

Difference in efficacy of proton pump inhibitor between new-onset and recurrent gastroesophageal reflux disease: Result from a study of on-demand versus continuous maintenance therapy in Japan

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Abstract

Background-Objective: No study has focused on the difference in efficacy of maintenance therapy between patients with new-onset and recurrent gastroesophageal reflux disease (GERD). The aim of this study is to reveal this point.

Methods: Endoscopically proven GERD patients who had completed 8-week initial therapy were sequentially randomized to continuous arm (Omeprazole 20mg od) or on-demand arm (Omeprazole 20mg on-demand). Patients filled in daily symptoms and tablet usages for 24 weeks. Patients underwent upper GI endoscopy at 24 weeks. Symptom relief was defined as no symptoms for >6 days during a week. The numbers of patients who achieved symptom relief and mucosal healing were compared between the new-onset and recurrent groups in the continuous arm and in the on-demand arm, respectively.

Results: Among new-onset GERD [n=82 (continuous: 42 patients, on-demand: 40)], continuous arm achieved significant symptom-relief than in on-demand arm at 4*,5*,6** and 17*week. Among recurrent GERD [n=36(continuous: 17 patients, on-demand: 19)], continuous arm achieved significant symptom-relief at 1**,2*,3*,4*,5**,7**,8**,17* and 18* week, respectively (*p<0.05, **p<0.01). The number of healed patients was significantly higher in new-onset group (60/68, 88.2%) than in recurrent group (17/30, 56.7%) (p<0.01).

Conclusion: Since therapeutic response during maintenance therapy was poor in recurrent GERD, continuous therapy is recommended in order to maintain symptom-relief and mucosal healing. Hippokratia 2015, 19 (1): 53-56.

Keywords: Gastroesophageal reflux disease, new-onset, recurrence, maintenance therapy, proton pump inhibitor

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Introduction

Regarding the therapeutic approach to gastroesophageal reflux disease (GERD), many physicians are aware of the importance of maintenance therapy, and a number of studies have described the clinical importance of maintenance therapy¹. However, there is disagreement on the safety of the long-term use of proton pump inhibitors (PPI), and it has been emphasized that they should be prescribed judiciously only to patients who really need them². According to this point of view, on-demand therapy during the maintenance therapy could be one option.

A systematic review reported that the prevalence of GERD is as high as 10%-20%, whereas its incidence is as low as 4.5-19.6 per 1000 person-years, suggesting that GERD is likely to persist for many years, on average 18-44 years³. In other words, GERD is considered likely to recur. Although the therapeutic response during maintenance

therapy might be different between patients with new-onset and recurrent GERD, no study has focused on this point. The aim of this study is to reveal whether there is any difference in symptom-relief between new-onset or recurrent GERD during the on-demand versus continuous maintenance therapy.

Methods

This is a post-hoc analysis of maintenance therapy of GERD consisting of non-erosive reflux disease (NERD) and reflux esophagitis (RE), which was designed as a prospective parallel randomized open label study at a single university hospital between April 2009 and April 2013⁴. The Juntendo University ethics committee approved the study protocol. The performance of this study adhered to the principles of the Declaration of Helsinki

Table 1. Characteristics of study groups at baseline. New-onset gastroesophageal reflux disease (GERD) group consisted of 82 patients (continuous: 42, on-demand: 40), while recurrent GERD group consisted of 36 patients (continuous: 17, on-demand: 19).

	New onset group n=82	Recurrent group n=36	p value
Mean age	59.6 ± 11.5	57.6 ± 11.4	n.s.
Gender M:F	53:29	22:14	n.s.
Continuous: On-demand	42:40	17:19	n.s.
BMI	23.3 ± 3.4	24.9 ± 3.7	<0.05
Smoking %	29.9%	33.3%	n.s.
Drinking %	44.4%	65.7%	<0.05
Hiatal hernia %	62.2%	61.1%	n.s.
LA classification			
Grade M	27	10	n.s.
Grade A	28	12	
Grade B	24	10	
Grade C	1	4	
Grade D	2	0	

Data shown are mean ± standard deviation, BMI: body mass index, LA classification: Los Angeles classification, M: male, F: female, ns: non significant.

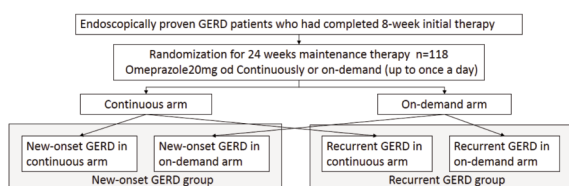
Table 2. Upper GI endoscopic diagnosis at 24 weeks..

	New onset group	Recurrent group	P value
Healed	60(88.2%)	17(56.7%)	p<0.01
Not healed	8(11.8%)	13(43.3%)	
(LA grade A:6, B:2, C:0, D:0)		(LA grade A:8, B:3, C:2, D:0)	

LA: Los Angeles classification grades A, B, C and D.

for medical research involving human subjects.

The original study design has been published previously⁴. In this study, patients were re-classified into new-onset GERD and recurrent GERD groups according to their patients' profile. Therefore, difference of patients' characteristics at baseline between new-onset and recurrent GERD was compared. This study analyzed the efficacy of PPI in patients who were new-onset or recurrent GERD by evaluating daily symptom charts during the maintenance therapy. Recurrent patients were defined as patient who had received internal medication for GERD. Briefly, endoscopically proven GERD patients who had completed 8 weeks initial therapy were sequentially randomized to a continuous arm (Omeprazole 20mg od) or a non-demand arm (Omeprazole 20mg on-demand). 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 the initial PPI treatment. The patients provided written informed consent to participate in this study. Grade M indicates a minimal change in the modified LA classification that expresses erythematous changes (red) and acanthotic changes (white)⁵. Randomization was conducted using a computer generated randomization list that was created by a third party. Patients filled in daily symptoms and tablet usages

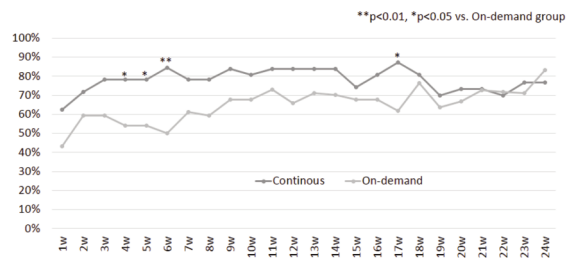
**Figure 1.** Overview of study design.

on the daily chart for 24 weeks. Symptom relief was defined as no-symptoms on 6 or more days a week. The numbers of patients who achieved symptom relief during a maintenance therapy were compared between the new-onset and recurrent groups in the continuous arm and in the on-demand arm, respectively. Upper GI endoscopy was performed at 24 weeks. We analyzed data from the daily chart using the full analysis set. Overview of study design is shown in Figure 1.

The results of the inter-group differences were analyzed using the Chi-square test and Fisher's exact test. Statistical significance was defined as $p < 0.05$ (two-sided).

Results

Among a total of 118 patients, 82 were new-onset GERD (mean age 59.6 years, men/women: 53/29) consisting of 42 patients in the continuous and 40 in the on-demand arm; 36 patients were recurrent GERD (mean age 57.6 years, men/women: 22/14) consisting of 17 patients in the continuous and 19 in the on-demand arm. Table 1 shows the characteristics of the patients at the time of enrollment. There were significant differences in body mass

**Figure 2.** Percentage of patients who were symptom free for 6 or more days a week as recorded on a daily chart in the new-onset GERD group. **p<0.01, *p<0.05 vs. On-demand group.

index (BMI) and alcohol drinking between the two groups at the time of randomization. Regarding results from the daily charts, among new-onset GERD patients, more patients in the continuous arm achieved symptom-relief than did those in the on-demand arm at 4, 5, 6 and 17 weeks (Figure2); in contrast, among recurrent GERD patients, those in the continuous arm showed a significant effect at 1, 2, 3, 4, 5, 7, 8, 17 and 18 weeks (Figure3). As shown in Figure 4, the mean tablet consumption per week showed no difference between new-onset and recurrent patients neither in the on-demand arm nor the continuous arm. A total of 98 patients underwent upper GI endoscopy at 24 weeks. Table 2 describes the endoscopic findings at 24 weeks. The number of healed patients was significantly higher in the new-onset group 60/68 (88.2%) than in the recurrent group 17/30 (56.7%) ($p < 0.01$). Among them, no patient with NERD develop reflux esophagitis (RE) at the end of the maintenance period.

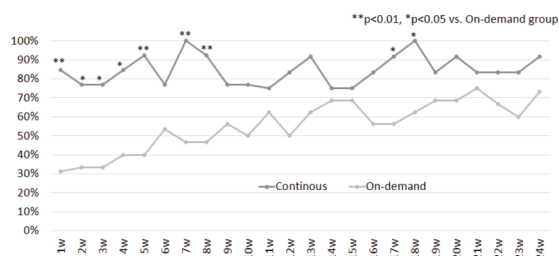


Figure 3. Percentage of patients who were symptom free for 6 or more days a week as recorded on a daily chart in the recurrent GERD group. ** $p < 0.01$, * $p < 0.05$ vs. On-demand group.

Discussion

Our previous study on maintenance therapy of GERD revealed that on-demand therapy was equally effective to continuous therapy in NERD, however, in patients with RE, symptoms were equally controlled by on-demand or continuous therapy, but insufficient mucosal healing was obtained in on-demand therapy⁴. This result clearly demonstrated the importance of continuous therapy as a maintenance therapy of GERD in the Japanese population.

GERD is known as being likely to recur. Indeed, the recurrence rate after 6 months without maintenance therapy was reported to be about 50% to 100%⁶⁻⁹. However, even though they took PPIs during maintenance therapy, some patients could not achieve mucosal healing. Several factors contribute to relapse. A meta-analysis revealed that pre-treatment severity of the disease, young age, non-smoking and moderate/severe regurgitation before trials were associated with a higher relapse rate⁶. A study on-Japanese patients described that relapse occurred in 11% of patient with RE under PPI administration, and that the risk factors were hiatal hernia, severe RE, *H. pylori* negativity, no mucosal atrophy, nonsmoking, female and < 150 cm height¹⁰. In this study, the characteristics of patients in the recurrent group demonstrated that they had higher BMI and were drinking more alcohol than did those in the new-onset group. Indeed, obesity is related to GERD^{11,12}.

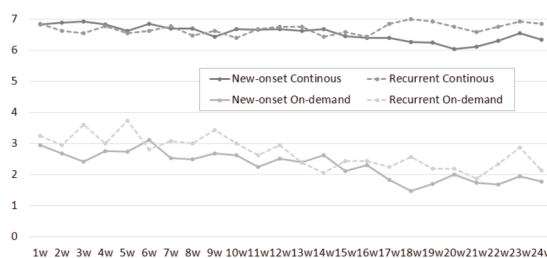


Figure 4. Mean number of consumed tablets per week recorded on a daily chart.

However, the BMI of patients in both groups was less than 25, which is within the normal range in this study. Therefore, BMI differences may have less clinical implications. Alcohol is reported as one of the risk factors for GERD^{13,14}. Since there were more alcohol drinkers in the recurrent group in this study it may suggest that drinking of alcohol is also a risk factor for recurrence of GERD. The mechanisms by which PPI resistance develop in GERD include ineffective control of gastric acid secretion, visceral hyper sensitivity, ultrastructural and functional changes in the esophageal epithelium¹⁵. Since it is well known that alcohol induce mucosal injury, alcohol would disturb pharmacological effect of PPI. That is, deterioration of PPI resistance by alcohol would result in recurrence.

Some studies on maintenance therapy described disease duration as related to patient demographics. Disease duration varies in different studies^{6,16-19}, however, checking the results of these studies carefully, it appears that about 80% of patients had disease duration of longer than 1 year and that about 40% of patients had longer than 5 year disease duration. Another study stated that the mean disease duration was 6.6 to 7 years⁹. It is difficult to believe that these patients with longer disease duration had not undergone treatment; therefore, they may probably have had many recurrences. Accordingly, the incidence of recurrent GERD is high, and many physicians are likely to encounter the problem of how to manage these recurrent GERD.

To the best of our knowledge, the different therapeutic approaches in managing recurrent GERD and new-onset GERD have not been analyzed, so this is the first study to shed light on this issue. This study demonstrated that the percentage of patients with symptom relief was lower in the on-demand arm than that in the continuous arm, especially in the recurrent disease group. Regarding the tablet consumption in each week, patients in both the continuous and on-demand arms took an equal number of tablets regardless of whether they had new-onset or recurrent GERD. These results suggest that on-demand therapy is insufficient and that patients should take PPI every day as a maintenance therapy in order to maintain symptom relief, especially those with recurrent GERD.

In addition to symptom relief, as shown in Table 2, the number of healed patients was significantly lower in the recurrent group than in the new-onset group according to

upper GI endoscopy at 24 weeks. Out of 13 patients who had not attained mucosal healing in the recurrent group, 10 patients belonged to the on-demand arm; and out of 8 patients who had not attained mucosal healing in the new-onset group, 6 patients belonged to the on-demand arm. Indeed, a study administering PPI to healthy volunteer revealed that PPI withdrawal induced acid-related symptoms by rebound acid hypersecretion²⁰. This effect could explain the worst clinical evolution of the on-demand strategy, especially in patients with recurrent GERD. These results suggest two things: in recurrent GERD it is difficult to attain mucosal healing, and continuous therapy should be administered in order to attain and maintain mucosal healing.

Conclusion

In the management of maintenance therapy in patients with recurrent GERD, continuous therapy is recommended in order to maintain symptom relief and mucosal healing.

Conflict of interest

Akihito Nagahara has served as a speaker for Astra Zeneca.

Acknowledgement

This study was presented in abstract form as P1023 at 2013 UEGW in Berlin (United European Gastroenterology Journal volume1 supplement 1; 2013, A408).

References

- Nagahara A, Hojo M, Asaoka D, Watanabe S. Maintenance therapy of gastroesophageal reflux disease. *Clin J Gastroenterol*. 2010; 3: 61-68.
- Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol*. 2010; 16: 2323-2330.
- Armstrong D. Systematic review: persistence and severity in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2008; 28: 841-853.
- Nagahara A, Hojo M, Asaoka D, Sasaki H, Watanabe S. 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: 409-417.
- Hongo M. Minimal changes in reflux esophagitis: red ones and white ones. *J Gastroenterol*. 2006; 41: 95-99.
- Carlsson R, Galmiche JP, Dent J, Lundell L, Frison L. 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: 473-482.
- Vakil NB, Shaker R, Johnson DA, Kovacs T, Baerg RD, Hwang C, 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: 927-935.
- Plein K, Hotz J, Wurzer H, Fumagalli I, Lühmann R, Schneider A. Pantoprazole 20 mg is an effective maintenance therapy for patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol*. 2000; 12: 425-432.
- Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Aliment Pharmacol Ther*. 1998; 12: 49-52.
- Fujimoto K, Hongo M; Maintenance Study Group. Risk factors for relapse of erosive GERD during long-term maintenance treatment with proton pump inhibitor: a prospective multicenter study in Japan. *J Gastroenterol*. 2010; 45: 1193-1200.
- Lee SW, Lien HC, Chang CS, Peng YC, Ko CW, Chou MC. Impact of body mass index and gender on quality of life in patients with gastroesophageal reflux disease. *World J Gastroenterol*. 2012; 18: 5090-5095.
- Emerenziani S, Rescio MP, Guarino MP, Cicala M. Gastroesophageal reflux disease and obesity, where is the link? *World J Gastroenterol*. 2013; 19: 6536-6539.
- Lee ES, Kim N, Lee SH, Park YS, Kim JW, Jeong SH, et al. Comparison of risk factors and clinical responses to proton pump inhibitors in patients with erosive oesophagitis and non-erosive reflux disease. *Aliment Pharmacol Ther*. 2009; 30: 154-164.
- Minatsuki C, Yamamichi N, Shimamoto T, Kakimoto H, Takahashi Y, Fujishiro M, et al. Background factors of reflux esophagitis and non-erosive reflux disease: a cross-sectional study of 10,837 subjects in Japan. *PLoS One*. 2013; 8: e69891.
- Cicala M, Emerenziani S, Guarino MP, Ribolsi M. Proton pump inhibitor resistance, the real challenge in gastro-oesophageal reflux disease. *World J Gastroenterol*. 2013; 19: 6529-6535.
- Tsai HH, Chapman R, Shepherd A, McKeith D, Anderson M, Vearey D, et al; COMMAND Study Group. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. *Aliment Pharmacol Ther*. 2004; 20: 657-665.
- Laursen LS, Havelund T, Bondesen S, Hansen J, Sanchez G, Sebelin E, et al. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomized dose-finding study. *Scand J Gastroenterol*. 1995; 30: 839-846.
- Venables TL, Newland RD, Patel AC, Hole J, Copeman MB, Turbitt ML. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10 milligrams omeprazole once daily in general practice. *Scand J Gastroenterol*. 1997; 32: 627-632.
- Bardhan KD, Müller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, Hosie J, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. *BMJ*. 1999; 318: 502-507.
- Reimer C1, Sønndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology*. 2009; 137: 80-87.