

On-demand versus half-dose continuous therapy with esomeprazole for maintenance treatment of gastroesophageal reflux disease

A randomized comparative study

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Abstract

Background and aims: No consensus has been established regarding optimal long-term maintenance therapy in symptomatic gastroesophageal reflux disease (GERD). The aim of this study was to compare the efficacies of on-demand and continuous therapy with esomeprazole as maintenance treatments for GERD.

Methods: Patients with upper gastrointestinal (GI) endoscopy-proven GERD who received initial proton pump inhibitor (PPI) therapy for 8 weeks were randomized to an on-demand group (esomeprazole 40 mg) or a continuous group (esomeprazole 20 mg). Intensities and frequencies of heartburn and acid regurgitation were assessed using a 6-point Likert scale (0 = no symptoms; 5 = very severe symptoms) and a 6-point frequency scale (0 = none; 5 = symptoms for > 5 days per week) at baseline (start of maintenance treatment) and after 12 weeks of treatment. Alleviation of symptoms was quantified using percentages of patients with a Likert scale or frequency scale of 0 or 1.

Results: Of the 88 patients enrolled, 8 patients were excluded due to follow-up loss in early period of this study, and finally, 39 in the on-demand group and 41 in the continuous group were analyzed. No significant intergroup difference was found between Likert scale or frequency scale of heartburn or regurgitation at baseline. Percentages of symptom alleviations in the on-demand and continuous groups for intensity of heartburn were 56.4%/48.8% at baseline ($P = .523$) and 82.1%/87.8% at 12 weeks ($P = .471$), for frequency of heartburn were 61.5%/46.3% at baseline ($P = .173$) and 76.9%/87.8% at 12 weeks ($P = .200$), for intensity of regurgitation was 53.8%/43.9% at baseline ($P = .374$) and 82.1%/87.8% at 12 weeks ($P = .471$), and for frequency of regurgitation was 61.5%/56.1% at the baseline ($P = .621$) and 82.1%/82.9% at 12 weeks ($P = .918$), respectively. Furthermore, no significant intergroup difference was found for convenience of medication or subjective satisfaction.

Conclusions: Intensities and frequencies of heartburn and regurgitation responded well to maintenance treatment in patients in the on-demand and continuous groups. On-demand therapy with esomeprazole 40 mg appears to be sufficient for maintenance treatment in GERD patients.

Abbreviations: GERD = gastroesophageal reflux disease, GI = gastrointestinal, PPI = proton pump inhibitor.

Keywords: continuous therapy, gastroesophageal reflux disease, maintenance, on-demand, proton pump inhibitor

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when reflux of stomach contents causes troublesome symptoms such as heartburn and regurgitation associated with

mucosal injury and/or complications.^[1] In Asia, it is known the prevalence of GERD is lower than in the West, and that serious complications, such as severe erosive esophagitis, esophageal stricture and Barrett's esophagus, are rare. However, its prevalence has increased over the last few decades in Asia and in Korea.^[2]

Most patients with GERD experience symptomatic relapse after discontinuing acid-suppressive medication.^[3] According to 1 report, symptomatic relapse was estimated to occur in ~80% of esophagitis patients after 6 to 12 months,^[4] and thus, most patients need long-term antisecretory therapy. Accordingly, GERD is a chronic condition, which means that maintenance and initial therapy are important components of its management.

Maintenance treatment of GERD is usually performed using 1 of 2 strategies, that is, by administering proton pump inhibitors (PPI) continuously or based on patient demand. Somewhat surprisingly, although a number of studies have described the clinical importance of maintenance therapy,^[5-7] no consensus has been established regarding optimal long-term maintenance therapy in symptomatic GERD. The on-demand use of PPIs has been compared with continuous use in several randomized clinical trials on non-erosive reflux disease (NERD) or GERD conducted in the West,^[8-13] and 2 studies have investigated on-demand maintenance therapy for GERD in Japan.^[14,15]

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However, no Korean study has compared the efficacies of on-demand and continuous maintenance treatments for GERD, and therapeutic responses may well vary between countries due to ethnic and environmental differences. In this prospective randomized study, we compared the efficacies of on-demand and continuous therapy for the maintenance treatments of GERD in Korea.

2. Methods

2.1. Study design

This prospective, open-label, randomized parallel-group study was conducted at a single university hospital between March 2015 and April 2017, and performed in accordance with the Helsinki Declaration and complied with Good Clinical Practice for medical research involving human subjects. The study protocol and the informed consent form used were approved beforehand by the institutional review board of Yeungnam university hospital.

2.2. Patients

Patients with upper gastrointestinal (GI) endoscopy proven GERD who completed initial PPI therapy for 8 weeks were considered for study entry. The diagnosis of GERD was established by upper GI endoscopy and classified according to the modified Los Angeles (LA) classification grades (M, A, B, C, or D) before initial PPI treatment. Grade M indicates a minimal change in mucosa, such as reddish and/or whitish turbidity, and categorized as minimal erosive reflux disease according to the modified LA classification.^[16] Patients eligible for inclusion were between 19 and 75 years of age.

Patients were excluded if they had gastric and/or duodenal ulcer; undergone previous esophageal, gastric or duodenal surgery; irritable bowel syndrome; malignancy; hematologic disorder, a history of alcohol or drug abuse; or a history of an adverse reaction to esomeprazole. In addition, those of American Society of Anesthesiologists Class III or IV, pregnant or lactating women, women hoping to become pregnant, and those unable to provide informed consent were also excluded.

2.3. Randomization and treatments

Eligible patients were randomized 1:1 (using a computer-generated code) to 1 of the 2 treatment groups for a 12-week maintenance treatment period. Patients in the continuous PPI treatment group received the half dose of PPI (esomeprazole 20 mg tablets, Esomezol, Hanmi Pharmaceutical Co., Seoul) once daily. Patients in the on-demand PPI treatment group received the standard dose of PPI (esomeprazole 40mg tablets, up to a maximum of 1 daily). The method of on-demand use was explained to patients in the following way: “You should commence treatment when you consider recurrence of your symptom is at a level incompatible with your well-being”, or on the other hand: You should discontinue treatment when the symptom of concern has been absent for 48 hours. Treatments that might have affected the study, such as, other PPIs, H₂-receptor antagonists, antacids, sucralfate, and prokinetic drugs, were not permitted during the maintenance treatment period.

2.4. Assessments and outcomes

Baseline demographic and clinical characteristics of all study subjects were collected at time of enrollment and included details on medical comorbidities and LA classification grade of GERD as determined by upper GI endoscopy.

Patients were examined 3 times (at randomization and at 4 and 12 weeks after treatment commencement) to assess symptom control, treatment tolerability, and medication consumption and compliance. Severities of symptoms (heartburn and acid regurgitation) were measured using a 6-point Likert scale (0 = none, 1 = minimal (present but causing little or no discomfort and easily ignored), 2 = mild (present but causing only mild discomfort and ignored with effort), 3 = moderate (cannot be ignored but does not influence daily activities), 4 = moderately severe (causes discomfort and some interference with daily activities), 5 = very severe (disabling and interferes considerably with daily activities)).

Mean frequencies of heartburn and acid regurgitation were determined by reviewing patients' diaries and were assessed using a 6-point scale, as follows: 0 = none, 1 = symptom for ≤ 1 days a week, 2 = symptom for >1 days and ≤ 2 days a week, 3 = symptom for >2 days and ≤ 3 days a week, 4 = symptom for >3 days and ≤ 5 days a week, 5 = symptom for >5 days a week.

The main objective of this study was to compare the percentages of patients that achieved alleviation of symptom at 4 and 12 weeks after treatment commencement in the on-demand and continuous groups. Alleviation of symptoms was defined as a Likert scale or frequency scale of 0 or 1 for the severity and frequency of heartburn or regurgitation.

Secondary variables included mean daily esomeprazole consumption, patient satisfaction and convenience of medication. Patient satisfaction with treatment was assessed by using a 5-point Likert scale (1 = “completely dissatisfied”, 2 = “quite dissatisfied”, 3 = “neither satisfied nor dissatisfied”, 4 = “quite satisfied”, 5 = “completely satisfied”) based on replies to the following question: “Did the effectiveness of the treatment you have received enable you to achieve a sufficient level of well-being?” Convenience of medication was also assessed using a 5-point Likert scale (1 = “completely inconvenient”, 2 = “quite inconvenient”, 3 = “neither convenient nor inconvenient”, 4 = “quite convenient”, 5 = “completely convenient”) based on replies to the following question: “How convenient or inconvenient are you with taking the drug?”

2.5. Statistical analysis

Sample size was calculated by assuming a 25% difference in rate of symptom relief. Based on the following assumptions; 65% of the patients would experience symptom relief from on-demand PPI therapy, that 90% would do so on continuous PPI therapy and an anticipated dropout rate of 10%. We calculated at least 88 participants were needed in the study to achieve a power of 80% at the 5% 2-sided significance level.

Continuous variables were expressed as means \pm standard deviations (SDs) and were compared using the Student *t* test or the Mann-Whitney test. Categorical variables were expressed as absolute numbers and proportions. Pearson χ^2 test or Fisher exact test was used to compare categorical variables. The analysis was performed using SPSS version 20.0 (Chicago, IL) and statistical significance was accepted for *P* values $< .05$.

3. Results

3.1. Patient characteristics

Eighty-eight patients were consecutively enrolled in this study, but 7 were lost for follow up in the early study period and were excluded (Fig. 1). The remaining 81 patients were randomized to

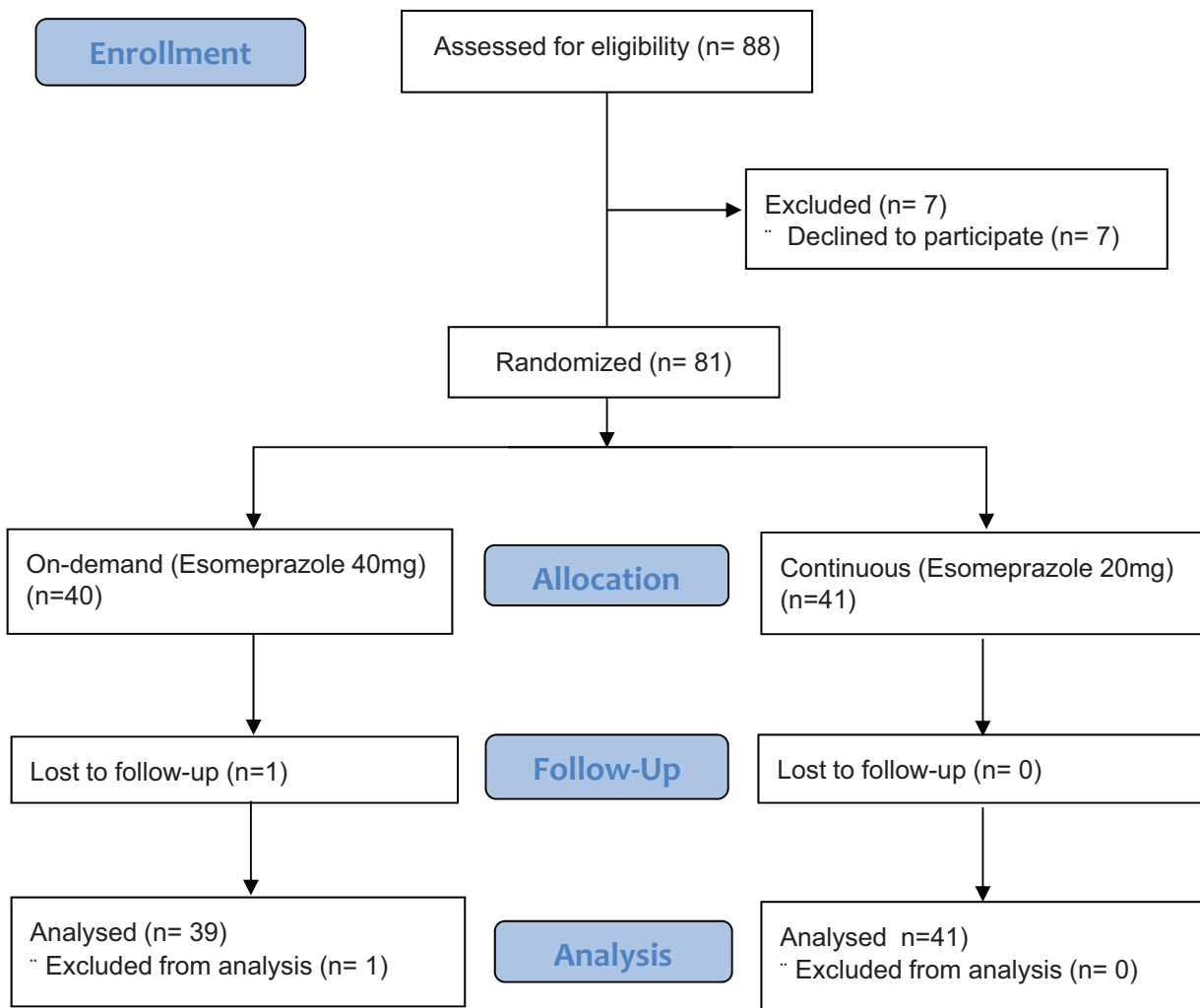


Figure 1. Study design. Flow chart showed the recruitment of the study patients.

the 2 study groups, that is, 40 to the on-demand group and 41 to the continuous group. After randomization, 1 in the on-demand group was lost for follow up, and finally, 39 in the on-demand group and 41 in the continuous group were analyzed.

Patient demographic and baseline characteristics at time of randomization are provided in Table 1. Mean age of the 80 study subjects was 60.5 ± 10.6 years (range, 28–73) and 51 (63.8%) were males. Age, sex, and BMI did not differ significantly in the on-demand and continuous groups ($P=.899$, $P=.526$, and $P=.262$, respectively). The presence of a medical comorbidity and risk factors for GERD, such as smoking and alcohol, were also non-significantly different. Based on upper GI endoscopic findings before initial PPI treatment, hiatal hernia was significantly more common in on-demand group (25/39 (64.1%) vs 13/41 (31.7%), $P=.007$). The majority of patients (54/80, 67.5%) presented no definite endoscopic evidence of erosive esophagitis (GradeM according to the Modified LA classification; on-demand group 25/39 (64.1%); continuous group 29/41 (70.7%). Upper GI endoscopic findings of GERD (gradesM, A, B, C, and D) were non-significantly different at baseline ($P=.296$), and Likert scale and frequency scales of intensity and frequency of heartburn were non-significantly different at baseline ($P=.376$ and $P=.091$, respectively). Furthermore, Likert scale and

frequency scales of intensity and frequency of acid regurgitation were also non-significantly different at baseline ($P=.444$ and $P=.371$, respectively).

3.2. Primary variables

We defined symptom alleviation as a Likert scale or frequency scale of 0 or 1 for the intensity or frequency of heartburn or regurgitation. Percentages of patients that achieved symptom alleviation in the on-demand and continuous groups at baseline and at 4 and 12 weeks after treatment commencement are shown in Figures 2 and 3. Percentages of symptom alleviations in the on-demand and continuous groups for intensity of heartburn were 56.4%/48.8% at baseline ($P=.523$), 82.1%/78% at 4 weeks ($P=.655$) and 82.1%/87.8% at 12 weeks ($P=.471$), respectively (Fig. 2a), and for frequency of heartburn were 61.5%/46.3% at baseline ($P=.173$), 82.1%/80.5 at 4 weeks ($P=.858$) and 76.9%/87.8% at 12 weeks ($P=.200$) (Fig. 2b), for intensity of regurgitation were 53.8%/43.9% at baseline ($P=.374$), 76.9%/82.9% at 4 weeks ($P=.502$) and 82.1%/87.8% at 12 weeks ($P=.471$) (Fig. 3a), and for frequency of regurgitation were 61.5%/56.1% at baseline ($P=.621$), 71.8%/87.8% at 4 weeks ($P=.074$) and 82.1%/82.9% at 12 weeks ($P=.918$) (Fig. 3b).

Table 1
Demographics and characteristics of the patients at baseline.

	On-demand (n = 39)	Continuous (n = 41)	P value
Age, years	60.4 ± 9.2	60.7 ± 11.6	.899
Sex (male)	23 (59.0)	28 (68.3)	.526
Weight, kg	64.0 ± 11.7	67.3 ± 10.9	.198
Height, cm	163.9 ± 7.8	165.7 ± 8.9	.338
BMI (kg/m ²)	23.7 ± 3.1	24.4 ± 2.9	.262
Comorbidity			
None	15 (38.5)	11 (26.8)	.267
Hypertension	9 (23.1)	13 (31.7)	.388
Diabetes	5 (12.8)	8 (19.5)	.417
Liver disease	4 (10.3)	8 (19.5)	.247
Others*	11 (28.2)	11 (26.8)	.890
Smoking	23 (59.0)	25 (61.0)	.855
Alcohol	23 (59.0)	23 (56.1)	.795
Hiatal hernia	25 (64.1)	13 (31.7)	.007
Modified LA classification before initial therapy			.296
M	25 (64.1)	29 (70.7)	
A	10 (25.6)	5 (12.2)	
B	3 (7.7)	6 (14.6)	
C	0 (0.0)	1 (2.4)	
D	1 (2.6)	0 (0.0)	
Intensity of heartburn [†]	1.5 ± 1.6	1.8 ± 1.6	.376
Frequency of heartburn [‡]	1.4 ± 1.6	2.1 ± 1.8	.091
Intensity of reflux [†]	1.5 ± 1.6	1.8 ± 1.5	.444
Frequency of reflux [‡]	1.3 ± 1.3	1.6 ± 1.4	.371

Values are presented as the means ± SDs or n(%).

BMI = body mass index.

* Others are kidney diseases, heart diseases and rheumatic diseases.

[†] Symptom intensity was measured using a 0 to 5 of Likert scale (0 = none; 5 = very severe).

[‡] Mean symptom frequency of symptoms was measured by reviewing patients' diaries using a 6-point scale as follows: 0 = none; 1 = symptom for ≤ 1 days a week; 2 = symptom for > 1 days and ≤ 2 days a week; 3 = symptom for > 2 days and ≤ 3 days a week; 4 = symptom for > 3 days and ≤ 4 days a week; 5 = symptom for > 5 days a week.

3.3. Secondary variables

Mean number of tablets consumed over the maintenance treatment period was significantly lower in the on-demand group than in the continuous group (Table 2). Average number of tablets consumed day at 0 to 4 weeks was 0.63 ± 0.34 in the on-demand group and 1.08 ± 0.38 in the continuous group (*P* = .003), and at 4 to 12 weeks was 0.47 ± 0.30 in the on-demand group and 1.00 ± 0.22 in the continuous group (*P* = .003). However, mean drug consumptions in the on-demand and continuous groups over the 12-week maintenance treatment were similar (20.8 ± 13.6 mg vs 20.4 ± 14.4, *P* = 1.000). Also, there were no significant differences in 5-point Likert scale scores for convenience of medication (*P* = .469) and subjective satisfaction (*P* = .545) between two groups.

4. Discussion

During the last few decades, GERD has become an increasing public health problem, especially in Asia. GERD causes many clinical problems and has a large associated economic burden. Furthermore, the disease is likely to recur with reported recurrence rates after 6 months without maintenance therapy of 50% to 100%.^[17–20]

In clinical practice, patients with symptomatic GERD are often treated empirically with PPIs based on patient reports and physical examination. After the symptoms of GERD, such as

heartburn and acid regurgitation, have subsided, 2 major strategies are available for long-term disease management, that is, continuous daily therapy or on-demand therapy.

Several studies have addressed on-demand use of PPI therapy for patients with NERD or GERD. A recent meta-analysis reported that on-demand PPI therapy is superior to continuous therapy in patients with mild GERD,^[21] and several reviews have concluded that on-demand maintenance therapy with a PPI offers an appropriate option for patients with mild reflux esophagitis (RE) or NERD.^[22–24] However, other studies that compared on-demand and continuous therapy in patients with RE and/or NERD, indicated continuous therapy is the better outcome,^[25–27] especially for symptom control in healed erosive esophagitis.^[13] It is likely these conflicting results were caused by study design, population characteristics, PPI type and dosage, ethnicity, and environmental differences. Furthermore, despite extensive research about on-demand PPI, this study is the first randomized study to be conducted on a Korean cohort to compare the effects of on-demand and continuous esomeprazole therapy in patients with GERD that responded to initial PPI treatment.

NERD is relatively common in Korea. According to an epidemiologic study, of Korean GERD patients diagnosed basis on reflux symptoms, the rate of endoscopic erosive esophagitis was only 14%,^[28] and the majority of patients with RE (96%) had mild forms (LA classification grade A or B).^[29] In the present study, the percentages of patients with NERD and erosive RE were 67.5% (54/80) and 32.5% (26/80), respectively, and percentage with mild esophagitis among those with erosive esophagitis was 92.3% (24/26), which are similar to those previously reported in Korea. This similarity is probably the result of the study design because it was intended to reflect Korean clinical settings, and thus, we included patients with reflux esophagitis and NERD.

The most important symptoms of GERD are heartburn and acid regurgitation, and failure to control these symptoms in the long-term is a major cause of poor quality of life among GERD patients. Thus, in the present study, we investigated the effectiveness of on-demand and continuous PPI maintenance therapies based on the intensity and frequency of heart burn and acid regurgitation. About half (40%–60%) of our study patients achieved symptom alleviation (Likert scale of 0 or 1; frequency scale 0 or 1) for heartburn or acid regurgitation baseline and no significant difference was observed between the 2 groups. Furthermore, this lack of significance was sustained throughout the 12-week maintenance period, although at 4 weeks, the rate of alleviation of frequency of regurgitation tended to be higher in the continuous group without statistical significance. At the end of the 12-week study period, about 80% of patients experienced symptom alleviation in both study groups.

Our results showed that after 8 weeks of initial treatment, 12 weeks of on-demand esomeprazole maintenance therapy (40 mg) was not inferior to 12 weeks of continuous therapy in terms of alleviating symptoms. Furthermore, these results were supported by the lack of a significant intergroup difference between mean group Likert scores for medication convenience or overall satisfaction with maintenance treatment.

The results of on-demand vs continuous therapy could theoretically be influenced by type of PPI. The majority of studies on this topic have used esomeprazole or rabeprazole, though some have used omeprazole.^[15,17,27] Esomeprazole provides more sustained acid suppression^[30] than lansoprazole^[31] or pantoprazole,^[32] and is reflected by higher rates for maintenance of reflux esophagitis healing and more rapid and

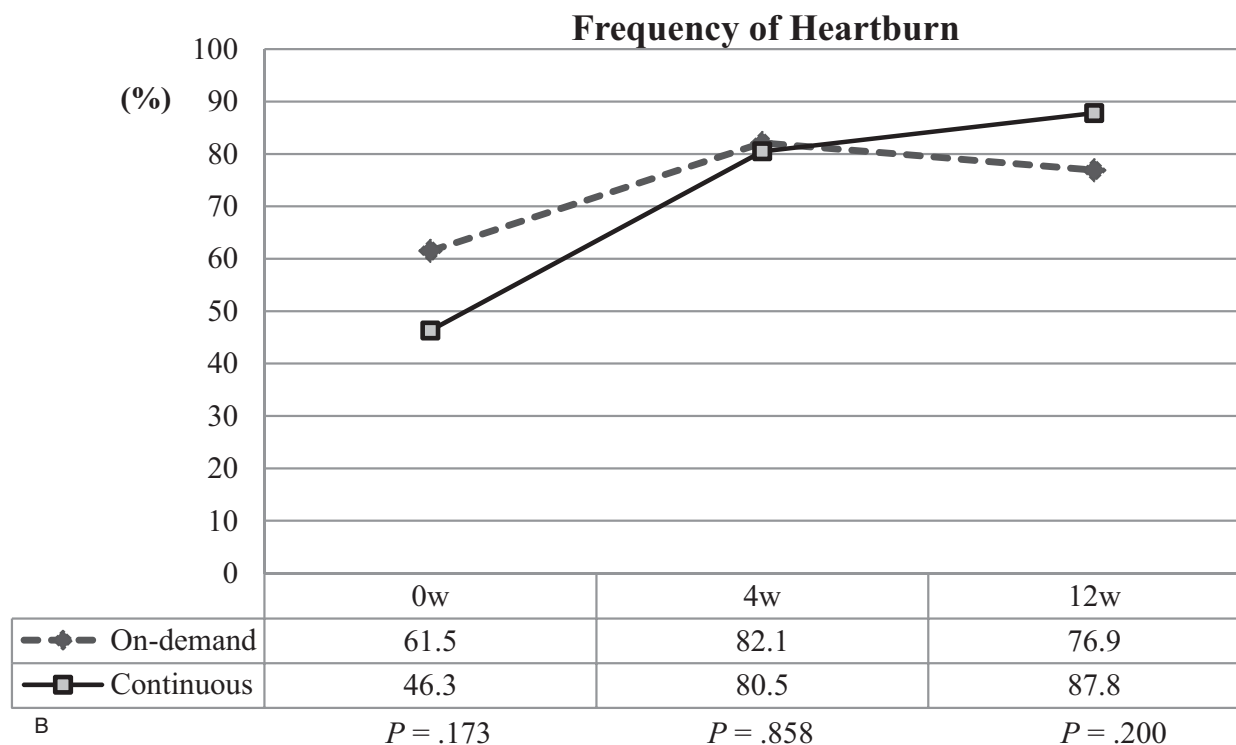
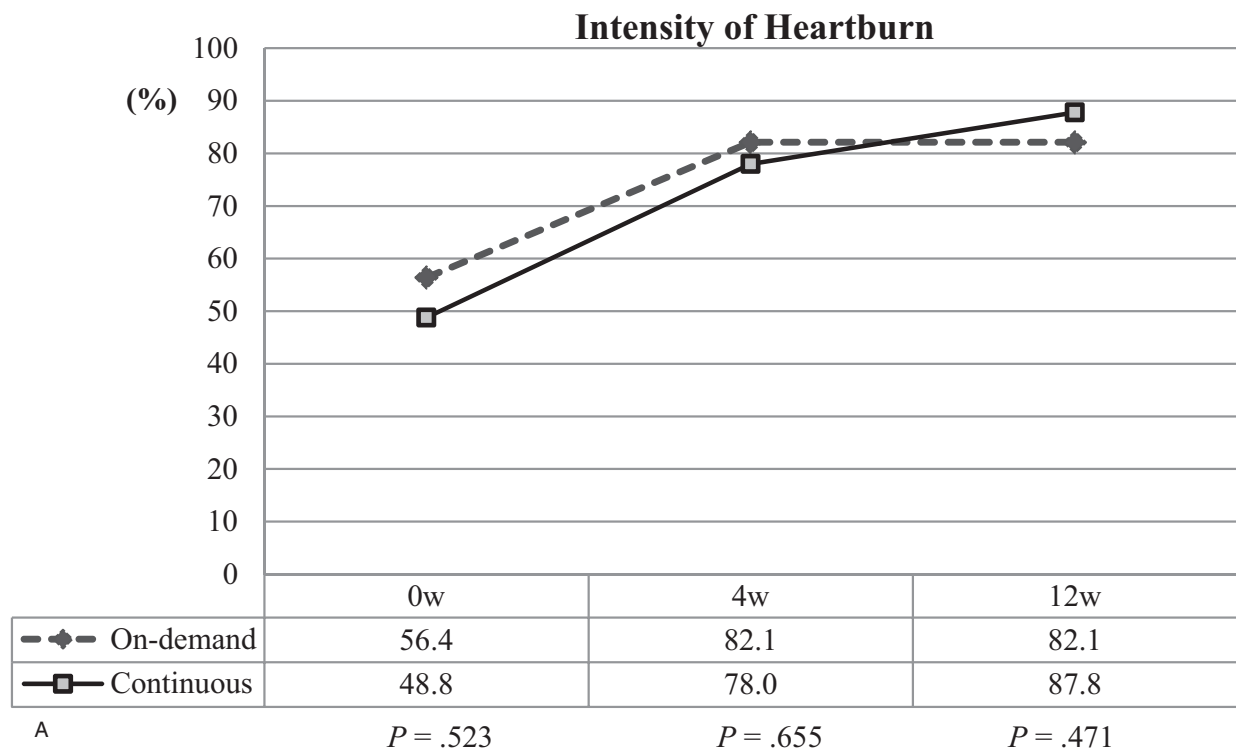


Figure 2. Percentages of patients that achieved alleviation of the intensity (Fig. 2a) and frequency (Fig. 2b) of heartburn in the on-demand and continuous group as determined by a Likert scale and frequent scales, respectively, at baseline and after 4 and 12 weeks of maintenance therapy. No significant between-group differences were found between percentages of patients that achieved alleviation of heartburn.

greater acid suppression.^[33] Furthermore, the efficacy of esomeprazole at 40 mg and 20 mg for the maintenance treatment of NERD has been demonstrated in placebo-controlled trials for on-demand^[34,35] and continuous therapy.^[36]

We used a standard dose (40mg) of esomeprazole for on-demand therapy and half the standard dose (20mg) for continuous therapy during the maintenance period. Although some studies have investigated on-demand therapy using a

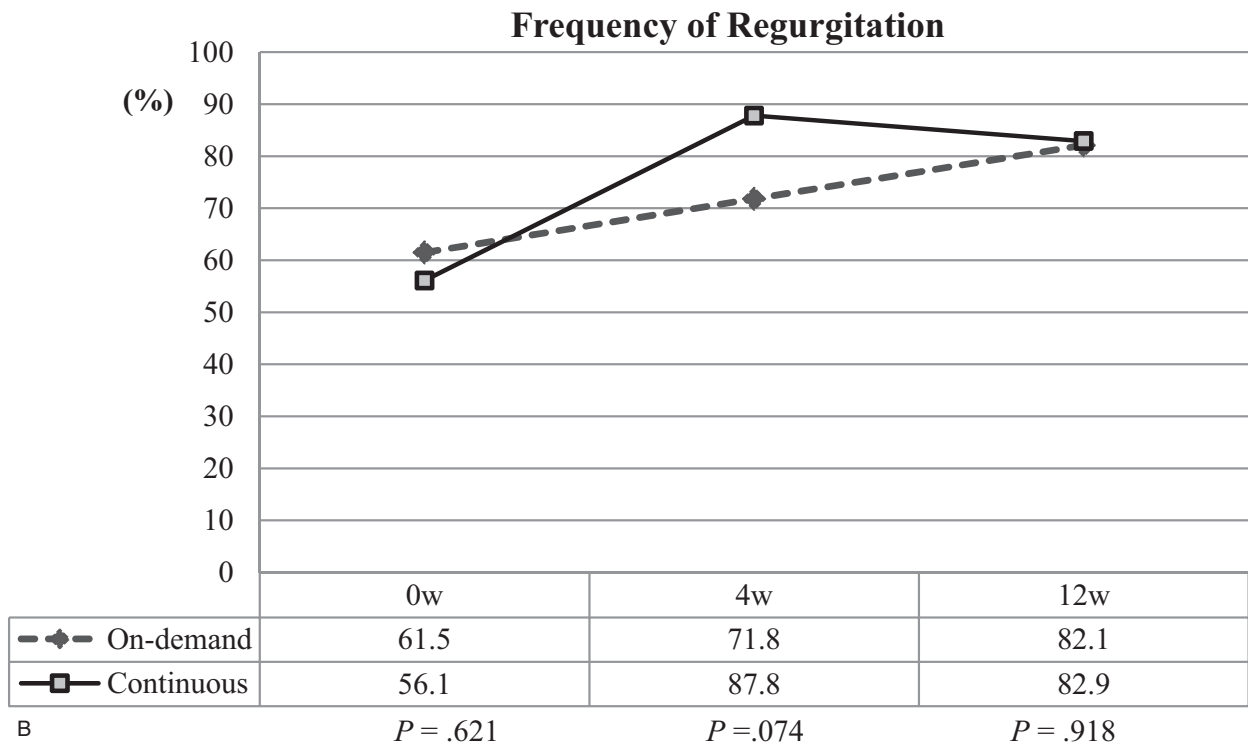
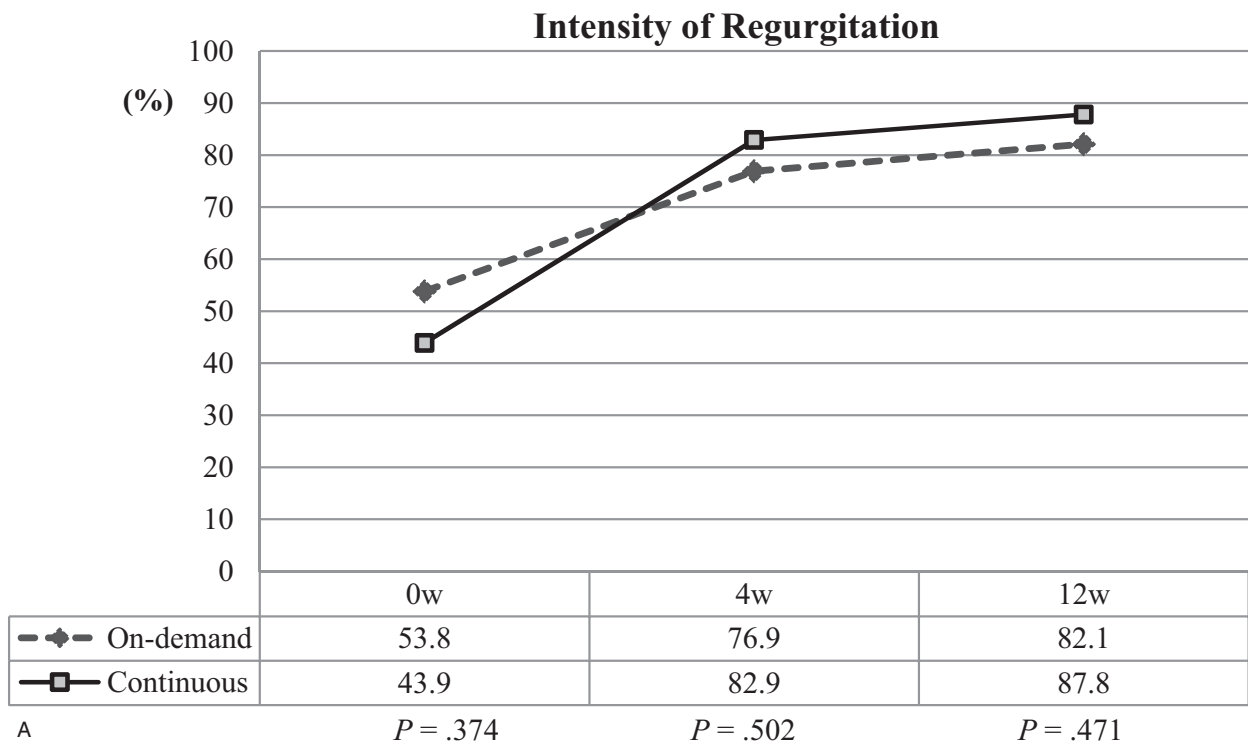


Figure 3. Percentages of patients that achieved alleviation of intensity (Fig. 3a) and frequency (Fig. 3b) of regurgitation in the on-demand and continuous groups as determined by a Likert scale and frequent scales, respectively, at baseline and after 4 and 12 weeks of maintenance therapy. No significant between-group differences were found between percentages of patients that achieved alleviation of regurgitation.

standard dose of PPI (rabeprazole 20 mg),^[26] most have used PPIs at half standard doses. Bour et al reported that the average number of rabeprazole (10 mg) tablets consumed per day was 0.31 in an on-demand group (n=55) and 0.96 in a continuous

group (n=67) ($P < .001$), and in a multicenter study, it was reported mean esomeprazole (20 mg/tablet) usage over a 6-month study period was 0.41 tablets per day in their on-demand group (n=295) and 0.91 tablets per day in their continuous group (n=

Table 2
Secondary variables in the 2 study groups.

	On-demand (n=39)	Continuous (n=41)	P value
Average n. of tablets consumed per day (0–12wks)	0.52 ± 0.34	1.02 ± 0.36	.003
Average n. of tablets consumed per day (0–4wks)	0.63 ± 0.34	1.08 ± 0.38	.003
Average n. of tablets consumed per day (4–12wks)	0.47 ± 0.30	1.00 ± 0.22	.003
Mean drug dosage consumed per day (0–12wks), mg	20.8 ± 13.6	20.4 ± 14.4	1.000
Convenience of medication*	4.40 ± 0.60	4.49 ± 0.67	.469
Overall satisfaction with maintenance treatment†	4.21 ± 0.77	4.05 ± 0.74	.356

Values are presented as the means ± SDs.

* Patient convenience was assessed by using a 5-point Likert scale (1 = “completely inconvenient”; 5 = “completely convenient”) in reply to the following question: “How convenient or inconvenient are you with taking the drug?”.

† Patient’s satisfaction with treatment was assessed by using a 5-point Likert scale (1 = “completely dissatisfied”; 5 = “completely satisfied”) in reply to the following question: “Did the effectiveness of the treatment you have received enable you to achieve a sufficient level of well-being?”.

286). Unlike the results of some previous studies, our study revealed no benefit for mean drug consumption in the on-demand group compared with the continuous group. In the present study, mean numbers of tablets consumed over the maintenance treatment period in the on-demand and continuous groups were 0.52 and 1.02 tablets/day, respectively, and although the mean tablet consumption was significantly lower in the on-demand group, mean drug consumption was similar in the 2 groups.

Several limitations of the present study warrant consideration. First, the follow-up period (12 weeks) was relatively short, and as a result, we were unable to investigate the long-term effectiveness of on-demand and continuous therapy. However, therapeutic effectiveness was not significantly different after 12 weeks of treatment. Second, the number of patients was relatively small. In particular, most patients were of grade M, 26 patients had mild erosive esophagitis (Grades A or B), and only 2 had severe esophagitis (Grades C or D), which pre-empted comparative subgroup analysis on the effectiveness of the 2 maintenance therapies on erosive esophagitis, especially severe degree (Grade C and D) erosive esophagitis. Third, the 24-hour pH monitoring test was not performed in this study, therefore, certain number of patients with NERD (Grade M) in this study might not be reflux disease. This might be the reason of the low symptom-relief rate at baseline of maintenance treatment. Certainly, the precise diagnosis of NERD is important for better study population, however, NERD is usually diagnosed by reflux symptoms without abnormal endoscopic findings in the esophagus in daily clinical settings.^[37] Nevertheless, this study is the first prospective randomized study to compare the efficacies of on-demand and continuous maintenance therapy for GERD in a Korean population.

The appropriate doses and durations of PPI therapy for on-demand and continuous maintenance treatment are unclear and domestic data about these are lacking. It is reasonable to individualize treatment strategies according to the severities of symptoms or endoscopic findings of individual patients until the result of larger scale research. Furthermore, as indicated by the present study, the 2 treatment strategies appear to be equally effective, and thus, decision-making should also take into account patient preference.

In summary, our results show the intensities and frequencies of heartburn and regurgitation in patients with GERD responded well to 12 weeks of maintenance on-demand therapy (esomeprazole 40 mg) and to maintenance continuous therapy on half-dose (esomeprazole 20 mg). In terms of relieving these symptoms, on-demand PPI maintenance therapy appears to be sufficient for

Korean adults that achieve symptom alleviation after 8 weeks of initial PPI treatment.

Author contributions

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 - Funding acquisition:** Tae Nyeun Kim.
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References

- [1] Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management: the Genval Workshop Report. *Gut* 1999;44: S1–6.
- [2] Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. *J Neurogastroenterol Motil* 2011;17:14–27.
- [3] Moayyedi P, Talley N. Gastroesophageal reflux disease. *Lancet* 2006; 367:2086–100.
- [4] Donnellan C, Sharma N, Preston C, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database Syst Rev* 2005;2:CD003245.
- [5] Nagahara A, Hojo M, Asaoka D, et al. Maintenance therapy of gastroesophageal reflux disease. *Clin J Gastroenterol* 2010;3:61–8.
- [6] Bak YT. Management strategies for gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2004;19:S49–53.
- [7] Pohle T, Domschke W. Results of short-and long-term medical treatment of gastroesophageal reflux disease. *Langenbecks Arch Surg* 2000; 385:317–23.
- [8] Tsai HH, Chapman R, Shepherd A, et al. Esomeprazole 20mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastroesophageal reflux patients: the COMMAND study. *Aliment Pharmacol Ther* 2004;20:657–65.

- [9] Pace F, Negrini C, Wiklund I, et al. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005;22:349–56.
- [10] Janssen W, Meier E, Gatz G, et al. Effects of pantoprazole 20 mg in mild gastroesophageal reflux disease: once-daily treatment in the acute phase, and comparison of on-demand versus continuous treatment in the long term. *Curr Ther Res Clin Exp* 2005;66:345–63.
- [11] Norman Hansen A, Bergheim R, Fagertun H, et al. A randomised prospective study comparing the effectiveness of esomeprazole treatment strategies in clinical practice for 6 months in the management of patients with symptoms of gastroesophageal reflux disease. *Int J Clin Pract* 2005;59:665–71.
- [12] Bour B, Staub JL, Chousterman M, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment. *Aliment Pharmacol Ther* 2005;21:805–12.
- [13] Sjöstedt S, Befrits R, Sylvan A, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive oesophagitis. *Aliment Pharmacol Ther* 2005;22:183–91.
- [14] Yoshida N, Kamada K, Tomatsuri N, et al. Management of recurrence of symptoms of gastroesophageal reflux disease: synergistic effect of rebamipide with 15 mg lansoprazole. *Dig Dis Sci* 2010;55:3393–8.
- [15] Nagahara A, Hojo M, Asaoka D, et al. A randomized prospective study comparing the efficacy of on-demand therapy versus continuous therapy for 6 months for long-term maintenance with omeprazole 20 mg in patients with gastroesophageal reflux disease in Japan. *Scand J Gastroenterol* 2014;49:409–17.
- [16] Hoshihara Y, Hashimoto M. Endoscopic classification of reflux esophagitis. *Nihon Rinsho* 2000;58:1808–12.
- [17] Carlsson R, Galmiche JP, Dent J, et al. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997;11:473–82.
- [18] Vakil NB, Shaker R, Johnson DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. *Aliment Pharmacol Ther* 2001;15:927–35.
- [19] Plein K, Hotz J, Wurzer H, et al. Pantoprazole 20 mg is an effective maintenance therapy for patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2000;12:425–32.
- [20] Jaspersen D, Diehl KL, Schoepfner H, et al. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Aliment Pharmacol Ther* 1998;12:49–52.
- [21] Jiang YX, Chen Y, Kong X, et al. Maintenance treatment of mild gastroesophageal reflux disease with proton pump inhibitors taken on-demand: a meta-analysis. *Hepatogastroenterology* 2013;60:1077–82.
- [22] Bardhan KD. Intermittent and on-demand use of proton pump inhibitors in the management of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003;98:S40–8.
- [23] Pace F, Porro GB. On-demand PPI therapy in GERD. *Curr Treat Options Gastroenterol* 2008;11:35–42.
- [24] Pace F, Tonini M, Pallotta S, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Pharmacol Ther* 2007;26:195–204.
- [25] Cibor D, Ciec'ko-Michalska I, Owczarek D, et al. Optimal maintenance therapy in patients with non-erosive reflux disease reporting mild reflux symptoms—a pilot study. *Adv Med Sci* 2006;51:336–9.
- [26] Morgan DG, O'Mahony MF, O'Mahony WF, et al. Maintenance treatment of gastroesophageal reflux disease: an evaluation of continuous and on-demand therapy with rabeprazole 20 mg. *Can J Gastroenterol* 2007;21:820–6.
- [27] Tepes B, Stabuc B, Kocijancic B, et al. Maintenance therapy of gastroesophageal reflux disease patients with omeprazole. *Hepatogastroenterology* 2009;56:67–74.
- [28] Cho YK, Kim GH, Kim JH, et al. Diagnosis of gastroesophageal reflux disease: a systematic review. *Korean J Gastroenterol* 2010;55:279–95.
- [29] Seo GS, Jeon BJ, Chung JS, et al. The prevalence of erosive esophagitis is not significantly increased in a healthy Korean population—could it be explained? A multi-center prospective study. *J Neurogastroenterol Motil* 2013;19:70–7.
- [30] Röhs K, Wilder-Smith C, Nauc'ler E, et al. Esomeprazole 20 mg provides more effective intragastric acid control than maintenance-dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers. *Clin Drug Investig* 2004;24:1–7.
- [31] Lauritsen K, Devière J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: metropole study results. *Aliment Pharmacol Ther* 2003;17:333–41.
- [32] Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. *Aliment Pharmacol Ther* 2005;22:803–11.
- [33] Modlin IM, Sachs G. *Acid Related Diseases: Biology and Treatment*. Lippincott, Williams and Wilkins, Philadelphia:2004.
- [34] Talley NJ, Lauritsen K, Tunturi-Hihnalä H, et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Aliment Pharmacol Ther* 2001;15:347–54.
- [35] 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;14:857–63.
- [36] Katz PO, Castell DO, Levine D. Esomeprazole resolves chronic heartburn in patients without erosive oesophagitis. *Aliment Pharmacol Ther* 2003;18:875–82.
- [37] Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005;40:275–85.