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GASTROENTEROLOGY

Frequency scale for symptoms of gastroesophageal reflux disease predicts the need for addition of prokinetics to proton pump inhibitor therapy

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Key words
Frequency scale for the symptoms of GERD (FSSG) questionnaire, gastroesophageal reflux disease, proton pump inhibitor therapy, prokinetics.

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Abstract

Background and Aim: Proton pump inhibitor (PPI) monotherapy cannot cure all cases of gastroesophageal reflux disease (GERD), and combination therapy with prokinetics and PPI achieves symptomatic improvement for some GERD patients. Few studies have been performed to predict the need for prokinetics.

Methods: Subjects were 163 patients (64 male, mean age 53.1 ± 16.6 years) with GERD symptoms. They were evaluated using the frequency scale for the symptoms of GERD (FSSG), a GERD-specific questionnaire developed in Japan[1] and endoscopy. They were administered with rabeprazole 10 mg daily. At 12 and 24 weeks of treatment, subjects were offered a choice of four treatment regimens according to their degree of satisfaction (1, no need for further treatment; 2, opt for continued PPI treatment; 3, step-down to H2RA; 4, dissatisfied with present treatment, so opt for combination treatment with prokinetics, mosapride 5 mg tid).

Results: The choice of treatment after 12 weeks of treatment placed 79.1% of subjects in the satisfied group (1, 21; 2, 98; 3, 10). After 24 weeks, 98.2% of subjects were in the satisfied group. Pretreatment FSSG scores were significantly higher in the dissatisfied group (4, 17.4 ± 1.4) than in the satisfied group (1, 12.3 ± 1.3; 2, 12.8 ± 0.8; 3, 10.2 ± 1.8) ($P < 0.05$).

Conclusions: The satisfaction rate with these treatment regimens was 98.2% at 24 weeks, suggesting that combination therapy with prokinetics was effective for patients dissatisfied with PPI monotherapy. The FSSG is a useful predictor of the necessity for combination therapy.

Introduction

Proton pump inhibitor (PPI) monotherapy cannot completely resolve symptoms in all cases of gastroesophageal reflux disease (GERD), and combination therapy with prokinetics and PPIs will further improve symptoms for some GERD patients. Few studies have been performed to predict the need for prokinetics. Recently, the frequency scale for the symptoms of GERD (FSSG), a GERD-specific questionnaire developed in Japan[1] has been used for screening GERD patients. The FSSG questionnaire comprises 12 questions concerning not only acid-related symptoms, but also dyspeptic (dysmotility) symptoms[1,2] (Fig. 1). Using the FSSG questionnaire, we retrospectively investigated whether pretreatment FSSG scores can be used to predict the need for prokinetics.

Patients and methods

The subjects of this study were 163 GERD patients (64 male, mean age 53.1 ± 16.6 years). Subjects were excluded if they were pregnant, or had a history of gastric surgery, eradication of *Helicobacter pylori* (*H. pylori*), or upper gastrointestinal diseases such as gastric cancer or peptic ulcers. Subjects had initially presented to the Department of General Internal Medicine of the Prefectural Hiroshima Hospital complaining of reflux symptoms (heartburn and/or reflux) at least twice weekly. At the time of the initial screening examination, a full medical history was taken and a complete physical examination performed. Blood samples were also taken for measurement of anti-*H. pylori* antibodies (IgG) at enrollment. All 163 subjects completed the FSSG questionnaire and underwent upper gastrointestinal endoscopy. Endoscopic findings were graded using the Los Angeles (LA) classification,[3] with mucosal breaks classified as erosive GERD of LA grades A–D. Patients with findings not meeting the definition of mucosal breaks in the LA classification, such as those who had prominent erythema without clear demarcation or whitish cloudiness of the lower esophageal mucosa obscuring the longitudinal blood vessels, were classified as having nonerosive GERD.[4]

FSSG questionnaire

DATE :

NAME (ID;) AGE GENDER M • F

*** Do you have any of following symptoms?**
If so, please circle the appropriate response below.

	Question	Fill-in space				
		NEVER	OCCA-SIONALLY	SOME-TIMES	OFTEN	ALWAYS
1	Do you get heartburn?	0	1	2	3	4
2	Does your stomach get bloated?	0	1	2	3	4
3	Does your stomach ever feel heavy after meals?	0	1	2	3	4
4	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
5	Do you ever feel sick after meals?	0	1	2	3	4
6	Do you get heartburn after meals?	0	1	2	3	4
7	Do you have an unusual (e.g. burning)sensation in your throat?	0	1	2	3	4
8	Do you feel full while eating meals?	0	1	2	3	4
9	Do some things get stuck when you swallow?	0	1	2	3	4
10	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
11	Do you burp a lot?	0	1	2	3	4
12	Do you get heartburn if you bend over?	0	1	2	3	4

TOTAL POINT

Please describe any other symptoms you experience.

SUM POINTS ☐ + ☐ + ☐ + ☐ = ☐

Acid reflux related symptom = ☐ POINTS

Dyspeptic (Dysmotility) symptom = ☐ POINTS

Figure 1 Frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) questionnaire.

Table 1 Profile of 163 GERD subjects

Age (year)	53.1 ± 16.6
Gender (M/F)	64/99
BMI (kg/m^2)	23.0 ± 0.3
Symptoms (typical/atypical)	44/119
Endoscopic findings (grade A–D/no erosion)	52/111
Helicobacter pylori infection rate (%)	26.8
Tobacco (%)	23.3
Alcohol (%)	44.2
Symptomatic constipation (%)	29.4
Cotherapy with Ca antagonist (%)	16.0

BMI, body mass index.

Profile of GERD patients

Background factors including body mass index (BMI), endoscopic findings (erosive or not erosive), *H. pylori* infection, tobacco, alcohol, symptomatic constipation, cotherapy with Ca antagonist, and pre-FSSG scores, were examined in all 163 enrolled subjects (Table 1). Constipation was defined in this study as passing stools less than three times a week. Smoking was defined as current smoking, and ex-smokers were excluded from this study. Alcohol consumption was defined as drinking more than two days a week.

Upper gastrointestinal endoscopy

Erosive GERD was diagnosed in 52 cases (31.9%), and nonerosive reflux disease (NERD) in 111 cases (68.1%). For the 52 cases of erosive GERD, the endoscopic findings according to the LA classification were A in 36 cases (69.2%), B in seven (13.5%), C in seven (13.5%), and D in two (3.8%).

Protocol

All 163 patients were administered a PPI (rabeprazole 10 mg/day) for 12 weeks (Fig. 2). After the initial PPI monotherapy, subjects completed the FSSG questionnaire again and evaluated their residual gastrointestinal symptoms themselves. We provided information about the medications for gastrointestinal symptoms to each subject as follows: 'Acid-suppressive medicines such as PPIs and H2 blockers suppress acid secretion, and prokinetics promote gastrointestinal motility.' Subjects were provided with a sheet displaying a choice of four treatment regimens according to their degree of satisfaction (1, satisfied group, no need for further treatment; 2, opt for continued PPI treatment; 3, step-down from PPI to H2RA; 4, dissatisfied with present treatment, so opt for combination treatment with prokinetics, additional of mosapride citrate 5 mg tid). Mosapride citrate, a selective 5-HT$_4$ receptor agonist,

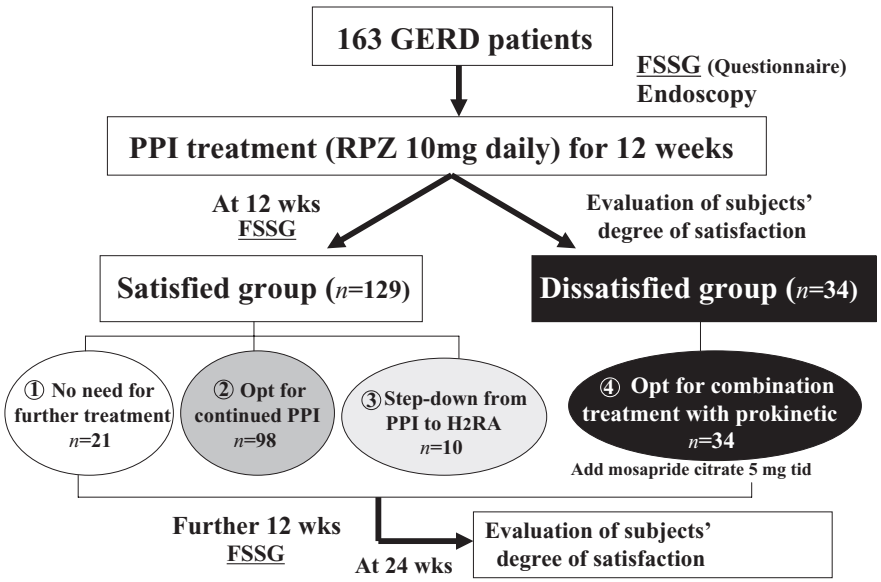

Figure 2 Study protocol.

stimulates upper gastrointestinal motor activity, and is free of dopamine D2 receptor antagonist properties.[5]

Subjects continued with the treatment of their choice for a further 12 weeks, following which they were again offered the same four choices according to their degree of satisfaction. GERD subjects' choice of treatment (at 12 and 24 weeks) and GERD subjects' satisfaction (at 12 and 24 weeks) were evaluated. The pre-FSSG score was compared between the four treatment regimens according to the degree of satisfaction at 12 weeks. Univariate analysis was performed for background factors (age, gender, BMI, endoscopic findings [erosive or not erosive], *H. pylori* infection, tobacco, alcohol, symptomatic constipation, combination therapy with Ca antagonist, and pretreatment FSSG score) prior to PPI treatment as predictors of the choice of treatment made by subjects at 12 weeks. All subjects gave written informed consent.

Statistical analysis

Data are presented as mean ± SD. Fisher's protected least significant difference (PLSD) test was used for comparisons of pretreatment FSSG scores between treatment regimens. *P*-values of less than 0.05 were considered significant. Odds ratios (OR) with confidence intervals (95% CI) were compared for risk factors of refractoriness to PPI monotherapy. Statistical analysis was performed using STATVIEW version 5.0J (SAS Institute Japan, Tokyo, Japan).

Results

1. Choice of GERD treatment at 12 and 24 weeks (Fig. 3)

The choice of GERD treatment at 12 weeks was as follows: 1, satisfied group, 21 subjects (12.9%); 2, 98 subjects (60.1%); 3, 10 subjects (6.1%); 4, dissatisfied group, 34 subjects (20.9%). The choice of GERD treatment at 24 weeks was as follows: 1, 50 subjects (30.7%); 2, 52 subjects (31.9%); 3, 34 subjects (20.9%); 4, 27 subjects (16.6%).

2. GERD patient satisfaction at 12 and 24 weeks

With the treatment regimens used, 79.1% (129/163) of subjects at 12 weeks and 98.2% (160/163) of subjects at 24 weeks were in the satisfied group.

3. Comparison of pretreatment FSSG score across treatment regimens at 12 weeks (Fig. 4)

Pretreatment FSSG scores were significantly higher in the dissatisfied group (4, 17.4 ± 1.4) than in the satisfied group (1, 12.3 ± 1.3; 2, 12.8 ± 0.8; 3, 10.2 ± 1.8) at 12 weeks ($P < 0.05$).

4. Univariate analysis of refractory factors in PPI monotherapy (Table 2)

Predictive factors for disease refractory to PPI monotherapy were the pretreatment FSSG score (OR 1.15, 95% CI: 1.03–1.28, $P = 0.007$), male gender (OR 0.12, 0.02–0.56, $P = 0.007$), BMI (OR 0.74, 0.60–0.91, $P = 0.005$), alcohol (OR 0.13, 0.03–0.63, $P = 0.011$), and symptomatic constipation (OR 21.6, 2.41–193.76, $P = 0.006$) in univariate analysis.

Discussion

This study is the first to demonstrate that the FSSG (GERD-specific questionnaire) is useful to predict prior to treatment the necessity for the addition of prokinetics to PPI therapy. A high pretreatment FSSG score may be a refractory factor for PPI monotherapy.

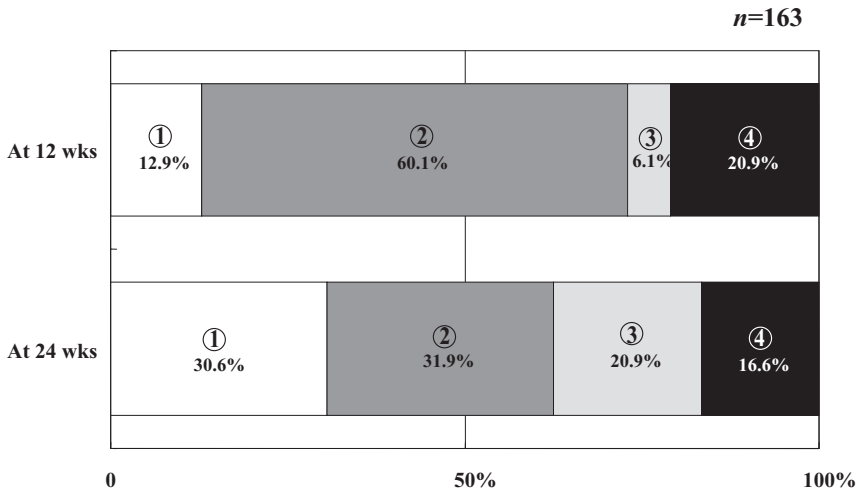

Figure 3 Choice of gastroesophageal reflux disease treatment at 12 weeks and 24 weeks. (1), No need for further treatment; (2), opt for continued PPI; (3), step-down from PPI to H2RA; (4), combination treatment with prokinetics.

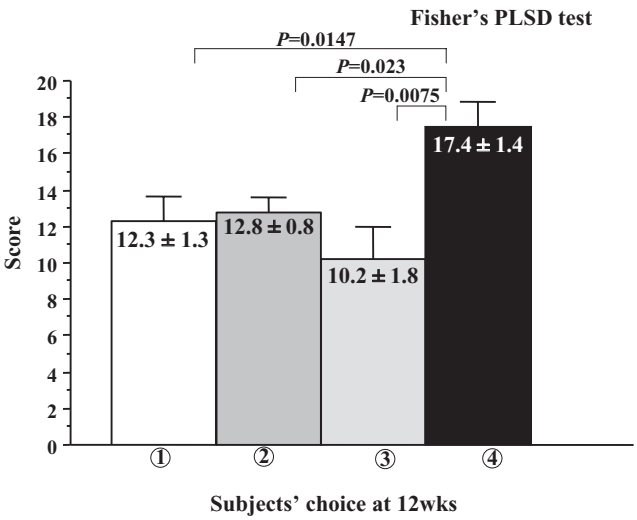

Figure 4 Comparison of pretreatment frequency of scale for the symptoms of gastroesophageal reflux disease (FSSG) scores. (1), No need for further treatment ($n = 21$); (2), opt for continued PPI ($n = 98$); (3), step-down from PPI to H2RA ($n = 10$); (4), opt for combination treatment with prokinetic ($n = 34$).

Table 2 Univariate analysis of predictive factors for the dissatisfied group

Factor	Odds ratio	95% CI	*P*-value
Age	1.011	0.97–1.06	0.603
Gender (M)	0.12	0.02–0.56	0.007*
BMI	0.74	0.60–0.91	0.005*
Endoscopic findings (no erosions)	0.82	0.37–1.83	0.636
Helicobacter pylori infection (negative)	1.87	0.29–12.0	0.511
Tobacco	1.55	0.16–15.1	0.705
Alcohol	0.13	0.03–0.63	0.011*
Symptomatic constipation	21.6	2.41–193.8	0.006*
Cotherapy with Ca antagonist	0.53	0.08–3.45	0.510
Pretreatment FSSG score	1.15	1.03–1.28	0.007*

BMI, body mass index; CI, confidential interval; FSSG, frequency scale for symptoms of gastroesophageal reflux disease.

Of the upper gastrointestinal diseases, GERD is an acid-related disease that remarkably reduces quality of life (QOL).[6] Undoubtedly, a PPI is the first choice regimen for GERD patients.[7] Reflux symptoms such as heartburn and reflux are generally regarded as typical symptoms of GERD, although it has been reported that other dyspeptic symptoms are also common in patients with GERD.[8] In some cases, combination therapy with a prokinetic is needed. There are several reports describing the efficacy of prokinetics in reflux disease. Vigneri *et al*. reported that cisapride (prokinetic agent, 5-HT_4 receptor agonist) has a synergistic effect with PPIs in maintenance therapy for reflux esophagitis.[9] In the USA and Japan, cisapride was withdrawn in 2000 due to an increased risk of cardiological events (severe cardiac arrhythmia) (http://www.fda.gov/bbs/topics/ANSWERS/ANS01007.htm/). As a replacement for cisapride, mosapride (prokinetic agent, 5-HT_4 receptor agonist) was developed for the symptomatic treatment of patients suffering various gastrointestinal disturbances.[10] Mosapride decreases the reflux of acid into the esophagus in patients with GERD.[10,11] Madan *et al*. reported that the addition of mosapride is more effective than pantoprazole alone in providing symptomatic relief to patients with erosive GERD, but offers no benefit over pantoprazole alone in NERD.[12] It has, however, been difficult until now to identify GERD patients who will benefit from the addition of a prokinetic to PPI therapy prior to treatment.

Recently, GERD symptom questionnaires such as the QUEST questionnaires,[13] the Gastrointestinal Symptom Rating Scale (GSRS),[14] and the Medical Outcomes Study Short Form-36 health survey (SF36)[15] have come into use for screening GERD and assessing treatment response. Stanghellini *et al*. stated that an ideal GERD symptom questionnaire should possess the following characteristics: sensitivity to patients with GERD; coverage of the frequency and intensity of typical and atypical GERD symptoms; multidimensionality (cover all symptom dimensions); and usefulness in assessing changes during and after therapy.[16] In this study, we used the FSSG questionnaire to evaluate GERD patients' reflux symptoms. The FSSG questionnaire is a GERD-specific question-

naire produced by Kusano *et al*. and developed in Japan.[1] They conducted a survey of the actual symptoms of Japanese GERD patients. A total of 124 patients with an endoscopic diagnosis of GERD completed a 50-part questionnaire (requiring only 'yes' or 'no' answers) that covered various symptoms related the upper gastrointestinal tract.[1] They extracted the 12 questions to which patients most often answered 'yes', and produced a multiple-choice questionnaire grading the frequency of each symptom (never = 0, occasionally = 1, sometimes = 2, often = 3, always = 4), called the frequency scales for symptoms of GERD (FSSG). The FSSG questionnaire comprises 12 questions that cover not only acid symptoms but also dyspeptic (dysmotility) symptoms.[1,2] The FSSG provides useful assistance for making the initial diagnosis of GERD, and also allows quantitative assessment of the effects of treatment and changes in symptoms over time.[1] In this study, using the system of subjects selecting their own medication themselves, the degree of satisfaction was 98.2% at 24 weeks, suggesting that combination therapy with prokinetics was effective in the group dissatisfied with PPI monotherapy.

In the present study, we also evaluated refractory factors for PPI monotherapy. A high pretreatment FSSG score, female gender, low BMI, low alcohol consumption, and symptomatic constipation are regarded as refractory factors for PPI monotherapy. The odds ratio was highest in patients with symptomatic constipation. Lin *et al*. reported that many GERD patients also suffer from constipation,[17] indicating that they may have reduced motility of the entire gastrointestinal tract. Symptomatic constipation may be a risk factor not only for the occurrence of GERD, but also a refractory factor for PPI monotherapy. In Japan, three PPIs (rabeprazole [RPZ] 10 mg, omeprazole [OPZ] 20 mg, and lansoprazole [LPZ] 30 mg) are covered by the medical insurance system for initial therapy of reflux esophagitis. Saitoh *et al*. reported that RPZ (10 mg/day) showed a faster onset of raising intragastric pH and a stronger inhibition of gastric acid secretion than did LPZ (30 mg/day) or OPZ (20 mg/day) in *H. pylori*–negative CYP2C19 extensive metabolizers.[18] Thjodleifsson *et al*. investigated preventing relapses of erosive or ulcerative GERD at 52 weeks. They concluded that RPZ 10 mg is therapeutically equivalent to RPZ 20 mg or OPZ 20 mg[19] We used RPZ 10 mg daily as the initial therapy for GERD in this study. Compared with people in Western countries, gastric acid secretion in Japanese people is estimated to be low.[20–22] Japanese physicians usually add further medication to the standard dose of a PPI (e.g. RPZ 10 mg/day) instead of doubling the dose of the PPI (e.g. RPZ 20 mg/day) for cases refractory to PPI monotherapy. Adding a new medication such as a prokinetic agent to the standard dose of PPI is more cost-effective than doubling the dose of the PPI under the Japanese medical insurance system. In this study, we used the standard dosages employed by Japanese primary care physicians for patients with GERD.

PPIs are unstable at a low pH. Retention of PPIs inside the stomach for a long time may result in an impaired acid suppressive effect,[23] so rapid transit of the PPI to the upper intestine will be of benefit. Takeuchi *et al*. reported that pharmacokinetic parameters including the mean peak concentration (C_{max}) and the area under the time-concentration curve 4 h of dosing (AUC_4) of the PPI omeprazole were significantly increased, and the time to reach C_{max} (T_{max}) significantly faster, with the addition of mosapride citrate. They concluded that mosapride citrate, a serotonin 5-HT_4 selective agonist, beneficially affects the pharmacokinetics of omeprazole by accelerating gastric emptying.[23] In this study, cases refractory to PPI monotherapy showed significant improvement not only in dyspeptic (dysmotility) scores (DS) but also in acid reflux scores (RS) by addition of a prokinetic agent to the PPI (RS: related to acid reflux symptoms such as heartburn and acid reflux, questions 1, 4, 6, 7, 9, 10, and 12 in Fig. 1; and DS: related to dyspeptic symptoms such as stomach heaviness and abdominal distension, questions 2, 3, 5, 8, and 11 in Fig. 1) (Fig. 5). The prokinetic agent mosapride may have contributed to not only improved gastrointestinal motility but also the improved pharmacokinetics of the PPI rabeprazole. Some GERD patients refractory to PPI monotherapy have dyspeptic (dysmotility) symptoms. Most of them respond to the addition of a prokinetic agent. The FSSG is useful for detecting not only reflux symptoms such as heartburn and/or reflux, but also dyspeptic (dysmotility) symptoms such as stomach heaviness and/or abdominal distension. The FSSG questionnaire can be used to predict the need for the addition of a prokinetic agent to PPI therapy prior to treatment.

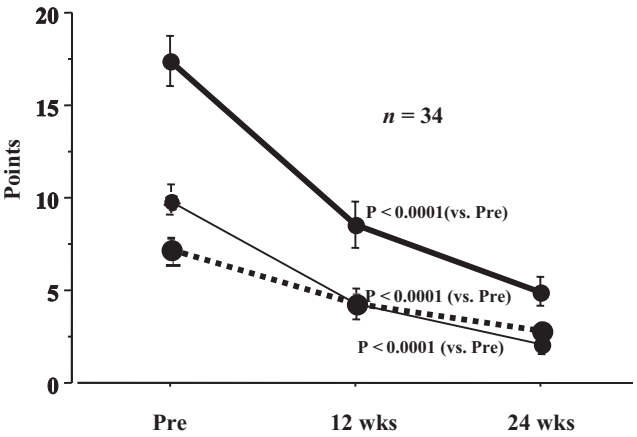

Figure 5 Effects of additional prokinetics in cases refractory to proton pump inhibitor monotherapy: Change of frequency scale for symptoms of gastroesophageal reflux disease (FSSG) score. (DS, dyspeptic score; RS, reflux score; TS, total score.) (▬), F total score (TS), $p = 0.0002$ (vs. Pre), 0.0002 (vs. 3M); (—), RS, $p = 0.0002$ (vs. Pre), 0.0003 (vs. 3M); (▪▪▪▪), DS, $p = 0.0002$ (vs. Pre), 0.0009 (vs. 3M).

Conclusions

The degree of satisfaction with our treatment regimens was 98.2% at 24 weeks, suggesting that combination therapy with prokinetics was effective in the group unsatisfied with PPI monotherapy. The FSSG predicted the need for the addition of prokinetics to PPI therapy.

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