Scoring of reflux symptoms associated with scleroderma and the usefulness of rabeprazole

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ABSTRACT

Objective. *The high frequency of gastroesophageal reflux disease (GERD) as a complication of scleroderma (systemic sclerosis, SSc) calls for treatment with powerful acid suppressants such as proton pump inhibitors (PPI). The present study used a GERD-specific questionnaire to assess the symptoms of GERD in SSc patients, and examine the effectiveness of rabeprazole (RPZ) for treating the symptoms of GERD.*

Methods. *The Frequency Scale for the Symptoms of GERD (FSSG), a medical questionnaire developed in Japan for evaluating GERD, and the Visual Analogue Scale (VAS) were used to evaluate GERD symptoms and the degree of pain, respectively, in 151 SSc subjects. These tools were also used to assess the effect of 8 weeks' treatment with the PPI RPZ (10 mg/day).*

Results. *Data on age and gender, and FSSG and VAS scores before treatment and after 4 and 8 weeks' RPZ treatment, were available for 84 subjects. The mean FSSG score was 13.9±9.7 before treatment, 8.3±8.1 after 4 weeks of treatment, and 7.0±7.0 after 8 weeks of treatment; the score reduction was significant ($p<0.001$) indicating the effectiveness of RPZ in improving subjective GERD symptoms. The VAS scores revealed a significant improvement in pain after both 4 and 8 weeks compared with baseline scores. Six subjects experienced adverse effects and five discontinued the analysis during the period.*

Conclusion. *Administration of RPZ 10 mg/day is effective for the* control *of the symptoms of GERD associated with SSc. In addition to assessing the symptoms of GERD, the FSSG questionnaire can be used to evaluate the therapeutic effect of drugs.*

Introduction

Scleroderma, or systemic sclerosis (SSc), is a systemic autoimmune disease that manifests as sclerotic changes in the skin and other organs. The pathology of the disease varies widely, even causing gastrointestinal tract lesions that can occur from the upper to the lower gastrointestinal tract. Among cases with gastrointestinal manifestations of SSc, reflux oesophagitis has been observed in 60 to 90% of patients (1). The extent of scleroderma also varies widely; anti-topoisomerase antibody-positive patients with the severe disease form, diffuse cutaneous SSc (dSSc), display a high incidence of complications including pulmonary fibrosis and other organ lesions, as well as a high rate of reflux oesophagitis. In contrast, in anti-centromere antibody-positive patients with the comparatively mild form of limited cutaneous SSc (lSSc), in which scleroderma is confined to the hands, forearms and face, pulmonary lesions and other organ complications are rare although reflux oesophagitis is an exception, occurring in 50 to 60% of cases. This highlights the need to diagnose and treat reflux oesophagitis even in lSSc cases with mild scleroderma.

In recent years, it has been reported overseas that untreated reflux oesophagitis reduces a patient's quality of life (QOL) even more than angina pectoris (2). Since reflux oesophagitis associated with SSc is extremely difficult to cure, control of the patient's subjective symptoms is the main goal. The characteristic subjective symptoms of reflux oesophagitis include heartburn, difficulty swallowing and abdominal discomfort. However, there are also other symptoms that are difficult for patients to describe adequately in words. This results in many cases where symptoms are not accurately

communicated to the doctor, which can have a large influence on patient QOL. The Frequency Scale for the Symptoms of GERD (FSSG) is a 12-item questionnaire used for evaluating the subjective symptoms of GERD (Table I). An FSSG score of 8 or more indicates a high likelihood of GERD (3). Unlike the previously established questionnaire for the diagnosis of reflux disease, QUEST (4), the FSSG can be used to assess the severity of GERD and the response to treatment. The FSSG score can also be divided into scores for acid reflux symptoms (7 questions) and gastrointestinal dysmotility symptoms (5 questions). This is a report of a study we conducted to assess GERD complications in scleroderma patients using the FSSG medical questionnaire developed in Japan for evaluating GERD, and the Visual Analogue Scale (VAS) for measuring pain. We also assessed the usefulness of the proton pump inhibitor (PPI), rabeprazole (RPZ), for treating the subjective symptoms and pain associated with GERD.

Materials and methods

Subjects

This study was conducted during the course of everyday care from August 2005 to December 2006. Patients were diagnosed with SSc at the Nagoya University School of Medicine, National Hospital Organization Nagoya Medical Center, Social Insurance Chukyo Hospital, Ichinomiya Municipal Hospital and Nagoya Ekisaikai Hospital. Patients had lSSc or dSSc, as defined by LeRoy *et al*. (5), and satisfied the American College of Rheumatology (formerly, the ARA) criteria for the classification of SSc (6). All subjects enrolled in this study had some form of gastrointestinal symptoms (FSSG score >0) for which the attending physicians thought treatment with RPZ would be useful. Patients with a past medical history of hypersensitivity to RPZ, those determined by their treating physician to be unsuitable for this study, those taking test drugs related to another study, and patients with gastrointestinal cancer or mixed connective tissue disease, were excluded from the study. Informed consent was obtained from each subject before study commencement, and this study was conducted in accordance with the Helsinki Declarations of 1975/83.

Dosage regimen and administration period

Subjects received RPZ 10 mg once daily for a period of 8 weeks. Any gastric acid secretion inhibitors (PPI or H_2-receptor antagonist) prescribed prior to commencement of the study were discontinued, and the study began after those subjects were switched to RPZ without a wash-out period. Before the start of the study, none of the subjects had taken RPZ. Concomitant use of mucosal protective agents was allowed.

Assessment

FSSG scores were entered in the questionnaire by the subjects themselves. Scores for FSSG total, acid reflux, and gastrointestinal dysmotility were recorded at the time of each assessment. Mean scores and standard deviations were calculated for each assessment timepoint. The effect of treatment was investigated by comparing the mean baseline scores with those after 4 and 8 weeks' RPZ treatment; scores at 4 weeks' and 8 weeks' treatment were also compared. To evaluate whether RPZ administration was useful for subjects with mild symptoms of GERD as well as those with severe symptoms, separate analyses were conducted for subjects with FSSG scores of 8 or more, and those with scores of less than 8.

The VAS, a rating scale often used for assessing pain, was used to determine the degree of pain caused by GERD in this study. Subjects marked the degree of pain they felt on a 100 mm visual analogue pain scale, with 0 mm indicating no pain and 100 mm indicating strong pain. To assess efficacy with the VAS, the mean scores and standard deviations were calculated for each assessment timepoint, and scores before and after treatment with RPZ were compared. Mean VAS scores at 4 weeks and 8 weeks were also directly compared.

Adverse events

All adverse events that occurred during administration of the drug were recorded in the questionnaire. In addition, details of all events were compiled in a table.

Statistical analysis

Differences between the baseline mean scores and those after 4 and 8 weeks of treatment, and between scores at 4 weeks' and 8 weeks' treatment were tested for statistical significance using a corresponding *t*-test. The level of significance was set at 0.05 either side.

Results

Subject characteristics

If any information on age, gender, and FSSG and VAS scores for any of three timepoints (before treatment, and after 4 weeks and 8 weeks of treatment) was missing for a subject, they were excluded from the analysis. Sixty-two cases were excluded from the analysis due to the absence of data on one or more of the items described above. Although most of the excluded subjects failed to come to the hospital at the proper timing for assessment, the detailed reasons for the absence of data for each case was not recorded. Five subjects discontinued the study due to adverse effects (described below in detail) before the week 4 assessment. Overall, 84 subjects in the study had full data on age and gender, and FSSG and VAS scores for all three timepoints (before treatment, and after 4 weeks and 8 weeks of treatment). Clinical characteristics of all 89 subjects are shown in Table II. Information was obtained from some subjects concerning organ involvement with SSc, according to the Japanese Classification of Severity and Guideline for Treatment (2004) (7, 8), and their data are included in Table II.

FSSG scores before treatment with RPZ

Before treatment with RPZ, the mean total FSSG score was 13.9±9.7, mean acid reflux score (7 questions; question 1, 4, 6, 7, 9, 10, and 12) was 8.2±6.1, and mean dysmotility score (5 questions; question 2, 3, 5, 8, and 11) was 5.6±4.3 (Fig. 1). The scores were high for some individual questions, reaching 1.7±1.4 for question 1 ("Do you get heartburn?"), 1.5±1.5 for question 9 ("Do some things get stuck when

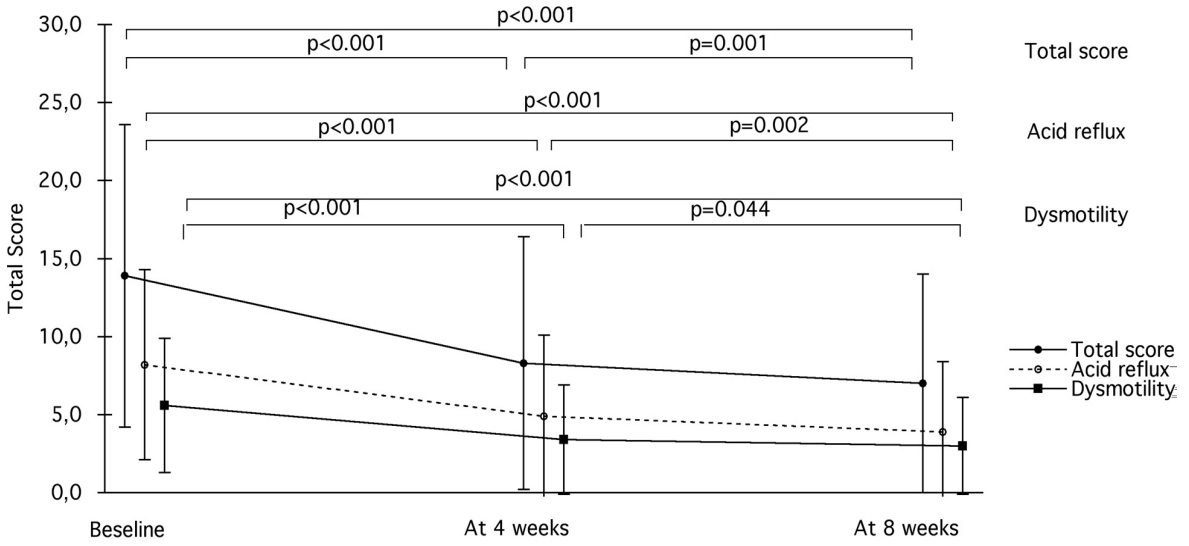

Fig. 1. Changes in FSSG scores after treatment with rabeprazole. Measured scores at each timepoint are expressed as mean ± SD.

Table I. Twelve questions from the FSSG with mean scores for subjects with GERD symptoms associated with scleroderma, at baseline and after 4 and 8 weeks with rabeprazole.

	Question	Baseline score (mean±SD)	Score after 4 weeks' treatment (mean±SD)	Test 1*	Score after 8 weeks' treatment (mean±SD)	Test 2**
1	Do you get heartburn?	1.7 ± 1.4	0.80 ± 1.1	p<0.001	0.69 ± 1.0	p<0.001
2	Does your stomach get bloated?	1.2 ± 1.5	0.82 ± 1.3	p=0.002	0.61 ± 1.0	p<0.001
3	Does your stomach ever feel heavy after meals?	1.4 ± 1.3	0.68 ± 1.0	p<0.001	0.80 ± 1.0	p<0.001
4	Do you sometimes subconsciously rub your chest with your hand?	0.77 ± 1.1	0.39 ± 0.74	p<0.001	0.35 ± 0.75	p<0.001
5	Do you ever feel sick after meals?	0.73 ± 1.3	0.33 ± 0.77	p<0.001	0.27 ± 0.61	p<0.001
6	Do you get heartburn after meals?	1.4 ± 1.5	0.64 ± 1.1	p<0.001	0.44 ± 0.87	p<0.001
7	Do you have an unusual (e.g. burning) sensation in your throat?	1.1 ± 1.5	0.90 ± 1.3	p=0.059	0.65 ± 1.2	p<0.001
8	Do you feel full while eating meals?	0.96 ± 1.4	0.77 ± 1.2	p=0.045	0.58 ± 1.1	p=0.002
9	Do some things get stuck when you swallow?	1.5 ± 1.5	1.1 ± 1.4	p<0.001	0.96 ± 1.3	p<0.001
10	Do you get bitter liquid (acid) coming up into your throat?	1.3 ± 1.3	0.76 ± 1.1	p<0.001	0.56 ± 0.99	p<0.001
11	Do you burp a lot?	1.4 ± 1.3	0.80 ± 1.2	p<0.001	0.75 ± 1.1	p<0.001
12	Do you get heartburn if you bend over?	0.52 ± 1.1	0.32 ± 0.82	p=0.055	0.29 ± 0.82	p=0.051

* Test 1: Applicable *t*-test (Baseline *vs*. 4 weeks).
** Test 2: Applicable *t*-test (Baseline *vs*. 8 weeks).

you swallow?"), and 1.4±1.3, 1.4±1.5, and 1.4±1.3 for question 3, 6, and 11, respectively (Table I). These findings indicate that there is a high incidence of GERD associated with SSc, with a particularly high incidence of heartburn, items becoming stuck when swallowed, belching and other major acid reflux symptoms of GERD.

Change in FSSG score 4 and 8 weeks after switching to treatment with RPZ 10 mg/day

After switching to RPZ, subjects were examined at 4 and 8 weeks and scores compared with baseline values. Total FSSG scores at 4 and 8 weeks were 8.3±8.1 and 7.0±7.0, respectively, compared with 13.9±9.7 before treatment, indicating a significant reduction with treatment (p<0.001 for both comparisons) (Fig. 1). A statistically significant reduction was also observed between 4 and 8 weeks of treatment (p=0.001). Compared with the baseline value (8.2±6.1), the FSSG acid reflux score was significantly reduced at both 4 weeks (4.9±5.2; p<0.001) and 8 weeks (3.9±4.5; p<0.001) of treatment. The reduction in FSSG acid reflux score between 4 weeks and 8 weeks was also statistically significant (p=0.002). Compared with a baseline FSSG dysmotility score of 5.6±4.3, the scores at 4 and 8 weeks were 3.4±3.5 and 3.0±3.1, respectively, indicating a significant reduction (p<0.001 for both comparisons). The difference between the scores at 4 and 8 weeks was also statistically significant (p=0.044).

In the group of 52 subjects with baseline FSSG scores of 8 or more (*i.e.* relatively severe reflux symptoms), the total score before treatment with RPZ was 19.5±8.2. After 4 and 8 weeks of treatment, the mean total scores were significantly reduced to 11.6±8.5 and 9.5±7.5, respectively (p<0.001 for both comparisons) (Fig. 2). The score at 8 weeks was also significantly lower than that at 4 weeks (p<0.001).

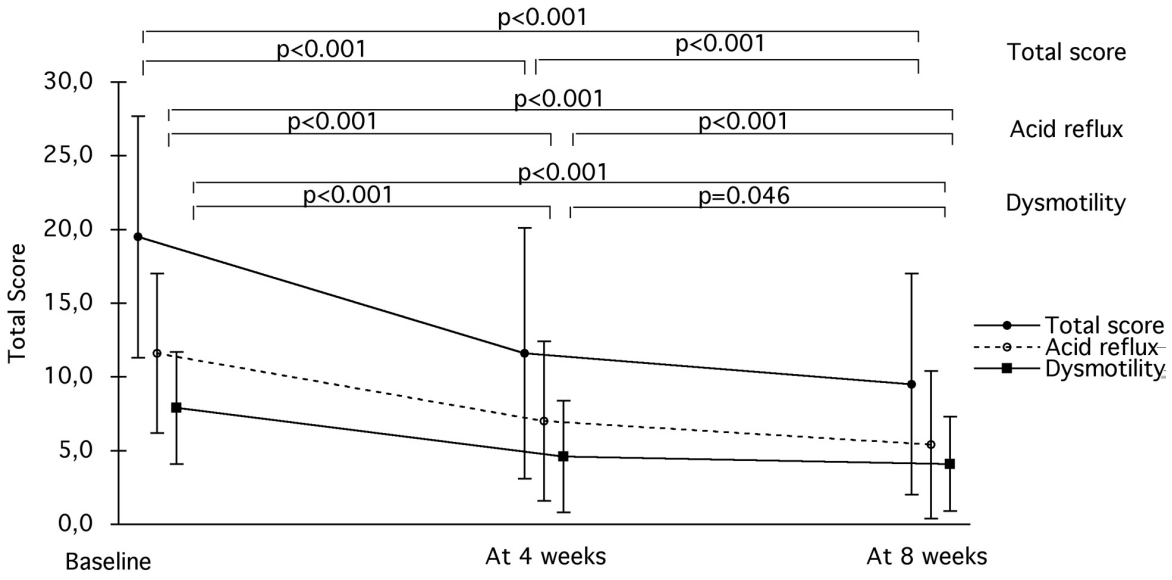

Fig. 2. Changes in FSSG scores for subjects with severe reflux. Data in this figure are derived from 52 subjects with baseline FSSG scores of ≥8. Data are expressed as mean ± SD.

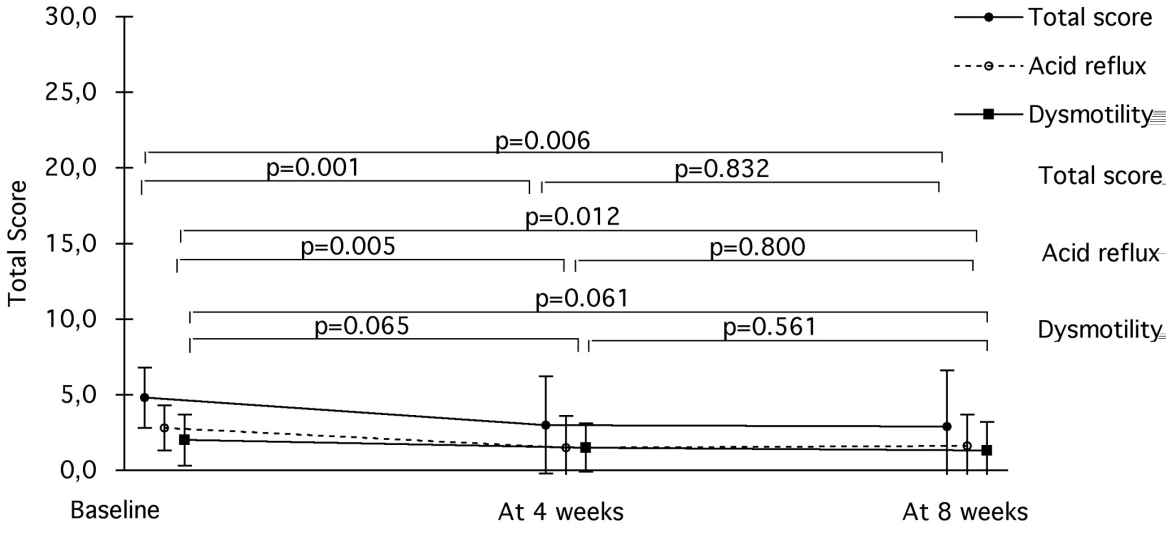

Fig. 3. Changes in FSSG scores for subjects with mild reflux. Data in this figure are derived from 32 subjects with baseline FSSG scores <8. Data are expressed as mean ± SD.

Similarly, the FSSG acid reflux scores were significantly reduced by treatment with RPZ (baseline: 11.6±5.4; 4 weeks: 7.0±5.4; 8 weeks: 5.4±5.0; $p<0.001$ for both comparisons). A significant reduction was also observed when comparing the scores at 4 weeks and 8 weeks ($p<0.001$). The FSSG dysmotility score before treatment with RPZ was 7.9±3.8; the scores at 4 and 8 weeks were significantly lower at 4.6±3.8 and 4.1±3.2, respectively ($p<0.001$ for both comparisons).

The baseline total FSSG score in the group of 32 subjects with baseline FSSG scores lower than 8 (*i.e.* mild reflux symptoms) was 4.8±2.0; total FSSG scores at 4 (3.0±3.2) and 8 weeks (2.9±3.7) were significantly lower than the baseline score ($p=0.001$ and $p=0.006$, respectively) (Fig. 3). Compared with an FSSG acid reflux score before RPZ treatment of 2.8±1.5, the scores at 4 and 8 weeks were 1.5±2.1 ($p=0.005$) and 1.6±2.1 ($p=0.012$), respectively, indicating significant reductions. The mean FSSG dysmotility score before treatment with RPZ was 2.0±1.7; the scores at 4 and 8 weeks decreased to 1.5±1.6 and 1.3±1.9, respectively, but neither change was statistically significant.

Change in individual FSSG question score after treatment with RPZ 10 mg/day

Changes in mean scores for each of the 12 FSSG questions were also assessed (Table I). For question 7 ("Do you have an unusual sensation in your throat?"), the change between baseline score and 4-week score was not statistically significant, but the change between baseline and 8 weeks was significant. For question 12 ("Do you get heartburn if you bend over?"), scores at both 4 and 8 weeks were not statistically significantly reduced, although the baseline score for this question was the lowest (0.52±1.1) of all 12 questions. Mean scores for all other questions improved significantly with treatment (Table II).

Change in VAS score 4 and 8 weeks after switching to treatment with RPZ 10 mg/day

In this study, VAS scores were used to assess the degree of pain caused by GERD. Mean VAS scores at 4 and 8 weeks were 2.9±2.3 and 2.5±2.1,

Table II. Subject baseline characteristics.

Variables	Classification		No. of subjects (%)
Gender	Male		9 (10.1)
	Female		80 (89.9)
Age	Mean age		62 years
	Standard deviation		11.3 years
	Median age		63 years
	Minimum age		24 years
	Maximum age		85 years
Scleroderma disease type	Diffuse		22 (24.7)
	Limited		59 (66.3)
	Difficult to classify or uncertain		8 (9.0)
Habits	Smoking	Yes	6 (6.7)
		No	73 (82.0)
		Uncertain	10 (11.2)
	Coffee	Every day	15 (16.9)
		Sometimes	34 (38.2)
		Never	29 (32.6)
		Uncertain	11 (12.4)
	Alcohol	Every day	61 (68.5)
		Sometimes	12 (13.5)
		Never	5 (5.6)
		Uncertain	11 (12.4)
Severity of organ involvement	Systemic	0	34 (38.2)
		1	11 (12.4)
		2	14 (15.7)
		3	16 (18.0)
		4	6 (6.7)
		unknown	8 (9.0)
	Vasculature	0	25 (28.1)
		1	36 (40.4)
		2	14 (15.7)
		3	6 (6.7)
		4	2 (2.2)
		unknown	6 (6.7)
	Skin	0	9 (10.1)
		1	45 (50.6)
		2	19 (21.3)
		3	8 (9.0)
		4	4 (4.5)
		unknown	4 (4.5)
	Joints	0	46 (51.7)
		1	15 (16.9)
		2	9 (10.1)
		3	5 (5.6)
		4	2 (2.2)
		unknown	12 (13.5)
	Upper digestive tract	0	0 (0)
		1	37 (41.6)
		2	29 (32.6)
		3	9 (10.1)
		4	3 (3.4)
		unknown	11 (12.4)
	Lower digestive tract	0	52 (58.4)
		1	10 (11.2)
		2	8 (9.0)
		3	5 (5.6)
		4	1 (1.1)
		unknown	14 (15.7)
	Interstitial pneumonia	0	42 (47.2)
		1	19 (21.3)
		2	12 (13.5)
		3	2 (2.2)
		4	1 (1.1)
		unknown	13 (14.6)
	Pulmonary hypertension	0	40 (44.9)
		1	3 (3.4)
		2	1 (1.1)
		3	0 (0)
		4	0 (0)
		unknown	45 (50.6)
	Cardiac	0	69 (77.5)
		1	5 (5.6)
		2	5 (5.6)
		3	0 (0)
		4	0 (0)
		unknown	10 (11.2)
	Renal	0	76 (85.4)
		1	3 (3.4)
		2	0 (0)
		3	0 (0)
		4	0 (0)
		unknown	14 (15.7)

respectively, compared with a baseline mean score of 4.4±2.4; the post-treatment scores were both significantly lower than baseline (p<0.001 for both comparisons). A significant improvement was also observed between the 4-week and 8-week mean scores (p<0.001) (Fig. 4).

Correlation between acid reflux score and the dysmotility score

To test for correlation between acid reflux scores and dysmotility scores in SSc subjects, correlation coefficients were calculated using Pearson's correlation test. The two parameters displayed significant correlation at all assessment timepoints – baseline (r=0.749), after 4 weeks of RPZ treatment (r=0.748) and after 8 weeks of RPZ treatment (r=0.698) (p<0.001 for all) (data not shown).

Adverse events

A total of 6 adverse events were reported by 6 subjects during the study period (Table III). The reported adverse events were diarrhea, abdominal fullness, flatulence, nausea, hepatic dysfunction and exacerbated mouth ulcers. The case of diarrhea was bearable and did not interfere with regular activities. Hepatic function was only minimally disturbed (ALT/AST/γGTP=30/33/81 U/L). All adverse effects resolved spontaneously or with cessation of RPZ, and none required hospitalization. One subject with flatulence chose to complete the study despite the adverse reaction.

Discussion

As 60 to 90% of SSc patients suffer from GERD or reflux oesophagitis., it is considered a serious complication that reduces QOL (1). If the symptoms of GERD/reflux oesophagitis are insufficiently controlled, reflux can increase the potential for scarring at the gastroesophageal junction, and cause severe dysphagia and other disorders in the future. Treating reflux oesophagitis with PPIs, which have a strong acid secretion inhibitory action, is known to significantly improve both the endoscopic healing rate and subjective symptoms (9). Since the onset of action of RPZ is

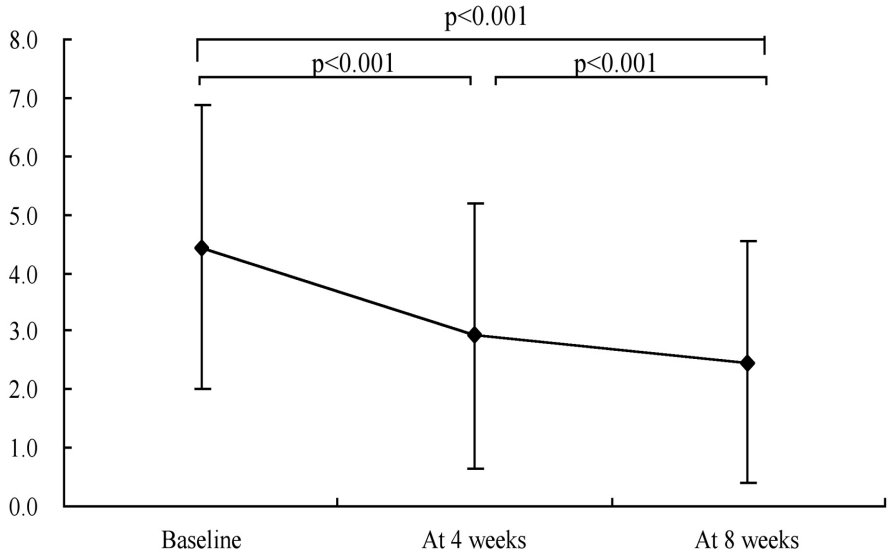

Fig. 4. Changes in VAS pain scores after treatment with rabeprazole
The VAS was used as a pain rating scale. Data are expressed as mean ± SD.

Table III. Adverse events reported during the treatment period.

Case number	Gender	Age (years)	Adverse event	Onset from study start (days)
M-2	Female	65	Diarrhea	3
M-13	Female	68	Abdominal fullness	8
M-15	Female	59	Flatulence	22
I-16	Female	70	Nausea	7
C-13	Female	75	Hepatic dysfunction	3
C-15	Male	68	Exacerbated mouth ulcers	3

faster than other PPIs, early improvement of subjective reflux oesophagitis symptoms can be anticipated (10). Furthermore, it has been reported that, because the main metabolic pathway of RPZ is a non-enzymatic reduction reaction and the contribution ratio of hepatic cytochrome P450 2C19 (CYP2C19) is lower than for other PPIs, it is less susceptible to the influence of CYP2C19 gene polymorphism, and the possibility of drug interactions is low (11, 12). Drug interactions are a particularly serious problem for SSc patients because they are often treated concurrently with multiple drugs.

The FSSG is a medical questionnaire, developed in Japan, that indicates a high likelihood of GERD/reflux oesophagitis with a score of 8 or more (3). Using the FSSG is convenient when it is not possible to conduct frequent endoscopic examinations. It is also a useful tool for rheumatism and dermatology department doctors not skilled at performing endoscopic examinations when treating outpatients. This is the first report of a study in which the FSSG was used to assess SSc patients.

In this study, all data were available for the analysis of FSSG and VAS scores for 84 subjects. However, for some other subjects data was missing for the VAS or both scores at 4 or 8 week's treatment. In fact, FSSG scores both at baseline and 4 weeks' treatment were available for 100 subjects (incomplete group 1), and scores both at baseline and 8 weeks' treatment for 90 subjects (incomplete group 2). In comparison to the 84 complete data sets, p values were similar or less for all the 20 FSSG questions after 4 and 8 weeks' treatment in the incomplete data sets, excepting only question 8 at 4 and 8 weeks (p=0.132 and 0.005, respectively) (Table I). For the acid reflux, dysmotility, and total scores (data shown in Fig. 1), significant differences persisted between scores at baseline and 4 weeks' treatment in the incomplete group 1, and between scores at baseline and 8 weeks' treatment for incomplete group 2 (p<0.001 for all 3 scores). According to these results, results obtained from the 84 complete data sets showed no bias in comparison to the whole study population.

A significant improvement was observed when the FSSG was used to determine the healing effect of RPZ at 4 and 8 weeks in cases of both mild and severe symptoms of GERD. A significant improvement was also observed when acid reflux and dysmotility scores where measured separately. Normal peristalsis repeatedly contracts and dilates the stomach. However, when gastric acid is retained, hypersensitivity increases. Gastric acid also disturbs gastric adaptive relaxation, causing the stomach to contract with difficulty. In turn, this delays gastric emptying, resulting in feelings of heaviness in the stomach and abdominal fullness, as well as other symptoms. The strong action of RPZ on inhibiting acid secretion has been established; this could also have the secondary action of improving gastrointestinal tract dysmotility scores. In some patients, symptoms due to reduced peristaltic motility (chest tightness, discomfort) may be caused by conditions other than GERD (13). In such cases, when PPIs are ineffective and the FSSG score is high, it may be worthwhile considering combined therapy with a PPI and a prokinetic agent (14) or H2 receptor antagonist (15).

The results of this study suggest that the FSSG scoring system is useful for evaluating reflux symptom complications in scleroderma patients and that RPZ effectively controls both mild and severe GERD symptoms in these patients. The use of this questionnaire does not discount barium swallow examinations and endoscopic examinations. Since this study did not include endoscopic examinations, we were not able to establish the diagnostic accuracy of the FSSG for GERD in SSc patients. However, the FSSG is strongly recommended for evaluating therapeutic efficacy in SSc patients with GERD without the need for repeated endoscopy.

Supplementary Table.

Figure	Items	Comparison	t-value	*p*-value	Power calculation
Figure 1	Total score	Baseline *vs*. 4 weeks	8.289	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	3.205	$p=0.001$	0.886
		Baseline *vs*. 8 weeks	8.712	$p<0.001$	0.999
	Acid reflux	Baseline *vs*. 4 weeks	7.575	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	3.149	$p=0.002$	0.875
		Baseline *vs*. 8 weeks	7.880	$p<0.001$	0.999
	Dysmotility	Baseline *vs*. 4 weeks	7.448	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	2.042	$p=0.044$	0.521
		Baseline *vs*. 8 weeks	8.124	$p<0.001$	0.999
Figure 2	Total score	Baseline *vs*. 4 weeks	8.790	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	3.513	$p<0.001$	0.930
		Baseline *vs*. 8 weeks	9.996	$p<0.001$	0.999
	Acid reflux	Baseline *vs*. 4 weeks	7.668	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	3.533	$p<0.001$	0.933
		Baseline *vs*. 8 weeks	8.602	$p<0.001$	0.999
	Dysmotility	Baseline *vs*. 4 weeks	8.457	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	2.039	$p=0.046$	0.512
		Baseline *vs*. 8weeks	9.706	$p<0.001$	0.999
Figure 3	Total score	Baseline *vs*. 4 weeks	3.430	$p=0.001$	0.912
		4 weeks *vs*. 8 weeks	0.213	$p=0.832$	0.038
		Baseline *vs*. 8 weeks	2.890	$p=0.006$	0.799
	Acid reflux	Baseline *vs*. 4 weeks	3.003	$p=0.005$	0.828
		4 weeks *vs*. 8 weeks	0.254	$p=0.800$	0.042
		Baseline *vs*. 8 weeks	2.652	$p=0.012$	0.727
	Dysmotility	Baseline *vs*. 4 weeks	1.909	$p=0.065$	0.448
		4 weeks *vs*. 8 weeks	0.587	$p=0.561$	0.078
		Baseline *vs*. 8 weeks	1.942	$p=0.061$	0.461
Figure 4	VAS score	Baseline *vs*. 4 weeks	6.894	$p<0.001$	0.999
		4 weeks *vs*. 8 weeks	3.955	$p<0.001$	0.973
		Baseline *vs*. 8 weeks	8.457	$p<0.001$	0.999

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