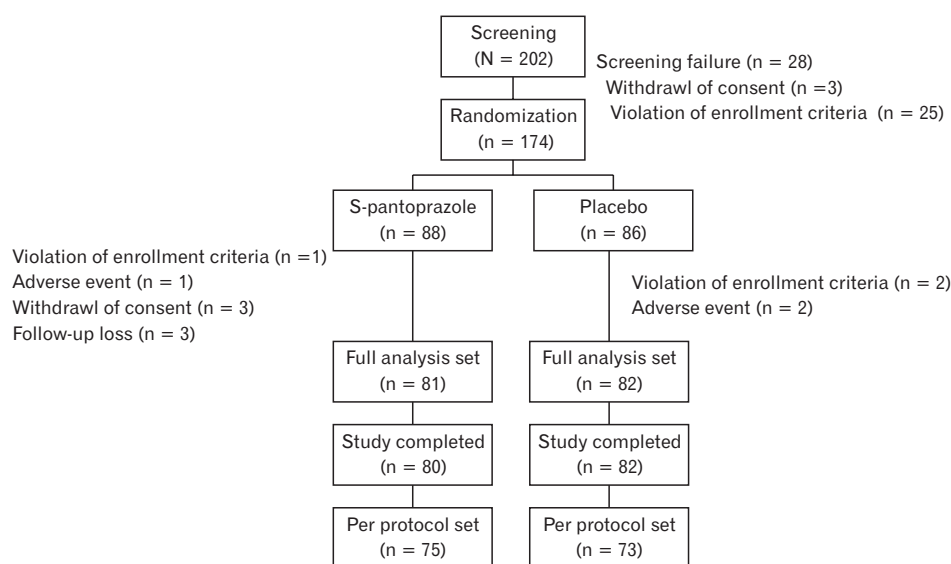


Figure. Patient disposition.

once. The FAS population included all patients who received a study drug at least once, in whom could obtain data on the primary efficacy endpoints after the study drugs were administered. The PPS population included all patients in the FAS with an evaluable primary endpoint who were randomized to a study treatment, completed their study treatment, and had no major protocol deviation. For the data on efficacy, in principle, the FAS analysis was the main analysis method, and additional PPS analysis was performed. For demographic data and data on safety, the Safety Analysis was the main analysis method.

Statistical Methods

All statistical analyses were done using StatView software for Windows (version 9.3; SAS Institute, Cary, NC, USA) in accordance with the statistical analysis plan. For continuous variables, the values are expressed as number of participants, mean, standard deviation, median, minimum, and maximum. For categorical variables, the values are presented as frequency and percentage. The results were analysed using Fisher’s exact test (two-sided) for differences in proportions and Friedman’s test (nonparametric repeated-measures ANOVA) for comparison of between-day scores (variation among column medians). A value of $P < 0.05$ was considered to indicate statistical significance.

Table 1. Baseline Demographics of S-pantoprazole and Placebo Groups (Safety Set)

Dermographics	S-pantoprazole	Placebo	P-value
Number of patients	86	85	
Gender (M:F)	25:61	32:53	0.230
Age (mean ± SD, yr)	43.7 ± 15.0	43.0 ± 13.1	0.770
BMI (mean ± SD, kg/m ²)	22.3 ± 2.8	23.3 ± 3.7	0.037
Smoker	15 (17.4%)	10 (11.8%)	0.063
Alcohol	39 (45.3%)	43 (50.6%)	0.560

M, male; F, female; BMI, body mass index.

Results

Patient Characteristics

This study was conducted at 6 tertiary university hospitals between October 2015 and November 2016. A total of 174 patients recruited were randomized to the S-pantoprazole (n = 88) or placebo (n = 86) group. Patient disposition is shown in Figure. Eight patients in the S-pantoprazole group and 4 in the placebo group discontinued the study prematurely. The reasons for premature discontinuation were protocol violation (n = 3), loss to follow-up (n = 3), AEs (n = 3), and withdrawal of consent (n = 3). A total of 162 patients including 80 patients in the S-pantoprazole group and 82 in the placebo group completed the study. FAS analysis was done in 81 patients in S-pantoprazole group and 82 in the placebo group. PPS analysis was done in 75 patients in the S-pantoprazole group and 73 patients in the placebo group. The baseline demographic

Table 2. Improvement of Symptoms After 4 Weeks of Treatment in S-pantoprazole and Placebo Groups (the Secondary Endpoint)

Symptoms	S-pantoprazole (n = 81)			Placebo (n = 82)			P-value ^a
	Baseline	4 wk	Δsymptom score	Baseline	4 wk	Δsymptom score	
Heartburn	2.82 ± 1.18	0.79 ± 1.12	-2.12 ± 1.42	2.70 ± 1.33	1.29 ± 1.42	-1.41 ± 1.59	0.005
Acid regurgitation	3.08 ± 1.17	0.86 ± 1.06	-2.22 ± 1.42	2.86 ± 1.38	1.91 ± 1.41	-0.95 ± 1.02	< 0.001
Epigastric discomfort	2.64 ± 1.39	1.07 ± 1.13	-1.58 ± 1.45	2.53 ± 1.42	1.64 ± 1.41	-0.90 ± 1.34	0.004
Overall reflux symptoms	2.95 ± 0.81	0.78 ± 0.89	-2.17 ± 1.12	2.78 ± 0.87	1.60 ± 1.21	-1.18 ± 1.05	< 0.001

Overall reflux symptom means sum of heartburn and acid regurgitation scores.

^aP-value means the statistical difference of Δsymptom score between S-pantoprazole and placebo groups per each symptom (intergroup difference).

Values are expressed as mean ± SD.

Table 3. The Factors Associated With Reflux Symptom Resolution

Factors	S-pantoprazole			Placebo		
	Complete relief	Incomplete relief	P-value	Complete relief	Incomplete relief	P-value
	n = 34	n = 47		n = 14	n = 68	
Baseline symptom score	11.38 ± 0.54	12.5 ± 0.51	< 0.001	9.93 ± 1.12	11.60 ± 0.43	< 0.001
Mean age (yr)	40.32 ± 2.60	44.81 ± 2.16	< 0.001	41.00 ± 3.64	42.87 ± 1.57	< 0.001
BMI (kg/m ²)	21.97 ± 0.46	22.64 ± 0.47	< 0.001	22.81 ± 0.73	23.28 ± 0.42	< 0.001
Female gender	24/34 (70.6%)	34/47 (72.3%)	< 0.05	8/14 (57.1%)	43/68 (63.2%)	< 0.05
smoker	5/34 (14.8%)	9/47 (19.1%)	< 0.001	4/14 (28.6%)	6/68 (8.9%)	< 0.001

BMI, body mass index.

Values are expressed as mean ± SD.

variables of the 2 groups are shown in Table 1. There were no significant differences in any of the baseline characteristics between the 2 groups, with the exception of a higher body mass index (BMI) in the placebo group.

Symptom Responses of Reflux Symptoms at 4 Weeks

After 4 weeks of treatment, reflux symptoms had resolved in a 41.98% (95% CI, 31.09-53.46; 34/81) of patients in the S-pantoprazole group compared with 17.07% (95% CI, 9.66-26.98; 14/82) of the placebo group ($P < 0.01$).

A larger percentage of the S-pantoprazole group had a > 50% higher rate of improvement in all reflux symptoms than the placebo group (66.0% vs 50.0%, $P = 0.010$ for heartburn; 64.2% vs 28.0%, $P = 0.010$ for acid regurgitation; and 51.9% vs 30.5%, $P = 0.030$ for epigastric discomfort). A higher percentage of the S-pantoprazole group showed complete resolution of symptoms than the placebo group (56.8% vs 34.1%, $P = 0.010$ for heartburn; 48.1% vs 17.1%, $P = 0.010$ for acid regurgitation; and 34.6% vs 22.5%, $P = 0.030$ for epigastric discomfort) at 4 weeks. The degree of improvement was greatest for acid regurgitation, followed by epigastric discomfort and heartburn.

Intergroup and Intragroup Analyses of Individual Symptoms

In the intragroup analysis, heartburn, acid regurgitation and epigastric discomfort significantly improved in each S-pantoprazole and placebo group after 4 weeks of treatment ($P < 0.001$). In the intergroup analysis, the degree of improvement in heartburn, acid regurgitation and epigastric discomfort after treatment was much better in the S-pantoprazole group than in the placebo group in all symptoms (Table 2).

Recurrence Rate

The rate of recurrence of reflux symptom at 4 weeks after cessation of the medication was evaluated. 9.09% (3/33) of patients in the S-pantoprazole group were found to have recurrence, lower than the 14.29% (2/14) in the placebo group, however, the difference between the 2 groups was not statistically significant ($P = 0.627$). Similar results were obtained when all 148 patients were subjected to a PPS analysis.

Factors Associated With Proton Pump Inhibitor Responsiveness

The factors associated with PPI responsiveness were evaluated. Thirty-four patients in the pantoprazole group and 14 in the placebo group whose symptoms had resolved were compared with patients whose symptoms had persisted. In both groups, as initial reflux symptoms were less severe, younger age, lower BMI, and male sex were associated with complete symptom resolution. In contrast, patients in both groups with reflux symptoms after 4 weeks tended to be older and female and to have a higher BMI and more severe baseline reflux symptoms (Table 3).

Safety

Safety was analyzed in 171 patients who received the study drug. Eleven patients (11/86, 12.8%) in the S-pantoprazole group and 11 patients (11/85, 12.9%) in the placebo group experienced AEs ($P = 0.981$). The rates of AEs were similar between the treatment groups. With the exception of 1 patient in the S-pantoprazole group who was lost to follow up, all AEs resolved completely during the study period. The majority of patients who experienced AEs had events that were mild or moderate in severity. The only serious AE experienced was 1 patient in the S-pantoprazole group who was admitted to the hospital because of a bile duct stone. The most frequently reported treatment-related AEs were gastrointestinal in both groups ($n = 9$). One AE in the S-pantoprazole group (1.2%) and 3 in the placebo group (3.5%) were considered to be related to the study drug ($P = 0.374$), and there were no serious adverse drug reactions in either group. One patient in the S-pantoprazole group and 2 in the placebo group discontinued the study drugs, primarily due to AEs.

Discussion

This study aimed to assess the efficacy and safety of 10 mg S-pantoprazole for symptom control in NERD patients in comparison with a placebo. Of the patients, 42.0% (34/81) experienced complete relief of reflux symptoms after 4 weeks of S-pantoprazole treatment, compared with 17.0% (14/82) who received the placebo. The symptom loss rate was higher than initially expected in both the S-pantoprazole and placebo groups. S-pantoprazole was superior to placebo for control of all reflux symptoms, 66.0%, 64.2%, and 51.9% of S-pantoprazole group showed a > 50% relief of heartburn, acid regurgitation, and epigastric discomfort, respectively, compared to 50.0%, 28.0%, and 30.5% for the placebo group.

S-pantoprazole, has higher systemic bioavailability and less pronounced inter-individual variation in the control of intragastric pH, it may be expected to produce a more consistent clinical response than would racemic pantoprazole.¹⁶ Several studies have evaluated 20 mg S-pantoprazole in reflux esophagitis patients.^{11,12} Half dose or low dose PPI is usually used as the maintenance treatment. We studied low dose (10 mg) S-pantoprazole for initial treatment of NERD.

In this study, complete relief of reflux symptoms was achieved in 42.0% (34/81) of patients. Several meta-analyses conducted in NERD patients have reported similar results.¹⁷⁻¹⁹ In 1 meta-analysis, the overall rate of symptom relief by PPIs in NERD patients was 51.4%.¹⁵ The PPI responsiveness depends on the definition of NERD used, whether 24-hour esophageal pH study was used or not to diagnose NERD.¹⁸ We defined NERD as symptomatic GERD with normal endoscopy findings without pH testing. A meta-analysis showed that if the NERD was defined as the same as our study, the pooled estimate of complete symptom relief after 4 weeks was 0.49 (95% CI, 0.44-0.55) and pooled estimate of partial symptom relief was 0.65 (95% CI, 0.61-0.69).¹⁷ If the response had been defined as > 50% symptom relief rate instead of complete relief, heartburn and acid regurgitation would have been considered relieved in 56.0% and 65.0% of patients, respectively. These values are similar to the 66.0% and 64.2% of > 50% symptom response rates in this study. In this study, acid regurgitation was more responsive than heartburn and epigastric discomfort.

We defined NERD as symptomatic GERD with normal endoscopy findings without pH testing. We used the validated RDQ, as it has been shown to increase the sensitivity of the GERD diagnosis.¹³ The study population may have included functional heartburn (if acid exposure is normal with no symptom reflux association on pH-impedance testing on PPI), and reflux hypersensitivity patients (if acid exposure is normal with positive symptom reflux association on pH impedance testing on PPI), which may have led to significantly underestimation of PPI efficacy. Definition of these phenotypes could be important, and functional overlap situations may have therapeutic approaches different from true refractory GERD.¹⁸ Functional heartburn is a functional disorder in which symptoms are related to psychological factors and disturbed visceral perception, not related to refluxate of gastric contents. Functional heartburn is found in approximately 50% of PPI nonresponders and in 25% of PPI responders.¹⁹⁻²¹ Therapies for functional heartburn remain largely empiric and may be tailored to the proposed pathophysiology of the condition, presumed mechanism of drug action, and underlying psychosocial issues.

The rate of recurrence at 4 weeks after reflux symptom resolution in the S-pantoprazole group was 9.2%, lower than the 14.3% of the placebo group, but the difference was not statistically significant. On demand by the patients therapy was not done. Therefore, 4 weeks of treatment may be short to prevent recurrence effectively. Standard dose PPI treatment for treatment of NERD is not yet covered by the Korea National Health Insurance which still recommends half dose PPI treatment rather than standard dose PPI for NERD patients as the initial and maintenance treatment. However, this study suggests the half dose PPI may be suboptimal to prevent recurrence effectively even though longer medication duration may act to obtain optimal acid suppression in NERD patients.

The factors associated with PPI responsiveness in NERD patients were evaluated. In both groups, patients whose reflux symptoms remained tended to be older and female and to have a higher BMI and more severe baseline reflux symptoms. More severe symptomatic patients may need a higher dose or longer duration of therapy. Obesity can influence the symptom response and recurrence rate. Old age and female sex have been reported to be associated with PPI non-responsiveness.²²⁻²⁵ In addition, psychological factors can influence the response to PPIs even though it was not evaluated by questionnaire in this study.

In conclusion, low dose of S-pantoprazole (10 mg) for 4 weeks was more efficacious than placebo in providing reflux symptom relief in patients with NERD, especially acid regurgitation. The complete symptom resolution was achieved in 42.0% of the S-pantoprazole group. Increased doses or longer periods of treatment with S-pantoprazole would be needed to completely eliminate symptoms.

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Conflicts of interest: None.

Author contributions: Myung-Gyu Choi, Hyojin Park, Ji Won Kim, Dong Ho Lee, Kwang Hyun Ko, Sang Gyun Kim, Hwoon-Yong Jung, Su Jin Hong, Yong Chan Lee, and Si Hyung Lee recruited the patients and performed this study; and Yu Kyung Cho analysed the data and wrote the manuscript.

References

1. Welage LS. Pharmacologic features of proton pump inhibitors and their potential relevance to clinical practice. *Gastroenterol Clin North Am* 2003;32(3 suppl):S25-S35.
2. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol* 2008;64:935-951.
3. Klieber M, Oberacher H, Hofstaetter S, et al. CYP2C19 phenocopy conversion by routinely prescribed proton pump inhibitors omeprazole and esomeprazole: clinical implications for personalized medicine. *J Pharmacol Exp Ther* 2015;354:426-430.
4. Ichikawa H, Sugimoto M, Sugimoto K, Andoh A, Furuta T. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. *J Gastroenterol Hepatol* 2016;31:716-726.
5. Talley NJ, Venables TL, Green JR, et al. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol* 2002;14:857-863.
6. Pai V, Pai N. Randomized, double-blind, comparative study of dexrabeprazole 10 mg versus rabeprazole 20 mg in the treatment of gastroesophageal reflux disease. *World J Gastroenterol* 2007;13:4100-4102.
7. Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2009;29:1261-1272.
8. Xie Z, Zhang Y, Xu H, Zhong D. Pharmacokinetic differences between pantoprazole enantiomers in rats. *Pharm Res* 2005;22:1678-1684.
9. Cao H, Wang MW, Sun LX, Ikejima T, Hu ZQ, Zhao WH. Pharmacodynamic comparison of pantoprazole enantiomers: inhibition of acid-related lesions and acid secretion in rats and guinea-pigs. *J Pharm Pharmacol* 2005;57:923-927.
10. Andersson T, Weidolf L. Stereoselective disposition of proton pump inhibitors. *Clin Drug Investig* 2008;28:263-279.
11. Pai VG, Pai NV, Thacker HP, Shinde JK, Mandora VP, Erram SS. Comparative clinical trial of S-pantoprazole versus racemic pantoprazole in the treatment of gastro-oesophageal reflux disease. *World J Gastroenterol* 2006;12:6017-6020.
12. Cho YK, Choi MG, Bak YT, et al. Efficacy of S-pantoprazole 20 mg compared with pantoprazole 40 mg in the treatment of reflux esophagitis: a randomized, double-blind comparative trial. *Dig Dis Sci* 2012;57:3189-3194.
13. Shaw MJ, Talley NJ, Beebe TJ, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. *Am J Gastroenterol* 2001;96:52-57.
14. EJ Gong, KW Jung, YW Min, et al. Validation of the Korean version of the gastroesophageal reflux disease questionnaire for the diagnosis of gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2019;25:91-99.
15. Center for Drug Evaluation and Research, Application number: 21-153/21-154 (NDA 21-153), Division of Gastrointestinal and Coagulation Drug Products Medical Officer's Review (Part 4, page 138 Table 44). Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21154_Nexium_medr_P4.pdf (accessed 6 March, 2021).
16. Zhou Q, Yan XF, Pan WS, Zeng S. Is the required therapeutic effect always achieved by racemic switch of proton-pump inhibitors? *World J*

- Gastroenterol 2008;14:2617-2619.
17. Zhang JX, Ji MY, Song J, et al. Proton pump inhibitor for non-erosive reflux disease: a meta-analysis. *World J Gastroenterol* 2013;19:8408-8419.
 18. Wejlenborg PW, Cremonini F, Smout AJ, Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. *Neurogastroenterol Motil* 2012;24:747-757, e350.
 19. de Bortoli N, Martinucci I, Savarino E, et al. Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they? *Neurogastroenterol Motil* 2014;26:28-35.
 20. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsistency in the diagnosis of functional heartburn: usefulness of prolonged wireless pH monitoring in patients with proton pump inhibitor refractory gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2015;21:265-272.
 21. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2015;13:884-891.
 22. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2010;10:CD002095.
 23. Labenz J, Armstrong D, Zetterstrand S, Eklund S, Leodolter A. Clinical trial: factors associated with freedom from relapse of heartburn in patients with healed reflux oesophagitis--results from the maintenance phase of the EXPO study. *Aliment Pharmacol Ther* 2009;29:1165-1171.
 24. Bytzer P, van Zanten SV, Mattsson H, Wernersson B. Partial symptom-response to proton pump inhibitors in patients with non-erosive reflux disease or reflux oesophagitis - a post hoc analysis of 5796 patients. *Aliment Pharmacol Ther* 2012;36:635-643.
 25. Becker V, Grotz S, Schlag C, et al. Positive predictors for gastroesophageal reflux disease and the therapeutic response to proton-pump inhibitors. *World J Gastroenterol* 2014;20:4017-4024.