The daily response for proton pump inhibitor treatment in Japanese reflux esophagitis and non-erosive reflux disease

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We investigated comparison according to reflux esophagitis and non-erosive reflux disease about "daily" symptom improvement for proton pump inhibitor treatment. We enrolled 57 reflux esophagitis and 90 non-erosive reflux disease patients. They took rabeprazole 10 mg/day for 28 days and completed "daily" in the Frequency Scale for the Symptoms of GERD from baseline until day 14, and after 28 days of treatment. The efficacy endpoint was the improvement rates in Frequency Scale for the Symptoms of GERD, based on baseline. Frequency Scale for the Symptoms of GERD was decreased in reflux esophagitis and non-erosive reflux disease ($p<0.001$) and was significantly lower in reflux esophagitis than in non-erosive reflux disease from the first day of treatment ($p<0.05$). Symptomatic improvement rates were also significantly higher in reflux esophagitis ($50.3 \pm 44.9\%$) than in non-erosive reflux disease ($31.7 \pm 43.2\%$) from the first day of treatment ($p<0.0001$). The symptomatic improvement rates in reflux esophagitis were significant increased from the second day of treatment until after 28 days of treatment ($p = 0.0006$), however, these in non-erosive reflux disease were significant increased from third days until after 28 days of treatment ($p = 0.0002$). In non-erosive reflux disease, the improvement of dysmotility symptom was particularly gradual as well as of reflux symptom, too. As for results of prediction of proton pump inhibitor response (completed symptom resolution) form early symptom improvement within 1 week, it was able to predict proton pump inhibitor response from the symptom improvement rate on 3 days in reflux esophagitis and on day 7 in non-erosive reflux disease. In conclusion, the prediction of the proton pump inhibitor response in non-erosive reflux disease was slow in comparison with reflux esophagitis. The cause was gradual improvement of dysmotility symptom.

Key Words: endoscopy: upper GI, esophagus,
            gastroesophagus reflux disease,
            the frequency scale for the symptoms of GERD

The prevalence of gastroesophageal reflux disease (GERD) has increased markedly in Japan since 1990.[1] Proton pump inhibitors (PPI) are the treatment of first choice for GERD in both Western countries[2] and Japan.[3] The therapeutic effect of PPIs is weaker for Non erosive reflux disease (NERD) than for reflux esophagitis (RE), and some cases are refractory to PPI treatment.[4] For prediction of PPI therapeutic effect, for NERD the symptom resolution rate after 7 days of treatment is reported to correlate with the symptom resolution rate after 28 days of treatment.[5] For RE, the symptom resolution rate on the first day of treatment correlates with the symptomatic improvement rate after 28 days of treatment.[6] A rapid onset of PPI effect is therefore reflected in the efficacy after 28 days of treatment, more so with RE than with NERD. It is reasonable to think that the rapid onset of PPI will provide adequate effect for RE and NERD symptoms in Japanese patients, who have a higher rate of *Helicobacter pylori* (*H. pylori*) infection than Westerners, as well as lower levels of gastric acid secretion.[7] However, there were no study in Japan for comparing the rapid onset of PPI response in RE and NERD. In addition, the most of western studies were "weekly" units in the timing of the symptom evaluation and were not evaluated "daily" symptom after PPI.

We investigated comparison according to RE and NERD about "daily" symptom improvement for PPI treatment and prediction of symptom resolution after 28 days form early symptom improvement within 1 week.

Methods

Entry patients.   This study was an open label trial in Japan. One hundred seventy four outpatients with at least one month of GERD symptoms were enrolled. The exclusion criteria were: 1) history of peptic ulcer disease, GI malignancy, primary esophageal motility disorder, previous upper GI surgery; 2) maintenance treatment with a PPI or histamine 2 receptor antagonists (H2RA) within 2 weeks; and 3) severe concurrent disease. PPIs, H2RA and Prokinetics use were not permitted during the study. The study protocol was approved by the relevant Institutional Review Board and an Independent Ethics Committee, and informed written consent was obtained from each participating patients.

Definition of RE and NERD.   After informed consent, all patients performed esophagogastroduodenoscopy. Endoscopy finding was evaluated according to 2nd modified Los Angeles (LA) classification (Grade N, no endoscopic mucosal changes; Grade M, minimal change; Grade A, one or more mucosal breaks <5 mm long that do not extend between the tops of two mucosal folds; Grade B, one or more mucosal breaks >5 mm long that do not extend between the tops of two mucosal folds; Grade C, one or more mucosal breaks that are continuous between the tops of two or more mucosal folds, but do not involve the entire esophageal circumference; and Grade D, a mucosal break that involves the entire esophageal circumference).[8,9] We were defined that RE was Grade A–D and NERD was Grade N–M.

PPI treatment.   After endoscopy, eligible patients took Rabeprazole 10 mg/day for 28 days. The compliance was assessed by counting the returned medication. They were considered to have complied with treatment if they took at least 90% of the dispensed medication. The patients attended our hospital at baseline, after 2 and 28 days of treatment.

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doi: 10.3164/jcbn.12-69
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J. Clin. Biochem. Nutr. | January 2013 | vol. 52 | no. 1 | 76–81

Question		frequency				
		never	occasionally	sometimes	often	always
Q1	Do you get heartburn?	0	1	2	3	4
Q2	Does your stomach get bloated?	0	1	2	3	4
Q3	Does your stomach ever feel heavy after meals?	0	1	2	3	4
Q4	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
Q5	Do you ever feel sick after meals?	0	1	2	3	4
Q6	Do you get heartburn after meals?	0	1	2	3	4
Q7	Do you have an unusual (e.g. burning) sensation in your throat?	0	1	2	3	4
Q8	Do you feel full while eating meals?	0	1	2	3	4
Q9	Do some things get stuck when you swallow?	0	1	2	3	4
Q10	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
Q11	Do you burp a lot?	0	1	2	3	4
Q12	Do you get heartburn if you bend over?	0	1	2	3	4

Please describe any other symptoms you experience.

SUM POINTS

☐ + ☐ + ☐ + ☐ = F-TS TOTAL POINTS

Acid Reflux Score	(F-RS)	= ☐ POINTS
Dysmotility Score	(F-DS)	= ☐ POINTS

Fig. 1. Frequency Scale for Symptoms of GERD (FSSG). Frequency Scale for the Symptoms of GERD (FSSG) is a multiple-choice questionnaire, comprising 12 questions (Q1–12), that grades the frequency of each GERD symptom (never = 0, occasionally = 1, sometimes = 2, often = 3, always = 4). The FSSG contains the 12 symptoms (FSSG total score: F-TS) most commonly experienced by patients with GERD, with 7 of the 12 related to reflux symptoms (FSSG reflux score: F-RS) and the remaining 5 related to dysmotility symptoms (FSSG dysmotility score: F-DS).

Symptom assessment. All patients were performed daily self-assessment of their symptoms from baseline until day 14 of treatment, and after 28 days of treatment. Their symptoms were evaluated using the Frequency Scale for the Symptoms of GERD (FSSG). The FSSG questionnaire is a multiple-choice question-naire, comprising 12 questions, that grades the frequency of each GERD symptom (never = 0, occasionally = 1, sometimes = 2, often = 3, always = 4).[10] The FSSG has been shown to correlate strongly with upper gastrointestinal endoscopic (UGIE) findings.[11] It contains the 12 symptoms (FSSG total score: F-TS) most commonly experienced by patients with GERD, with 7 of the 12 related to reflux symptoms (FSSG reflux score: F-RS) and the remaining 5 related to dysmotility symptoms (FSSG dysmotility score: F-DS) (Fig. 1).[12]

The efficacy endpoint was the improvement rates in F-TS, based on baseline score = 100. "PPI responder" was defined by the complete resolution (F-TS = 0) after 28 days of treatment.

Statistical analysis. All data are presented as mean ± standard deviation (SD). The Mann-Whitney U test was used to compare the mean values of continuous variables between RE and NERD. In each RE and NERD, the change from baseline to 14 days and 28 days for FSSG score were analysed using an analysis of covariance (ANCOVA) model. The chi-square test was used for comparison of categorical variables. A multiple logistic regression analysis was performed to determine the improvement rates of F-TS on days 1, 2, 3 and 7 after treatment associated with PPI responder (complete symptom resolution) Results are presented as odds ratios with 95% confidence intervals (CI). P values less than 0.05 were considered statistically significant. Statistical analysis

was performed using SPSS ver.19 (Chicago, IL).

Results

Patient characteristics. As shown in Table 1, a total of 174 patients were enrolled. The number of patients who took rabepra-zole in the efficacy analysis was 147 (RE: 57, NERD: 90), after excluding 27 patients: 23 for whom no data were available at baseline; 2 for whom did not performed endoscopy and 2 who never visited our hospital after informed consent. Patient charac-teristics at baseline were summarized in Table 1. Only about gender, the ratio of man in RE (61.4%) was higher than in NERD (44.4%, $p = 0.0622$) tendency. Other characteristics and symptom score (FSSG) at baseline were no significant difference between RE and NERD.

Comparison of PPI effect: RE vs NERD. A significant decrease was seen in the F-TS both in RE and NERD from the first day of treatment ($p<0.001$) (Fig. 2). From the first day of treatment until after 28 days of treatment, the F-TS was significantly lower in RE (6.4 ± 6.3) than in NERD (9.1 ± 7.9, $p = 0.0217$). Symptomatic improvement rates were also significantly higher in RE ($50.3 \pm 44.9\%$) than in NERD ($31.7 \pm 43.2\%$) from the first day of treatment ($p<0.0001$). The symptomatic improvement rates in RE were significant increased from the second day of treatment until after 28 days of treatment (second day: $62.6 \pm 40.6\%$, $p = 0.0006$), however, these in NERD were significant increased from third days until after 28 days of treatment (third day: $41.8 \pm 40.2\%$, $p = 0.0002$) (Fig. 3).

Table 1. Patients characteristics

		RE (*n* = 57)	NERD (*n* = 90)	*p* value
	N	0	55	
	M	0	35	
Endoscopy Findings (2nd modified	A	23	0	
Los Angeles classification)	B	26	0	
	C	7	0	
	D	1	0	
Age		63.9 ± 16.3	66.6 ± 13.9	0.7979
Gender (Male/Female)		35/22	40/50	0.0622
Height (cm)		155.4 ± 9.6	158.3 ± 10.8	0.1222
Weight (kg)		55.5 ± 10.5	56.5 ± 10.4	0.3942
BMI (kg/m^2)		22.9 ± 3.6	22.5 ± 3.2	0.5727
Current Smoking (%)		14.6	17.5	0.7866
Current Drinking (%)		29.3	33.3	0.826

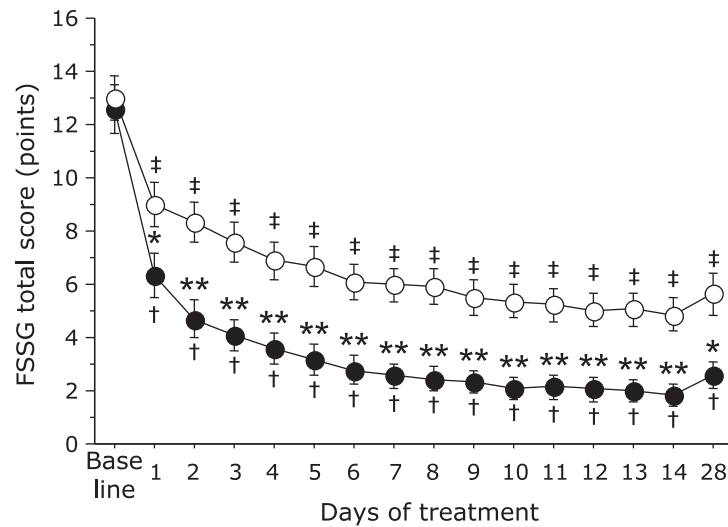RE: reflux esophagitis, NERD: non-erosive reflux disease.

Fig. 2. Comparison of F-TS (Total Score) between RE and NERD. A significant decrease was seen in the FSSG in both RE (closed circle -●-) and NERD (opened circle -○-) from the first day of treatment. From the first day of treatment until after 28 days of treatment, the FSSG was significantly lower in RE than in NERD. *$p<0.05$ RE vs NERD. **$p<0.001$ RE vs NERD. †$p<0.05$ vs F-TS at baseline: RE. ‡$p<0.05$ vs F-TS at baseline: NERD.
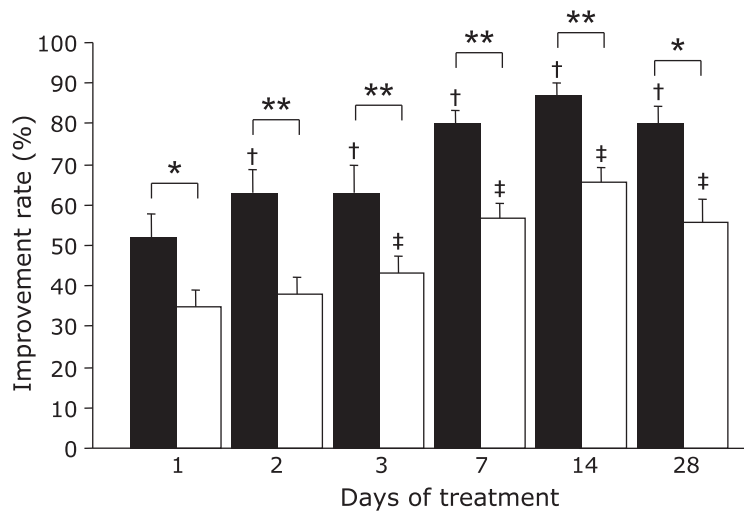

Fig. 3. Improvement Rates of F-TS between RE (black bar) and NERD (white bar). The symptomatic improvement rates in RE were significant increased from the second day until after 28 days of treatment, however, these in NERD were significant increased from third day until after 28 days of treatment. *$p<0.05$ RE vs NERD. **$p<0.001$ RE vs NERD. †$p<0.05$ vs improvement rate on Day 1 in RE. ‡$p<0.05$ vs improvement rate on Day 1 in NERD.
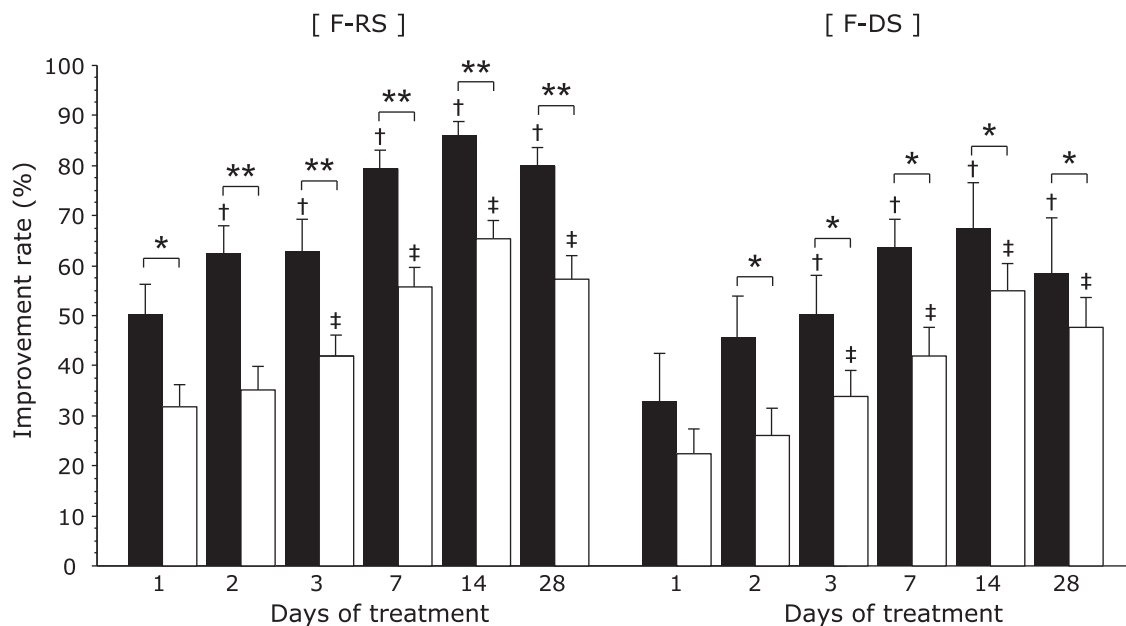
Fig. 4. Improvement Rates of F-RS (left side) and F-DS (right side) according to RE (black bar) and NERD (white bar). The symptomatic improvement rates of F-RS in RE were significant increased from the second day until after 28 days of treatment, however, these in NERD were significant increased from third days until after 28 days of treatment. The symptomatic improvement rates of F-DS in RE and NERD were significant increased from the third day until after 28 days of treatment. *$p<0.05$ RE vs NERD. **$p<0.001$ RE vs NERD. †$p<0.05$ vs improvement rate on Day 1 in RE. ‡$p<0.05$ vs improvement rate on Day 1 in NERD.

Table 2. Prediction of PPI response from early symptom improvement within 1 week according to RE and NERD

		RE		NERD	
		Odds (95% CI)	p value	Odds (95% CI)	p value
Symptom Improvement Rates	On day 1	0.990 (0.957–1.024)	0.575	0.996 (0.971–1.021)	0.743
	On day 2	0.978 (0.934–1.024)	0.337	0.995 (0.970–1.022)	0.73
	On day 3	1.066 (1.000–1.135)	0.049	1.000 (0.984–1.015)	0.967
	On day 7	1.137 (1.020–1.267)	0.021	1.052 (1.022–1.084)	0.001

RE: reflux esophagitis, NERD: non-erosive reflux disease, CI: confidence intervals.

Improvement rates of F-RS and F-DS according to RE and NERD. As shown in Fig. 4, the symptomatic improvement rates of F-RS in RE (55.1 ± 44.1) were significant higher than in NERD (36.9 ± 62.2) from first day of treatment ($p = 0.0201$). These in RE were significant increased from the second day until after 28 days of treatment (67.2 ± 41.0, $p = 0.0010$), however, these in NERD were significant increased from third days until after 28 days of treatment (42.4 ± 91.8, $p = 0.0043$). The symptomatic improvement rates of F-DS in RE and NERD were no significant difference on first day, these in RE (45.5 ± 54.2) were significant higher than in NERD (26.1 ± 49.8) from second day of treatment ($p = 0.0308$). The symptomatic improvement rates of F-DS in RE (50.2 ± 50.2, $p = 0.0143$) and NERD (33.8 ± 47.6, $p = 0.0046$) were significant increased from the third day until after 28 days of treatment.

Prediction of PPI response from early symptom improvement within 1 week according to RE and NERD. A multiple logistic regression analysis was performed to determine the improvement rates of F-TS on day 1, 2, 3 and 7 after treatment associated with PPI responder (complete symptom resolution) (Table 2). In RE, the improvement rates on day 3 (odds ratio: 1.066, 95% CI: 1.000–1.135, $p = 0.049$) and day 7 (odds ratio: 1.137, 95% CI: 1.020–1.267, $p = 0.021$) were associated with significantly increased likelihood of PPI responder. However, in NERD, only improvement rates on day 7 (odds ratio: 1.052, 95% CI: 1.022–1.084, $p = 0.001$) was associated with significantly increased likelihood of PPI responder.

Discussion

From the report by Fujiwara *et al.*,[1] we know that the incidence of GERD has risen markedly in Japan from 1990 until now. Reasons for this trend include the Westernization of the Japanese diet, increased gastric acid secretion in the Japanese population,[13] reduced prevalence of *H. pylori* infection,[14] and increased obesity associated with Westernized eating habits.[15] A global consensus has been reached that it is important to improve GERD-related symptoms with inhibitors of gastric acid secretion such as PPIs, thereby reversing impairment of Quality of life by GERD.[16] The therapeutic effect of PPIs is weaker for NERD than for RE, and some cases are refractory to PPI treatment.[4] In western studies, PPI efficacy in NERD is lower than in RE at 4 and 8 weeks.[17] We demonstrated a significantly higher PPI therapeutic effect in RE than in NERD. Daily efficacy assessments revealed significant symptomatic improvement in both RE and NERD from the first day of treatment, with significantly greater improvement in RE than in NERD from the first day. The symptomatic improvement rates in RE were significant increased from the second day of

treatment until after 28 days of treatment (second day: 62.6 ± 40.6%, $p = 0.0006$), however, these in NERD were significant increased from third days until after 28 days of treatment (third day: 41.8 ± 40.2%, $p = 0.0002$). (Fig. 3)

About improvement effect with PPI, RE was prompt and NERD was gradual. To clarify this reason, we examined F-TS separately for F-RS as reflux symptoms and F-DS as dysmotility symptoms. About the improvement of F-RS, in RE was prompt and in NERD was gradual. As for the improvement of F-DS, both in RE and in NERD were gradual. Acid reflux-related symptoms improve or disappear relatively quickly in response to suppressors of gastric acid secretion, whereas improvement in dysmotility symptoms is more gradual.[18] Dysmotility symptoms are stronger in functional heartburn, considered unresponsive to PPIs,[4] than in NERD with abnormal acid reflux.[19] GERD symptom is common in patients with pulmonary disease and PPI was limited efficacy for improvement of respiratory symptoms in chronic obstructive pulmonary disease (COPD) patients with GERD.[20] The COPD patients had more dysmotilityrelated symptoms than disease control patients.[21] The resolution rate for heartburn symptoms with PPI treatment is lower in the presence of multiple dysmotility symptoms.[22] The improvement of dysmotility symptoms is a key factor for PPI response in RE and NERD.[23] Doubling the PPI dosage had been reported to increase the cure rate by 6% in patients with RE,[24] and increase the symptomatic improvement rate by 22–26% in patients with NERD,[25] suggesting that the responsiveness to suppression of gastric acid secretion is actually higher in NERD than RE. In patients with NERD, the symptomatic response rate after 28 days of PPI therapy correlates with the degree of gastroesophageal acid reflux, and is low in patients with minimal acid reflux.[26] These reports reinforce the sensitivity of NERD to gastric acid.

If it were possible to predict the therapeutic effect of PPIs after 28 days of treatment, particularly in the early days of treatment, new treatment strategies could be devised, prompting a number of clinicians to investigate predictors of treatment response to PPIs. In patients with NERD, the symptom resolution rate after 7 days of treatment is reported to correlate with the symptom resolution rate after 28 days of treatment.[5] For RE, the symptom resolution rate on the first day of treatment correlates with the symptomatic improvement rate after 28 days of treatment.[6] A rapid onset of effect is therefore reflected in the efficacy after 28 days of treatment, more so with RE than with NERD.

We investigated the therapeutic effect over time of a PPI in the treatment of RE and NERD, when the therapeutic effect should be evaluated, and when the therapeutic effect can be predicted. As for results of Prediction of PPI response form early symptom improvement within 1 week, it was able to predict PPI response from the symptom improvement rate on 3 days in RE. It was more slowly in NERD that the symptom improvement rate on 7 days was able to predict PPI response.

Our result and the western studies were similar on the effect predictable day in NERD. However, the effect predictable day in RE by our studies was slower than by the western studies.

We think that this reason is a senior citizen whose majority of our person who is being studied are 65 years old or more. As for this reason, we think that the most patients in our study were elderly and more than 65 years old were 62%. It is considered to be one reason that the most patients in our study were Low Grade RE: Grade A and B according to LA classification, 86.0% (49/97). Low grade RE was associated with endoscopic positive RE patients who do not complain of symptoms.[27] In our study, the rate of Low Grade RE who had less complained of symptoms was high, a result, there is the effect predictable day in RE was slowed. In the examination of the efficacy of PPIs in the treatment of GERD, "daily" surveys of symptoms are extremely important in predicting the response after 28 days of treatment. In particular in patients with NERD, where the overall therapeutic effect is low, PPI efficacy after 28 days on treatment can be predicted from the day 7 response for NERD, but from the day 3 response for RE. The rapid response to PPI is an important of PPI efficacy after 28 days in Japanese GERD patients.

Acknowledgments

Conflict of Interest

No potential conflicts of interest were disclosed.

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