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Original Article

Randomized Multicenter Study to Evaluate the Efficacy and Safety of Fexuprazan According to the Timing of Dosing in Patients With Erosive Esophagitis

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Background/Aims
Fexuprazan, a novel potassium-competitive acid blocker, was developed for treating acid-related disorders. Pharmacokinetic and pharmacodynamic properties of fexuprazan, unlike those of proton pump inhibitors, are independent of food effect. This study aims to evaluate differences in efficacy and safety of fexuprazan in patients with erosive esophagitis (EE) according to the timing of dosing.

Methods
In this multicenter, open-label noninferiority study, patients who had typical reflux symptoms with endoscopically confirmed EE were randomized 1:1 to receive fexuprazan 40 mg daily 30 minutes before or after meal. Treatment was completed after 2 weeks or 4 weeks when healing was endoscopically confirmed. The primary endpoint was the proportion of patients with healed EE confirmed by endoscopy up to week 4. Safety endpoints included treatment-emergent adverse events (TEAEs).

Results
In the prior-to-meal group (n = 89) and after-meal group (n = 86), 4-week EE healing rates were 98.77% and 100.00% (difference, 0.01%; 95% CI, –0.01% to 0.04%) and 2-week EE healing rates were 95.77% and 97.14% (difference, 0.01%; 95% CI, –0.05% to 0.07%), respectively. TEAEs were 9.78% and 8.70% in the prior-to-meal group and the after-meal group, respectively.

Conclusions
Non-inferiority analysis revealed that taking fexuprazan after meal was non-inferior to taking fexuprazan before meals in patients with EE. The frequency of adverse events was similar between the 2 study groups. The drug is safe and effective for healing EE regardless of the timing of dosing.
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Key Words
Esophagitis; Gastroesophageal reflux; Potassium-competitive acid blocker; Proton Pumps

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Introduction

Gastroesophageal reflux disease (GERD) is a condition in which gastric contents reflux back into the esophagus, causing symptoms or complications that can meaningfully interfere with daily life.[1,2] Although the presence of mucosal breaks or complications is not required for the diagnosis of GERD, the disease is classified into erosive esophagitis (EE) and non-erosive reflux disease based on the presence or absence of endoscopically visible mucosal damage.[1]

The goal of treatment for GERD is to improve symptoms, heal esophagitis, prevent complications, and prevent recurrence. Therefore, acid secretion inhibitors are administered for treatment, with histamine 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) being widely used. However, H_2RAs are less effective in inhibiting gastric acid secretion than PPIs. In addition, they are subject to rapid resistance.[3] Thus, PPIs are recommended as the first-line treatment for GERD.

PPIs are absorbed as prodrugs and then activated by gastric acid. Activated PPIs are very unstable in the intra-gastric environment. In addition, PPI enters the canaliculi as prodrugs before meal, which is then activated by meal-induced acid secretion into the canaliculi. Therefore, it is recommended to take them before meals due to their low effectiveness when taken after meals. It is also difficult to suppress gastric acid secretion at night.[4] In addition, PPIs are subject to genetic polymorphisms in CYP450 2C19, which is involved in their metabolism, leading to individual differences in effectiveness and a high potential for drug interactions.

Potassium-competitive acid blockers (P-CABs) with reversible inhibitory mechanisms are being developed as an alternative to address these limitations and unmet market needs. These drugs do not require activation by gastric acid, resulting in rapid onset of action. They are expected to inhibit gastric acid secretion overnight with a longer half-life than PPIs.[5,6] In addition, they are expected to be convenient to take regardless of meals. They are mainly metabolized by the CYP450 3A4 metabolic pathway, which has an advantage of fewer individual differences in effectiveness.[6]

Currently, P-CAB class drugs licensed in Korea includes tegoprazan. In addition, fexuprazan (Daewoong Pharmaceutical Co, Ltd, Seoul, Korea) has recently been approved for treating GERD.[7] In Korea, a therapeutic trial of fexuprazan for EE was completed in November 2019.[8,9] Its recommended dose is 40 mg once daily for 4 weeks,[10] with an additional 4 weeks of treatment if the effect is insufficient at that time. Recent studies have shown that the antacid effect of this drug has minimal racial differences.[10] Moreover, fexuprazan has few drug interactions with aspirin.[11]

The purpose of this study is to perform a non-inferiority analysis of the therapeutic effect of postprandial administration of fexuprazan compared to preprandial administration in GERD patients with endoscopically confirmed EE and to determine the safety of this drug.

Materials and Methods

Patients and Study Design

A randomized, open-label, multi-center (18 institutions in Korea) study was performed from March 2021 to May 2022. Eligible participants were patients aged 19 to 75 years having typical reflux symptoms (heartburn and/or acid regurgitation) within 7 days before starting study treatment who were confirmed to have EE (Los Angeles [LA] classification grades A to D) in an upper endoscopy performed up to 14 days before starting study treatment. The LA classification of EE was determined by endoscopists with more than 10 years of endoscopic experience.

Exclusion criteria were: Barrett's esophagus (> 3 cm); gastroesophageal varix, esophageal stricture; gastrointestinal bleeding; active peptic ulcers or ulcer-related stenosis; pancreatitis, eosinophilic esophagitis; esophageal motility disorder; inflammatory bowel diseases; irritable bowel syndrome; Zollinger-Ellison syndrome; history of gastric acid suppression surgery; psychiatric disorders; acquired immune deficiency syndrome; viral hepatitis; significant morbidities in the cardiovascular, respiratory, hepatic, renal, neurologic, endocrine, hematologic, and urologic systems; history of ma-

lignancies within 5 years; drug or alcohol abuse; medication history of PPIs, P-CABs, and/or other similar drugs within 2 weeks prior to the endoscopy or requires continuous administration during the clinical trial; and hypersensitivity to drugs containing active constituents of PPIs, P-CABs, and/or other similar drugs. Those who had abnormal laboratory values (more than twice the normal upper limit), including aspartate transaminase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, blood urine nitrogen, and creatinine, pregnant or lactating women, and women with child-bearing potential who did not consent to appropriate contraceptive methods used during this study were also excluded. After screening evaluations, subjects who met the selection criteria without meeting the exclusion criteria were randomly assigned. Baseline characteristics of patients included age, sex, body mass index (BMI), LA grade, and underlying diseases.

Randomization

Stratified block randomization was used to set LA Grade A/B or C/D as a stratification factor so that it could be assigned to each stratified administration group at a 1:1 ratio. A statistician who was not directly related to this clinical trial generated a randomized list based on the stratification factor (LA grade) using the PLAN (Proc Plan) procedure of SAS version 9.4 (SAS Institute, Cary, NC, USA). Subjects were assigned to each group in the order of being registered in the clinical trial according to the randomized code using an interactive web response system.

Protocol

The study protocol is schematically described in Figure 1. Participants were randomly assigned 1:1 to receive fexuprazan 40 mg 30 minutes pre- or post-meal administration (the prior-to-meal group and the after-meal group). The study medication was administered for up to 4 weeks from the date of randomization. Healing of mucosal breaks was confirmed through upper endoscopy at 2 weeks and 4 weeks after administration of the drug. Treatment was completed when healing was endoscopically confirmed. EE healing was defined as a complete absence of mucosal defects. Therefore, if clear mucosal defects (LA grade A to D) were observed on follow-up endoscopy, EE healing was considered to have not occurred. LA grade M was not included as a mucosal defect in our study. For subjects whose mucosal defect had been completely cured at 2 weeks, drug administration was ended. Subjects who were not cured in the second week took the drug for 2 more weeks and underwent follow-up endoscopy in the fourth week. The primary efficacy endpoint was the proportion of patients with endoscopically confirmed EE healing at week 4. The secondary efficacy endpoint was EE healing rate at week 2.

This study was approved by the Institutional Review Board (IRB) of Konkuk University School of Medicine which confirmed that this study was conducted following ethical guidelines of the

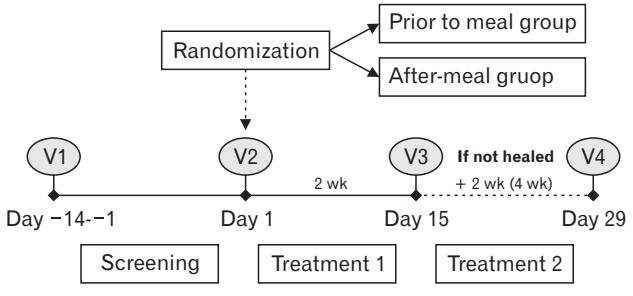

Figure 1. Study schema. V, visit; ◆, upper endoscopy.

Table 1. Baseline Characteristics of All the Randomized Subjects

Variables	Prior-to-meal group (n = 94)	After-meal group (n = 92)	*P*-value
Age (yr)[a]	53.85 ± 13.70	49.87 ± 14.98	0.066
Range	25-74	23-73	
≥ 65 yr	26 (27.7)	20 (21.7)	0.349
Male sex	58 (61.7)	59 (64.1)	0.732
BMI (kg/m^2)[a]	25.08 ± 3.20	24.38 ± 3.02	0.127
Range	17.26-33.35	18.46-32.15	
Comorbidity			
Diabetes	6 (6.4)	5 (5.4)	
Hypertension	21 (22.3)	15 (16.3)	
Dyslipidemia	3 (3.2)	2 (22.0)	
Ischemic heart disease	2 (2.1)	0 (0.0)	
Stroke	0 (0.0)	1 (1.1)	
Cancer	1 (1.1)	0 (0.0)	
COPD or asthma	0 (0.0)	1 (1.1)	
LA grade[b]			0.856
Grade A	66 (70.2)	69 (75.0)	
Grade B	24 (25.5)	20 (21.7)	
Grade C	3 (3.2)	3 (3.3)	
Grade D	1 (1.1)	0 (0.0)	

[a]Continuous variables are summarized as mean ± SD and analyzed by the 2-sample *t* test or Wilcoxon rank sum test. All other data are presented as n (%) and analyzed by the chi-square test or Fisher's exact test.
[b]Grade A: 1 (or more) mucosal break(s) no longer than 5 mm, that does not extend between the tops of 2 mucosal folds, Grade B: 1 (or more) mucosal break(s) more than 5 mm long, that does not extend between the tops of 2 mucosal folds, Grade C: 1 (or more) mucosal break(s) that is continuous between the tops of 2 or more mucosal folds, but which involve(s) less than 75% of the esophageal circumference, and Grade D: 1 (or more) mucosal break(s) which involve(s) at least 75% of the esophageal circumference.
BMI, body mass index; LA, Los Angeles classification.

Helsinki Declaration (KUMC2020-10-026). After the IRB approval, this study was registered in the ClinicalTrials.gov ID: NCT04888819. All authors had access to the study data and reviewed and approved the final manuscript.

Compliance With Medication

Compliance with medication was defined as the ratio between the total number of tablets actually taken and the total number of tablets to be taken. Participants verified compliance by returning unused portions and empty packaging at each visit. As a result, the total number of tablets to be taken, of tablets actually taken, and of returned tablets and empty packaging in each participant were calculated. When treatment compliance was less than 80% or more than 120%, the importance of administration of drugs for clinical trials was retrained.

Safety Evaluation

Participants were evaluated for safety through interviews at each visit after dosing, with additional tests and procedures if applicable. Safety results were measured by analysis of adverse events, vital signs, physical examinations, electrocardiogram findings, and clinical laboratory tests. Concomitant drugs and frequency, severity, and seriousness of adverse events were monitored throughout the study. Treatment-emergent adverse events (TEAEs) were defined as newly occurring adverse events after randomization and the first administration of study medication. Adverse drug reactions (ADRs) were considered as unexpected and unintended responses to the study drug that could not rule out causality. Serious TEAEs included death, life-threatening, hospitalization, significant disability, congenital anomaly, birth defect, and other medically important events.

Sample Size

In Phase 2 (DW_DWP14012002) and Phase 3 (DW_DWP14012301) studies of this drug, percentages of subjects with complete healing of mucosal defects by week 4 in fexuprazan 40 mg dose group were 88.24% (45/51) and 90.29% (93/103), respectively.[8] Based on results of this study, the predicted proportion of subjects with complete healing of mucosal defects by 4 weeks in pre- and post-prandial arms of this study was set at 88.00% to

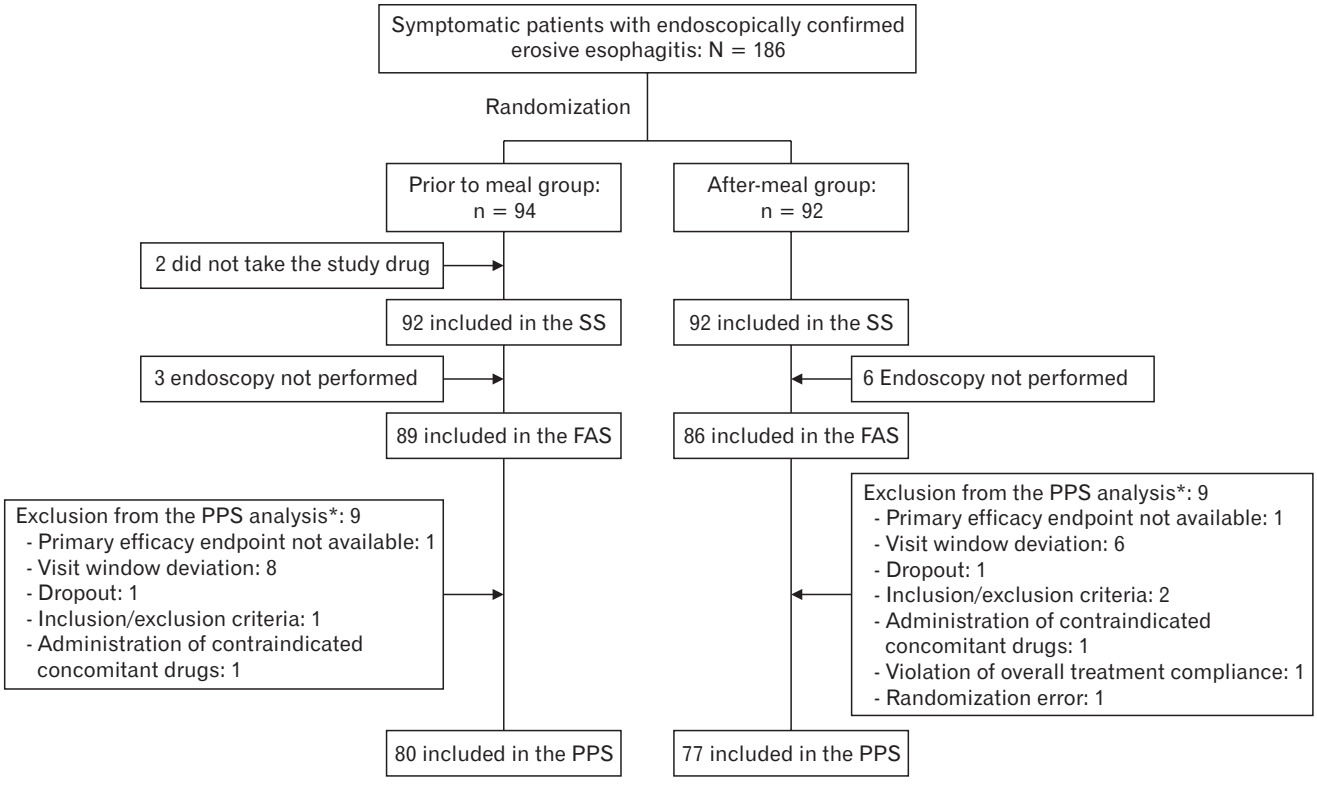

Figure 2. Flowchart showing the selection of study patients. *Reasons for exclusion may overlap. SS, safety set; FAS, full analysis set; PPS, per-protocol set.

be conservative. The noninferiority limit for this study was set at −15.00% based on the fact that previous noninferiority studies in GERD used the same value.[12,13] According to this threshold parameter, the sample size was 93 patients per treatment group using the following conditions of the PASS program: a one-sided significance level of 2.50%, a statistical power of 80.00%, an actual difference of 0, a drop-out rate of 20.00%, and a 1:1 randomization.

Statistical Methods

Efficacy was evaluated by both the full analysis set (FAS) and per-protocol set (PPS). FAS findings were interpreted as the main results. However, summaries of baseline characteristics of participants were presented in all randomized subjects. The FAS, which was based on the intention-to-treat principle, included patients who received at least 1 dose of the study drug after randomization and had at least 1 primary efficacy assessment. The PPS included patients who completed the study without any major protocol deviation. For safety assessment, statistical analysis was performed on the safety set (SS). The SS group included all subjects who received the study drug at least once after randomization.

Results are summarized as mean ± standard deviation or number (%), as appropriate. Continuous data were compared using

Table 2. Compliance With Medication and Erosive Esophagitis Healing Rate at Weeks 2 and 4 in the Full Analysis Set and Per-protocol Set

Variables	Prior-to-meal group (n = 89)	After-meal group (n = 86)	*P*-value
Full analysis set			
Compliance with medication[a] (%)[b]	98.17 ± 4.13	99.34 ± 4.33	0.033
Range (%)	81.25-107.14	78.95-110.71	
Acceptable compliance			0.491
< 80%	0 (0.00)	1 (1.26)	
≥ 80 % and ≤ 120%	89 (100.00)	85 (98.84)	
> 120%	0 (0.00)	0 (0.00)	
EE healing rate at weeks 2			
Number of patients who underwent endoscopy	71	70	
Number of completely healed patients	68 (95.77)	68 (97.14)	
Common risk difference [95% CI]	1.37% [–4.73%, 7.46%]		
EE healing rate at weeks 4			
Number of patients who underwent	81	80	
Number of completely healed patients	80 (98.77)	80 (100.00)	
Common risk difference [95% CI]	1.23% [–1.17%, 3.64%]		
Variables	**Prior-to-meal group (n = 80)**	**After-meal group (n = 77)**	***P*-value**
Per-protocol set			
Compliance with medication[a] (%)[b]	98.54 ± 3.95	99.88 ± 3.70	0.012
Range (%)	81.25-107.14	80.95-110.71	
Acceptable compliance			> 0.999
< 80%	0 (0.00)	0 (0.00)	
≥ 80 % and ≤ 120%	80 (100.00)	77 (100.00)	
> 120%	0 (0.00)	0 (0.00)	
EE healing rate at weeks 2			
Number of patients who underwent endoscopy	69	67	
Number of completely healed patients	67 (97.10)	66 (98.51)	
Common risk difference [95% CI]	1.41% [–3.50%, 6.32%]		
EE healing rate at weeks 4			
Number of patients who underwent endoscopy	80	77	
Number of completely healed patients	79 (98.75)	77 (100.00)	
Common risk difference [95% CI]	1.25% [–1.18%, 3.68%]		

[a]Compliance of medication = The total number of tablets actually taken/the total number of tablets to be taken ×100.
[b]Continuous variables were summarized as mean ± SD and analyzed by the 2-sample *t* test or Wilcoxon rank sum test. All other data were presented as n (%) or n, and analyzed by the chi-square test. The non-inferiority analysis was performed by the Cochran-Mantel-Haenszel test.
EE, erosive esophagitis.

a two-sample *t* test or Wilcoxon rank-sum test, whereas categorical data were analyzed using a chi-squared test or Fisher's exact test. Common risk difference of healing rate of EE up to weeks 2 weeks and 4 between the 2 groups and corresponding two-sided 95% CI using the Cochran-Mantel-Haenszel method adjusted by a stratification factor (baseline LA grade) were determined. Non-inferiority of 'the after-meal group' to 'the prior-to-meal group' was determined if the lower limit of its 2-sided 95% CI was larger than the non-inferiority margin of −15%. Noninferiority would be shown if the lower boundary of the 95% CI for the between-group difference was not less than 0.85. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and a *P*-value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Of a total of 186 patients (117 men [62.9%]) included in this study, 94 and 92 were assigned to the prior-to-meal group and the after-meal group, respectively. The mean age and BMI of the prior-to-meal group were 53.85 ± 13.70 (range, 25-74) years and 25.08 ± 3.20 (range, 17.26-33.35) kg/m^2 and those of the after-meal group were 49.87 ± 14.98 (range, 23-73) years and 24.38 ± 3.02 (range, 18.46-32.15) kg/m^2, respectively (Table 1). In the prior-to-meal group, the LA classification on initial endoscopy was A in 66 subjects (70.20%), B in 24 (25.50%), C in 3 (3.20%), and D in 1 (1.10%). In the after-meal group, the LA classification was A in 69 (75.00%), B in 20 (21.70%), and C in 3 (3.30%). There was no statistically significant difference in age, sex, BMI, or LA grade between the 2 groups.

A total of 175 patients were included in the FAS (n = 89 in the prior-to-meal group and 86 in the after-meal group) (Fig. 2). Eighteen patients with protocol deviation (visit window or study medication-related) or consent withdrawal were excluded from the FAS (9 in the prior-to-meal group and 9 in the after-meal group). Therefore, a total of 157 patients completed the study on the PPS (n = 80 in the prior-to-meal group and 77 in the after-meal group). The SS included 92 patients each in the 2 groups.

Erosive Esophagitis Healing Rate at 4 Weeks

In the FAS, 4-week EE healing rates were 98.77% and 100.00% in the prior-to-meal group and after-meal group, respectively. In this set, the common risk difference was 1.23% (95% CI, −1.17%, 3.64%; Table 2). In the PPS, 4-week EE healing rates were 98.75% and 100.00% in the prior-to-meal group and after-meal group, respectively. The common risk difference was 1.25% (95% CI, −1.18%, 3.68%). These indicated a non-inferiority of the after-meal group because CIs did not include the predefined inferiority margin (Fig. 3).

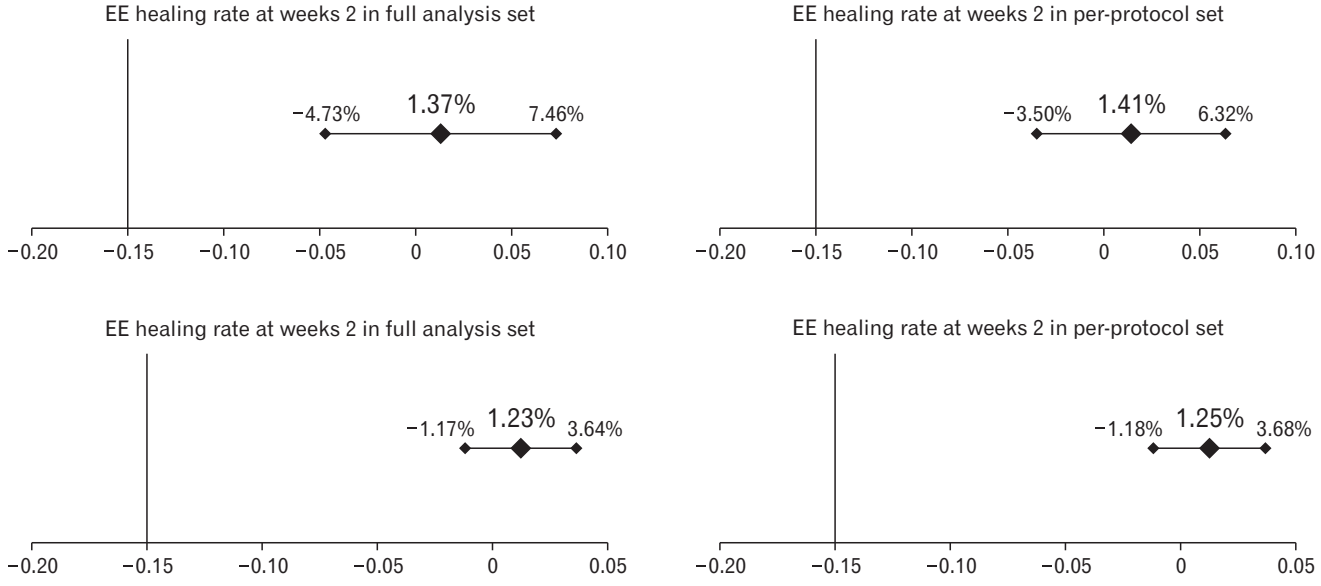

Figure 3. Non-inferiority in erosive esophagitis (EE) healing rate at weeks 2 and 4 in the full analysis set and per-protocol set. The light gray vertical line represents the non-inferiority margin (–15.00%). The dark gray horizontal line is the confidence interval (CI) of study results. The diamond shape in the middle means risk difference. In all analyses, CIs (horizontal line) did not include the non-inferiority margin (vertical line). Thus, non-inferiorities were proven.

Erosive Esophagitis Healing Rate at Weeks 2

In the FAS, 2-week EE healing rates were 95.77% and 97.14% in the prior-to-meal group and after-meal group, respectively. In this set, the common risk difference was 1.37% (95% CI, −4.73%, 7.46%). In the PPS, 2-week EE healing rates were 97.10% and 98.51% in the prior-to-meal group and after-meal group, respectively. The common risk difference was 1.41% (95% CI, −3.50%, 6.32%). These CIs did not include the noninferiority margin either (Fig. 3). In the PPS, all subjects with severe esophagitis (LA grade C/D) achieved EE healing at both 2 weeks and 4 weeks.

Adverse Events

Total duration of doses and total dosages were not significantly different between the two groups: 18.10 ± 7.38 days and 705.22 ± 273.41 mg in the prior-to-meal group vs 17.48 ± 7.60 days and 693.91 ± 297.00 mg in the after-meal group (Table 3). TEAEs occurred in 9 (9.78%) patients in the prior-to-meal group and 8 (8.70%) patients in the after-meal group. ADRs were noticed in 4 (4.35%) patients in the prior-to-meal group and 5 (5.43%) patients

Table 3. Overall Summaries of Teatment-emergent Averse Eents and Averse Drug Reactions in the Safety Set

TEAEs and ADRs	Prior-to-meal group (n = 92)	After-meal group (n = 92)	*P*-value
Degree of drug exposure			
Total duration of dose (day)[a]	18.10 ± 7.38	17.48 ± 7.60	0.3185
Total dosage (mg)[a]	705.22 ± 273.41	693.91 ± 297.00	0.9432
Subjects with TEAEs	9 (9.78)	8 (8.70)	> 0.999
Total number of events,[b] [95% CI]	11, [4.57-17.76]	8, [3.83-16.42]	
Abdominal pain/distension	1/0	0/1	
Erosive gastritis	0	2	
Constipation/diarrhea	0/1	1/0	
Dry mouth/nausea	1/1	0/0	
Creatine Phosphokinase increased	1	1	
Liver enzyme increased	0	1	
Headache	1	1	
Insomnia	2	0	
Acute myocardial infarction	1	0	
COVID-19	1	0	
Injury (ligament rupture)	0	1	
Skin rash	1	0	
Subjects with ADRs	4 (4.35)	5 (5.43)	> 0.999
Total number of events,[b] [95% CI]	6, [1.20-10.76]	5, [1.79-12.23]	
Abdominal pain/distension	1/0	0/1	
Erosive gastritis	0	2	
Diarrhea	1	0	
Nausea	1	0	
Liver enzyme increased	0	1	
Headache	1	1	
Insomnia	1	0	
Skin rash	1	0	
Subjects with serious TEAEs	1 (1.09)	1 (1.09)	1.000
Total number of events,[b] [95% CI]	1, [0.03-5.91]	1, [0.03-5.91]	
Acute myocardial infarction	1	0	
Injury (ligament rupture)	0	1	
Subjects with serious ADRs	0	0	

[a]Continuous variables were summarized as mean ± SD and analyzed by the 2-sample *t* test or Wilcoxon rank sum test. Categorical data were presented as n (%) or n, and analyzed by Fisher's exact test.
[b]In some cases, multiple adverse events were collected from a single subject.
TEAEs, treatment-emergent adverse events; ADRs, adverse drug reaction.

in the after-meal group. Two serious TEAEs were reported: a myocardial infarction in the prior-to-meal group and a ligament rupture in the after-meal group. However, serious ADRs did not occur in either group. Incidences of TEAE, ADR, and serious TEAE did not differ significantly between the 2 groups.

Discussion

Our study demonstrates that fexuprazan is effective for healing EE regardless of the timing of dosing. Four-week EE healing rates for prior-to-meal and after-meal groups were 98.77% and 100.00%, respectively. The after-meal group's healing rate was not inferior to that of the prior-to-meal group. The 2-week EE healing rate for the after-meal group was not inferior to that of the prior-to-meal group either. This non-inferiority was also confirmed for the PPS. Therefore, we can conclude from this study that fexuprazan, like other P-CABs, can be prescribed as a postprandial medication for treating GERD. This emphasizes the convenience of taking the drug in addition to its many other advantages.

PPIs should be taken within 1 hour before breakfast. Their acid suppression is significantly more effective when the medication is taken at least 15 minutes before breakfast than when it is not.[14,15] Therefore, sub-optimal PPI dose timing can limit efficacy. However, a previous study has found that 54.00% of patients are dosed PPIs sub-optimally and that only 12.00% are dosed in a manner that could maximize acid suppression.[16] As shown in our study, fexuprazan can be taken at any time of day, which may improve compliance. Fexuprazan can inhibit the secretion of gastric acid by controlling (H+/K+)-ATPase within parietal cells of the gastric mucosa in a dose-dependent, competitive, and reversible manner.[17,18] Therefore, this drug has no food effect. It is well known that P-CAB such as tegoprazan and vonoprazan is effective when taken after a meal. However, this study is the first to show that fexuprazan, a newer P-CAB, is as effective in EE when taken after meals as when taken before meals.

The EE healing rate at week 2 was much higher than we expected. In our study, the 2-week EE healing rate was 96.45% and the 4-week EE healing rate was 99.38%, regardless of when the drug was taken. This suggests that the drug is very effective in treating esophagitis. However, more research is needed to determine whether EE can be cured after 2 weeks of medication. In a previous study, mucosal healing rate at 4 weeks of PPIs was 73.20% after treatment with pantoprazole and 75.60% after treatment with esomeprazole.[13] Tegoprazan had a mucosal healing rate of 91.30% at 4 weeks in a study.[19] Although this varied between studies, vonoprazan had a mucosal healing rate of 85.29-96.59%.[6,20,21] Therefore, although there are no direct comparative studies, fexuprazan is expected to be as effective as P-CABs and PPIs.

As confirmed by previous studies, this agent is very safe.[8-10] All TEAEs were mild in intensity. They were spontaneously resolved in both previous studies and the present study. No serious ADRs were observed. Additionally, the timing of dosing was not associated with the frequency of adverse events. The frequency of adverse events was similar between the 2 study groups. However, further research is needed to determine the long-term safety of this agent.

This study had some limitations. Firstly, our study only looked at improvement in endoscopic esophagitis without looking at symptomatic improvement. Further research is needed to determine whether the timing of medication is irrelevant to the improvement of symptoms. Second, very few patients in our study had severe esophagitis (LA grade C/D). Therefore, it may be difficult to conclude definitively about the association between drug efficacy and timing of dosing in patients with severe esophagitis. However, given the distribution of EE patients in East Asia,[22] it is unlikely that the recruited patient population is heterogeneous. Third, we did not consider lifestyle factors, such as drinking alcohol, smoking, consuming caffeinated beverages, or taking medications, which are well-established factors that affect the clinical course of erosive esophagitis. Fourth, open-label trials like our study have significant limitations, especially in studies evaluating drug efficacy. However, this study was conducted at different dosing times of the same medication, so patient's bias is unlikely to have been significant.

In conclusion, this study demonstrated the non-inferiority of the therapeutic effect of postprandial administration of fexuprazan compared to preprandial administration in GERD patients with endoscopically confirmed EE. In addition, there was no difference in the frequency of adverse events based on the timing of dosing. Thus, fexuprazan can be used safely and effectively to treat EE regardless of the timing of dosing.

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