



# On-demand Versus Continuous Maintenance Treatment With a Proton Pump Inhibitor for Mild Gastroesophageal Reflux Disease: A Prospective Randomized Multicenter Study

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## Background/Aims

It remains unclear which maintenance treatment modality is most appropriate for mild gastroesophageal reflux disease (GERD). We aimed to compare on-demand treatment with continuous treatment using a proton pump inhibitor (PPI) in the maintenance treatment for patients with non-erosive GERD or mild erosive esophagitis.

## Methods

Patients whose GERD symptoms improved after 4 weeks of standard dose PPI treatment were prospectively enrolled at 25 hospitals. Subsequently, the enrolled patients were randomly assigned to either an on-demand or a continuous maintenance treatment group, and followed in an 8-week interval for up to 24 weeks.

## Results

A total of 304 patients were randomized to maintenance treatment (continuous, n = 151 vs on-demand, n = 153). The primary outcome, the overall proportion of unwillingness to continue the assigned maintenance treatment modality, failed to confirm the non-inferiority of on-demand treatment (45.9%) compared to continuous treatment (36.1%). Compared with the on-demand group, the GERD symptom and health-related quality of life scores significantly more improved and the overall satisfaction score was significantly higher in the continuous treatment group, particularly at week 8 and week 16 of maintenance treatment. Work impairment scores were not different in the 2 groups, but the prescription cost was less in the on-demand group. Serum gastrin levels significantly elevated in the continuous treatment group, but not in the on-demand group.

## Conclusions

Continuous treatment seems to be more appropriate for the initial maintenance treatment of non-erosive GERD or mild erosive esophagitis than on-demand treatment. Stepping down to on-demand treatment needs to be considered after a sufficient period of continuous treatment.

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## Key Words

Gastroesophageal reflux; Maintenance; Proton pump inhibitors

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## Introduction

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder with an increasing worldwide prevalence.<sup>1</sup> Currently, proton pump inhibitors (PPIs) are used as the initial treatment for GERD. However, GERD symptoms and mucosal lesions commonly recur after discontinuation of the initial treatment. Approximately 90% of patients with erosive esophagitis (EE) and 75% of patients with non-erosive GERD are known to experience relapse.<sup>2,3</sup> Because of the chronic nature of GERD, it may have a considerable economic burden and impact on quality of life.<sup>4</sup> PPIs are recommended for initial and long-term maintenance treatment for GERD.<sup>5-7</sup> However, many patients and clinicians still worry about the potential adverse effects of long-term PPI use. In addition, the cost-effectiveness of continuous PPI use needs to be evaluated, particularly in patients with mild GERD.

There are several modalities of maintenance treatment using PPIs for GERD. Typically, continuous maintenance treatment, defined as the administration of a PPI daily, and on-demand maintenance treatment, defined as the repeated administration of a PPI for several days whenever GERD symptoms recur, are commonly used in clinical practice. Three meta-analyses comparing the continuous and on-demand treatment modalities in the long-term maintenance treatment of GERD are reported, but it remains unclear yet which maintenance treatment modality is most appropriate for mild GERD. Therefore, we carried out a prospective randomized multicenter trial to compare on-demand treatment with continuous

treatment using a PPI in the maintenance treatment for patients with non-erosive GERD or mild EE.

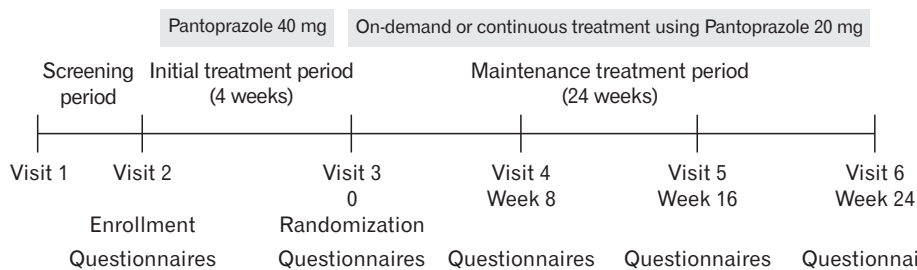
## Materials and Methods

### Study Design

This prospective randomized multicenter trial was performed at 25 referral institutions. Between September 2020 and December 2022, we enrolled patients with GERD symptoms and non-erosive GERD or mild EE (Los Angeles [LA] grade A or B). The presence and severity of reflux esophagitis was evaluated by endoscopy performed within 12 weeks before enrollment in the study. During the 4-week initial treatment, the patients orally took 40 mg of pantoprazole once daily. When the total score of the self-evaluation questionnaire for GERD symptoms (SEQ-GERD) decreased by 50% or more, or the score of each item of SEQ-GERD that was 2 or more in frequency and intensity decreased to 0 or 1 after the initial treatment, random assignment in a 1:1 ratio to either an on-demand or a continuous maintenance treatment group was performed. After randomization, the patients were followed for 8, 16, and 24 weeks (Fig. 1). The institutional review boards of each participating institution approved the study protocol, and the study was registered at [cris.nih.go.kr](http://cris.nih.go.kr) (KCT0005281). All authors had access to the study data. They reviewed and approved the final manuscript.

### Study Subjects

Written informed consent was obtained from all patients before enrollment in the study. Inclusion criteria were as follows: (1)



**Figure 1.** The study design.

age range from 19 to 75 years, (2) endoscopically confirmed non-erosive GERD or mild EE within 12 weeks, (3) the presence of typical reflux symptoms for the past 3 months before enrollment, and (4) the occurrence of heartburn or regurgitation over 2 days within 1 week. Exclusion criteria were as follows: (1) endoscopically confirmed esophageal stricture, esophageal varix, long segment Barrett's esophagus, active peptic ulcer, gastrointestinal bleeding, malignancy, or eosinophilic esophagitis; (2) a history of primary esophageal motility disorders; (3) a history of gastrointestinal resection (except for endoscopic resection); (4) hypersensitivity to antacid or PPIs; (5) malignancy within 5 years before enrollment; (6) clinically significant disorders in the cardiovascular, respiratory, endocrine, or central nervous system; (7) clinically significant disorders of liver or kidney; (8) serum creatinine, alanine aminotransferase or aspartate aminotransferase levels higher than twice the upper normal at the screening; (9) pregnant and lactating subjects; (10) a history of psychological disorders; and (11) hospitalization or surgical treatment during the study period. Concomitant medications which could affect the study's results were not permitted during the study period.

## Study Protocol

The patients were not allowed to take a PPI at least 2 weeks before study enrollment to assess the baseline symptoms. During the screening period, we investigated the demographics, medical history, concomitant medications, laboratory tests, and symptom questionnaires such as SEQ-GERD, GERD–health-related quality of life (GERD-HRQL), EuroQol-5 dimension (EQ-5D), and Work Productivity and Activity Impairment questionnaire for GERD (WPAI-GERD). The patients who had endoscopically confirmed non-erosive GERD and mild EE within 12 weeks before enrollment and met the inclusion/exclusion criteria were enrolled in the study. After enrollment, they orally took a standard dose (40 mg) of pantoprazole once daily before meals for 4 weeks. After 4 weeks of initial treatment, we evaluated the total score of SEQ-GERD. When the score of SEQ-GERD decreased by 50%

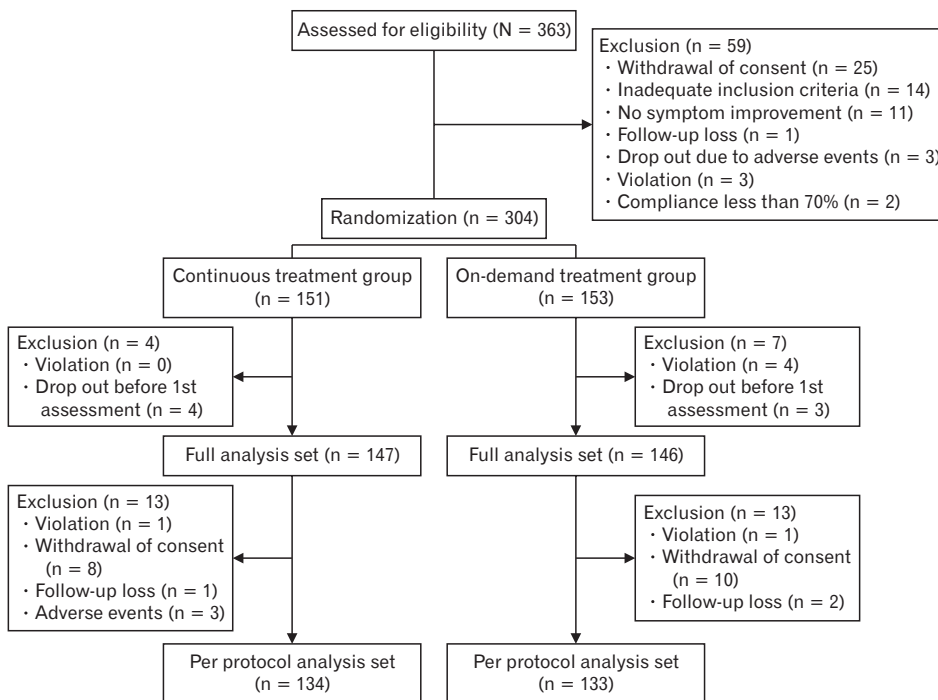
or more, or the score of each item of SEQ-GERD that were 2 or more in frequency and intensity decreased at 0 or 1, random assignment in a 1:1 ratio to either an on-demand or a continuous maintenance treatment group was performed using a central registration method. Stratified block randomization was performed for each EE (LA grade A or B) and non-erosive GERD. After randomization, patients took a half-dose (20 mg) of pantoprazole in a continuous or an on-demand manner according to the random assignment during the maintenance treatment period up to 24 weeks. In the continuous treatment group, 20 mg of pantoprazole was orally taken once daily by patients during the maintenance period. In the on-demand treatment group, the patients took 20 mg of pantoprazole once per day if the patients felt GERD symptoms and stopped taking the medication when symptoms improved sufficiently for at least 2 days. After that, pantoprazole was administered again if GERD symptoms recurred. Patients recorded the medication diary about pantoprazole intake. Physical examination and vital sign measurements were done at every visit. The frequency and severity of adverse events and concomitant medications were monitored throughout the study.

## Primary and Secondary Outcomes

The primary outcome was the proportion of unwillingness to continue the assigned maintenance treatment modality during the maintenance treatment period. Secondary outcomes included the change in the total scores of the SEQ-GERD and GERD-HRQL, and the 5-scale Likert score about overall satisfaction. Adverse events associated with PPIs and laboratory findings were also investigated.

## Sample Size Calculation

Based on previous reports,<sup>8</sup> we hypothesized that the difference in the proportion of unwillingness to continue the assigned treatment in patients with non-erosive GERD or mild EE between continuous and on-demand treatment groups was 8%. We chose a non-inferiority margin of –10% as the minimum threshold for the on-demand treatment's unacceptable loss of efficacy. The sample



**Figure 2.** The flow chart of patients enrolled in the study.

size was calculated using a significance level of 0.025 (one-tailed) and a statistical power of 0.8 ( $\alpha = 0.025$  [one-tailed];  $1 - \beta = 0.8$ ). The calculated sample size was 116 patients in each arm. Finally, in the consideration of a 20% dropout rate, a total of 290 patients who showed improvement of GERD symptoms after 4 weeks of initial PPI treatment were estimated as the sample size for the study.

### Cost-effectiveness Analysis

To assess the economic impact, we compared the costs, quality of life and work impairment associated with GERD in both maintenance treatment modalities. The Korean version of the EQ-5D was used to measure health-related quality of life. The EQ-5D is a generic instrument for measuring health-related quality of life. It consists of 5 items of 5 domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on a 3-level scale. The EQ-5D index is a composite scoring of each domain's calculation and yields a value between 0 (worst health state) and 1 (full health state).<sup>9</sup> A WPAI-GERD questionnaire was used to assess the work impairment. WPAI-GERD is a valid self-reported questionnaire that evaluates GERD symptoms' effect on work productivity.<sup>10,11</sup> Direct costs included outpatient care fees, diagnostic tests, and medication. In the clinical study setting, all patients received the same number of visits and diagnostic tests. Therefore, we compared the costs for the medication taken in each group.

### Statistical Methods

Continuous variables are presented as means  $\pm$  standard deviations, and discrete variables are presented as frequencies (%). Student's *t* test and Wilcoxon's rank sum test were used for continuous variables. Pearson chi-square test and Fisher's exact test were used for categorical variables. The primary and secondary outcomes were calculated in the full analysis set (FAS) population. Besides the FAS analysis ( $n = 293$ ), the per protocol set analysis ( $n = 267$ ) was also performed as a supplement. Statistical analyses were performed using SPSS statistics software for Windows (version 25.0; IBM Corp, Armonk, NY, USA) and R-studio software version 4.1.2 (<http://www.R-project.org>). A *P*-value less than 0.05 was required for statistical significance.

## Results

### Study Subjects

Of the 363 enrolled patients, 304 who responded to the 4-week initial treatment were randomized to either the continuous treatment group or the on-demand treatment group (continuous;  $n = 151$  vs on-demand;  $n = 153$ ). A total of 267 patients completed the study (Fig. 2). There was no difference in the demographic characteristics between the continuous and on-demand groups (Table 1).

The mean intake rates of a PPI during the maintenance treatment period were 95.2% and 49.6% in the continuous and on-demand groups, respectively ( $P < 0.001$ ). Thirty-seven patients (11.2%) did not complete the study (17 and 20 from the continuous and on-demand groups, respectively). Figure 2 shows the details of the flow chart of patients enrolled in the study.

**Table 1.** Baseline Characteristics of the Study Subjects

Variables	On-demand group (n = 146)	Continuous group (n = 147)	P-value <sup>a</sup>
Age (yr)	52.4 ± 13.0	51.2 ± 14.1	0.447
Sex			0.219
Male	76 (52.1)	87 (59.2)	
Female	70 (47.9)	60 (40.8)	
Smoking	21 (14.4)	31 (21.1)	0.307
BMI (kg/m <sup>2</sup> )	24.9 ± 5.0	24.3 ± 3.6	0.220
Duration of GERD symptoms			
Heartburn (mo)	30.7 ± 41.3	27.1 ± 37.9	0.443
Regurgitation (mo)	24.2 ± 34.2	23.4 ± 30.1	0.862
Endoscopic findings			0.961
Non-erosive	86 (58.9)	87 (59.2)	
Erosive (LA-A/B)	60 (41.1)	60 (40.8)	

<sup>a</sup>P-value was calculated by independent t test for continuous variables and Pearson chi-square test for categorical variables.

BMI, body mass index; GERD, gastroesophageal reflux disease; LA, Los Angeles classification.

Data are presented as mean ± SD or n (%).

## The Primary Outcome

Table 2 describes the proportion of unwillingness to continue the assigned maintenance treatment modality in the FAS population. The proportion of unwillingness to continue the assigned treatment modality failed to confirm the non-inferiority of on-demand treatment (45.9%) compared to continuous treatment (36.1%). On-demand treatment did not show non-inferiority compared to continuous treatment in patients with non-erosive GERD as well as in those with mild EE. The reasons for the unwillingness to continue the assigned maintenance treatment modality in the on-demand and continuous treatment groups included poorly controlled symptoms (35.8% vs 17.0%,  $P = 0.009$ ), no more symptoms (32.8% vs 37.7%,  $P = 0.849$ ), concern about adverse events (1.5% vs 7.6%,  $P = 0.371$ ), and dislike for intake of medicine (3.0% vs 7.6%,  $P = 0.686$ ).

## Secondary Outcomes

Table 3 describes the change in the score of SEQ-GERD and GERD-HRQL in the FAS population. The score of SEQ-GERD and GERD-HRQL significantly improved compared to the baseline in both on-demand and continuous treatment groups. However, compared with the on-demand group, the SEQ-GERD and GERD-HRQL scores significantly more improved in the continuous treatment group, particularly at week 8 and 16 of maintenance treatment. The 5-scale Likert score about overall satisfac-

**Table 2.** The Proportion of Unwillingness to Continue the Assigned Maintenance Treatment Modality in the Full Analysis Set Population

Patients	On-demand group	Continuous group	Non-inferiority tests	
			P-value	95% CI
Total patients (N = 293)	n = 146	n = 147		
Week 8	34 (23.8)	16 (11.2)	> 0.999	0.039-0.214
Week 16	14 (12.4)	11 (8.6)	0.136	-0.040-0.121
Week 24	24 (24.0)	24 (21.1)	0.222	-0.082-0.143
Total period	67 (45.9)	53 (36.1)	0.977	-0.014-0.209
Non-erosive GERD (n = 173)	n = 86	n = 87		
Week 8	19 (22.4)	14 (16.5)	0.497	-0.061-0.179
Week 16	11 (16.4)	7 (9.7)	0.569	-0.047-0.187
Week 24	18 (32.7)	18 (28.1)	0.524	-0.118-0.212
Total period	46 (53.5)	40 (46.0)	0.742	-0.073-0.220
Erosive GERD (n = 120)	n = 60	n = 60		
Week 8	15 (25.9)	2 (3.5)	> 0.999	0.106-0.355
Week 16	13 (6.5)	4 (7.1)	0.136	-0.115-0.113
Week 24	6 (13.3)	6 (12.0)	0.222	-0.126-0.159
Total period	21 (35.0)	13 (21.7)	0.977	-0.028-0.290

GERD, gastroesophageal reflux disease.

Data are presented as n (%).

tion was significantly higher in the continuous group at week 8 and 16 of maintenance treatment, compared with the on-demand group. However, that score was not significantly different at week 24 of maintenance treatment (Table 4).

Safety analysis was performed for 327 patients who received at least 1 dose of the study drug. Treatment-emergent adverse events (TEAEs) were defined as an AE after the participant received the study drug. The incidence of drug-related TEAEs did not differ between the on-demand (0.7% [1/153]) and continuous (2.0% [3/151]) treatment groups ( $P = 0.369$ ). At the last visit of maintenance treatment, significantly elevated serum gastrin levels were observed in the continuous treatment group, compared with the baseline levels ( $51.8 \pm 52.2$  pg/mL vs  $79.3 \pm 69.4$  pg/mL,  $P < 0.001$ ). Serum gastrin levels were not significantly altered in the on-demand treatment group ( $65.5 \pm 88.8$  pg/mL vs  $69.6 \pm 66.9$  pg/mL,  $P = 0.855$ ).

**Table 3.** The Change in the Score of the Self-evaluation Questionnaire for Gastroesophageal Reflux Disease Symptoms and Gastroesophageal Reflux Disease–Health-related Quality of Life From the Baseline During the Maintenance Treatment in the Full Analysis Set Population

Questionnaire	On-demand group (n = 146)	Continuous group (n = 147)	P-value <sup>a</sup>
SEQ-GERD			
Week 8	$-7.18 \pm 6.36$	$-8.97 \pm 6.91$	0.024
Week 16	$-6.94 \pm 6.48$	$-9.44 \pm 6.43$	0.003
Week 24	$-8.37 \pm 6.99$	$-9.66 \pm 6.69$	0.170
GERD-HRQL			
Week 8	$-6.46 \pm 6.54$	$-8.69 \pm 7.18$	0.007
Week 16	$-6.03 \pm 6.64$	$-9.73 \pm 7.56$	< 0.001
Week 24	$-7.16 \pm 6.50$	$-9.46 \pm 7.46$	0.018

<sup>a</sup>P-value between the on-demand and continuous treatment groups (Student's *t* test).

SEQ-GERD, the self-evaluation questionnaire for GERD symptoms; GERD-HRQL, GERD–health-related quality of life.

Data are presented as mean  $\pm$  SD.

**Table 4.** The 5-scale Likert Score About Overall Satisfaction During Maintenance Treatment in the Full Analysis Set Population

Visit time	On-demand group (n = 146)		Continuous group (n = 147)		P-value <sup>b</sup>
	Mean $\pm$ SD	P-value <sup>a</sup>	Mean $\pm$ SD	P-value <sup>a</sup>	
Week 8	$3.63 \pm 0.94$		$3.92 \pm 0.88$		0.009
Week 16	$3.90 \pm 0.84$	0.019	$4.13 \pm 0.83$	0.074	0.034
Week 24	$4.15 \pm 0.85$	< 0.001	$4.15 \pm 0.81$	0.092	0.994

<sup>a</sup>P-value compared with week 8 (Paired *t* test).

<sup>b</sup>P-value between the on-demand and continuous treatment groups (Student's *t* test).

## Cost-effectiveness

Health-related quality of life using EQ-5D score was not different in the continuous and on-demand treatment groups at the baseline (0.960 vs 0.948,  $P = 0.202$ ) and at the last visit (0.926 vs 0.927,  $P = 0.899$ ). Overall work impairment due to GERD presented as WPAI score was improved after maintenance therapy in both groups, compared with the baseline. There was no significant difference in WPAI score between the continuous and on-demand treatment groups at the baseline (0.279 vs 0.271,  $P = 0.790$ ) and the last visit (0.054 vs 0.080,  $P = 0.202$ ). During maintenance treatment, patients in the on-demand group took PPIs on average 3.2 days a week, which was significantly less than in the continuous group (6.7 days a week). When the prescription costs were calculated according to the actual drug intake day, 36 950 South Korean won was less in

**Table 5.** Cost-effective Analysis During Maintenance Treatment in the Full Analysis Set Population

Parameters	On-demand group (n = 146)	Continuous group (n = 147)	P-value <sup>a</sup>
EQ-5D (mean)			
Week 8	0.955	0.961	0.202
Week 16	0.958	0.962	0.476
Week 24	0.927	0.926	0.442
WPAI (mean)			
Week 8	0.101	0.074	0.132
Week 16	0.097	0.067	0.153
Week 24	0.080	0.054	0.202
Mean pill usage per week			
Week 8	3.5	6.6	< 0.001
Week 16	3.2	6.7	< 0.001
Week 24	3.0	6.7	< 0.001
Total cost (South Korean won)	146 966	183 916	-

<sup>a</sup>P-value between the on-demand and continuous treatment groups (Student's *t* test).

EQ-5D, EuroQol-5 dimension; WPAI, work productivity and activity impairment.

the on-demand group during the study period (Table 5).

## Discussion

GERD is a chronic disease and mostly needs maintenance treatment using PPIs. We compared the proportion of unwillingness to continue the assigned maintenance treatment modality between the continuous and on-demand treatment groups. Unlike our expectation, in the present study, we failed to confirm the non-inferiority of on-demand treatment compared to continuous maintenance treatment. On-demand treatment did not show non-inferiority compared to continuous treatment in patients with non-erosive GERD as well as in those with mild EE. In the analysis of the reasons for the unwillingness to continue the assigned maintenance treatment modality, the proportion of poorly controlled symptoms was significantly higher in the on-demand group than in the continuous treatment group. Compared with the on-demand group, GERD symptom and health related quality of life scores were significantly more improved, and the overall satisfaction score was significantly higher in the continuous group, particularly at week 8 and 16 of maintenance treatment. Therefore, continuous treatment seems to be more appropriate for the initial maintenance treatment of mild GERD than on-demand treatment. However, when considering that there were no significant differences in the change of GERD symptom scores and the overall satisfaction score between 2 modalities at week 24 of maintenance treatment, and serum gastrin levels significantly elevated only in the continuous treatment group at the last visit of maintenance treatment, stepping down to on-demand treatment needs to be considered after a sufficient period of continuous treatment, particularly in the long-term maintenance treatment for mild GERD.

Continuous maintenance treatment using a PPI is recommended for patients with severe EE (LA grade C or D) and GERD complications such as peptic stricture or Barrett's esophagus.<sup>12</sup> In general, GERD guidelines or consensus recommend 4 to 8-week initial PPI treatment for non-erosive GERD and mild EE, whereas 8-week initial treatment is recommended for severe EE. In maintenance treatment using a PPI for patients with non-erosive GERD or mild EE, the use of the lowest effective dose is generally recommended.<sup>7</sup> Thus, on-demand therapy has been suggested as a long-term maintenance treatment modality, particularly in patients with mild GERD.<sup>5,7,13,14</sup> Three meta-analyses comparing on-demand and continuous maintenance treatment modalities have been reported until now.<sup>8,15,16</sup> The most recent meta-analysis including 11 studies (9 from the West and 2 from Asia) revealed

that the treatment failure rate did not significantly differ between the on-demand and continuous treatment groups (9.1% vs 7.3%) with relative risk (RR) 1.26 (95% CI, 0.76-2.07;  $P = 0.372$ ).<sup>8</sup> However, outcomes used for the assessment of treatment failure were different in included studies. Moreover, the dosage and type of PPIs used for maintenance treatment were different in included studies as well. As a result, very high heterogeneity ( $I^2$ ) (84%) was observed.<sup>8</sup> Unlike the results of the recent meta-analysis, we failed to show the non-inferiority of on-demand treatment compared to continuous treatment. In the analysis of the reasons for the unwillingness to continue the assigned maintenance treatment modality, significantly higher proportion of poorly controlled symptoms was observed in the on-demand group than in the continuous treatment group. The findings of the secondary outcomes including the change in the scores of SEQ-GERD and GERD-HRQL, and the 5-scale Likert score about overall satisfaction showed a better effect of continuous maintenance treatment compared to on-demand treatment, particularly in the initial maintenance treatment period (week 8 and week 16). Therefore, continuous treatment seems to be more appropriate as the initial maintenance treatment modality for patients with non-erosive GERD or mild EE rather than on-demand treatment.

Economic burden and impact on quality of life should be considered when choosing maintenance treatment modalities. The lower pill usage in the on-demand group has important economic implications associated with cost-benefit in the maintenance treatment.<sup>17,18</sup> In GERD patients, persistent symptoms or symptom recurrence are associated with worsened health-related quality of life.<sup>19,20</sup> In the present study, the choice between on-demand and continuous maintenance treatment modalities did not make a difference in quality of life after treatment. A meta-analysis reported work productivity loss in GERD ranged from 6-42%.<sup>21</sup> In our study, overall work impairment scores improved after maintenance treatment for GERD, and there was no difference according to the method of maintenance treatment. In the on-demand group, drug cost was reduced because there were fewer days of actual drug use than in the continuous group. In this clinical trial setting, both groups were expected to visit the same number of visits. However, in real-world situation, fewer visits to medical institutions are required in the on-demand group if the same number of medications was prescribed. Therefore, the difference in treatment cost between the 2 groups could be a slightly greater than that observed in the present study. If medical staffs actively educate patients that it is unnecessary to take medication every day if there are no symptoms, cost savings are expected by reducing drug intake more effectively

in the on-demand treatment group.

Many studies have reported the potential association of PPIs with several adverse effects.<sup>22,23</sup> Large observational studies have shown that long-term PPI treatment is associated with various adverse events, including *Clostridium difficile* or other bacterial gastroenteritis, bacterial overgrowth in the small intestine, pneumonia, chronic kidney disease, bone fracture, dementia, and myocardial infarction.<sup>24,25</sup> However, the causality relationship is uncertain yet because of confounding factors. Nevertheless, it is recommended that PPIs are administered at the lowest effective dose that controls the patient's symptoms and esophagitis, and the appropriateness of treatment should be periodically reevaluated.<sup>26</sup> In the present study, serum gastrin levels in the continuous treatment group significantly elevated at the last visit of maintenance treatment, whereas those levels were not significantly altered in the on-demand treatment group. Although the clinical significance of modest elevation in serum gastrin levels remains uncertain yet, there are concerns about the relationship of hypergastrinemia with the development of polyps or neoplasia in the stomach.<sup>27-29</sup> Thus, it seems to be desirable to avoid prolonged hypergastrinemia. When considering the cost-effectiveness and the effect on serum gastrin levels, stepping down to on-demand treatment needs to be considered eventually, particularly in patients with non-erosive GERD and mild EE. Moreover, at week 24 of maintenance treatment, there was no significant difference in the overall satisfaction score between the 2 modalities, which suggests that on-demand treatment can be considered after a sufficient period of continuous maintenance treatment. The secondary outcomes, including the scores of SEQ-GERD and GERD-HRQL, and the 5-scale Likert score about overall satisfaction, are more objective parameters than the primary outcome, and showed significant improvement at week 24 in the on-demand group, which may explain no significant difference in the secondary outcome scores between the 2 modalities at week 24. Those findings indicate that slow or step-by-step transition to on-demand therapy is desirable even in the maintenance treatment for patients with non-erosive GERD or mild EE.

Although there are 2 reported Asian studies comparing the on-demand and continuous maintenance treatment modalities for GERD,<sup>30,31</sup> the number of enrolled patients is small. One of the strengths of the current study is that it is a prospective randomized study with a large number of subjects conducted in Asia. The majority of Asian patients with GERD have non-erosive GERD or mild EE, which are the targets of the present study. Because we enrolled patients who responded to initial PPI treatment, it is unlikely that patients with reflux hypersensitivity, functional heartburn,

or refractory GERD participated in the study. However, our study has several limitations. First, we enrolled patients only in the referral hospitals in South Korea. Therefore, the influence of the national health care service system could not be excluded entirely. Under the Korean national health care system, patients generally like to take more drugs during a longer period of time, because the expense for the medication and visits is relatively cheap, and making visit schedules at referral hospitals are usually difficult because of too many patients. Therefore, in South Korea, patients are likely to prefer continuous drug treatment and regular visits. Therefore, in South Korea, patients are likely to prefer continuous drug treatment and regular visits. Secondly, we did not evaluate the mucosal healing of the esophagus during the maintenance treatment period. Third, the maximal period of maintenance treatment was up to 24 weeks.

In conclusion, continuous treatment seems to be more appropriate as the initial maintenance treatment modality for patients with non-erosive GERD or mild EE rather than on-demand treatment. However, when considering the cost-effectiveness and the effect on serum gastrin levels, stepping down to on-demand treatment needs to be considered after a sufficient period of continuous maintenance treatment.

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