INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Therapeutic Response to Twice-daily Rabeprazole on Health-related Quality of Life and Symptoms in Patients with Refractory Reflux Esophagitis: A Multicenter Observational Study

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Abstract

Objective To investigate the effect of twice-daily rabeprazole doses on health-related quality of life in refractory patients.

Methods and Patients Reflux esophagitis patients with an insufficient response to once-daily proton pump inhibitor therapy (Los Angeles Classification grade A-D) received rabeprazole 10 mg or 20 mg twice daily for 8 weeks. The health-related quality of life (SF-8™) and symptoms, using the Frequency Scale for the Symptoms of Gastroesophageal reflux disease, were evaluated before treatment and at weeks 4 and 8. Endoscopy was performed at baseline and at weeks 8 and 32 where possible. The rabeprazole dose was determined by the attending physician.

Results There were 1,796 patients analyzed for the efficacy of the twice-daily treatment. Of these cases, 1,462 were treated with rabeprazole 10 mg twice daily, and 334 were treated with rabeprazole 20 mg twice daily. The factors that affected the selection of the twice-daily rabeprazole dose by physicians were evaluated, and as expected, "endoscopic findings when treatment was started" had a strong effect on the selection of the rabeprazole dose. With both regimens, health-related quality of life and subjective symptoms were significantly improved at weeks 4 and 8 compared to baseline ($p<0.001$). The recurrence rate of erosive esophagitis at week 32 was 9.7% in rabeprazole twice daily-treated patients and 28.4% in proton pump inhibitor (PPI) once daily-treated patients. Both regimens were well tolerated.

Conclusion Twice-daily treatment with rabeprazole improved the subjective symptoms and health-related quality of life in patients with refractory reflux esophagitis more effectively than the standard once-daily dose.

Key words: quality of life, rabeprazole, refractory reflux esophagitis, twice daily

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Introduction

The standard dosage regimen of proton pump inhibitors (PPIs) for initial treatment of reflux esophagitis (RE) is once-daily (q.d.) administration for 8 weeks. The endoscopic healing rate with an 8-week PPI q.d. regimen is reported to be approximately 90%. Thus, 10% of patients with RE are resistant to initial standard treatment with a PPI (1-3). In addition, the rate of PPI resistance in high-grade RE is reported to be 20-30% (4). In addition, health-related quality of life (HRQOL) is significantly lower in non-responders with subjective symptoms, compared to responders, after the initial standard PPI treatment (5).

The gastroesophageal reflux disease (GERD) clinical practice guidelines (6) of the Japanese Society of Gastroen-

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terology (JSGE) recommend changing the PPI treatment regimen for patients with resistant esophagitis or severe symptoms despite standard initial PPI treatment (omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 10 mg, or esomeprazole 20 mg). Guidelines in other countries also recommend that the PPI dose be doubled or switched to a twice-daily (b.i.d.) regimen for patients resistant to a standard dose (7, 8). The same dose of a PPI when given b.i.d. instead of q.d. was reported to provide not only superior gastric acid suppression (9, 10), but also better healing of esophagitis and more complete relief of heartburn (11). These treatment regimens, including doubling the PPI dose, can cure RE and relieve symptoms (12).

This prospective observational study investigated the effects of rabeprazole sodium (RPZ) b.i.d. as a second-line PPI therapy on the HRQOL in patients with esophageal mucosal lesions refractory to treatment with a standard PPI q.d. regimen.

Materials and Methods

Patients

This study included patients with endoscopically confirmed refractory RE (Los Angeles Classification grade A-D). Regardless of continued treatment with a standard q.d. regimen of a PPI approved in Japan (omeprazole 10 mg or 20 mg, lansoprazole 15 mg or 30 mg, RPZ 10 mg or 20 mg, esomeprazole 10 mg or 20 mg) within 8 weeks of starting the study drug (RPZ) b.i.d., endoscopic confirmation of mucosal injury (Los Angeles Classification grade A-D) was defined as PPI-refractory RE. These patients were switched to RPZ 10 mg b.i.d. or RPZ 20 mg b.i.d., with the dose selected by the attending physician.

The treatment duration of b.i.d. regimens was 8 weeks, as approved in Japan. Endoscopic healing of RE was monitored during the follow-up period until week 32. Assessment for *Helicobacter pylori* (*H. pylori*) infection, selection of the PPI before RPZ b.i.d. treatment, and maintenance treatment during the follow-up period from week 8 to week 32 were left to the discretion of the treating physician. No concomitant drugs were prohibited.

This prospective observational non-interventional study was conducted in compliance with Good Post-Marketing Study Practice (GPSP), the standard for the implementation of post-marketing surveys of drugs issued by the regulatory authority in Japan. Patients received full explanations about the purpose and methodology of the study prior to enrolment, but written, informed consent was not mandatory, as such consent is not required for noninvasive observational studies according to the GPSP and Ethical Guidelines for Clinical Research issued by the Ministry of Health, Labour and Welfare.

Evaluation endpoints

The SF-8 Health Survey (Japanese version) (13, 14) was used to assess the HRQOL. A self-administered questionnaire was given at baseline before treatment and at weeks 4 and 8. The eight subscales of the SF-8 (general health perception, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional) were measured, and the two summary scores (physical component summary [PCS] and mental component summary [MCS]) were calculated.

The Frequency Scale for the Symptoms of GERD (FSSG) (15) was used to assess the subjective symptoms. This self-administered questionnaire was also completed at baseline before treatment and at weeks 4 and 8. The total FSSG score (12 items), the 7 items for the acid reflux score, and the 5 items for the dysmotility score were calculated (16).

Endoscopy was performed at baseline and at weeks 8 and 32 (at the end of the follow-up period), when the attending physicians decided its necessity. The endoscopic findings were classified according to the Los Angeles Classification grading system.

Statistical analysis

Multivariate logistic analyses were performed to explore the patients' characteristics with respect to selection of the RPZ b.i.d. dose by physicians.

For HRQOL as the primary endpoint, summary statistics were calculated for the changes from baseline in the eight subscale and two summary scores at each dose. For FSSG as the secondary endpoint, summary statistics were calculated for the changes from baseline in the total 12-item score, the acid reflux score, and the dysmotility score at each dose. Statistical analyses were performed to compare the scores at each point with the baseline for each dose by paired *t*-tests. p values were not adjusted for multiplicity.

The endoscopic findings at each evaluation (when performed) were assessed according to the Los Angeles Classification grade. Improvement in the endoscopic findings to Grade O (Grade N or M) was defined as "healing".

The number of patients with adverse reactions and the incidence of adverse reactions were evaluated using the Medical Dictionary for Regulatory Activities. This included the system organ class and preferred terms.

This study was registered with ClinicalTrials.gov (Registration number NCT01321567).

Results

Patients' characteristics

Among the 2,157 patients that were enrolled at 570 medical institutions in Japan, data were analyzed from 2,131 patients, excluding 26 patients from whom surveys were not available for some reason from the participating medical institution. In this study, 87 patients were excluded from the safety analysis, and 248 were excluded from the efficacy analysis. The major reasons for exclusion, including double

Table 1. Baseline Patient Characteristics.

Category		Overall (n=1,796)	10 mg b.i.d. (n=1,462)	20 mg b.i.d. (n=334)
Sex	Male	752 (41.87)	610 (41.72)	142 (42.51)
	Female	1,044 (58.13)	852 (58.28)	192 (57.49)
Age (years)	<65	670 (37.31)	550 (37.62)	120 (35.93)
	≥65	1,124 (62.58)	911 (62.31)	213 (63.77)
	Unknown	2 (0.11)	1 (0.07)	1 (0.30)
BMI (kg/m^2)*	<25	547 (32.99)	446 (32.82)	101 (33.78)
	25≤ <30	174 (10.49)	140 (10.30)	34 (11.37)
	≥30	35 (2.11)	25 (1.84)	10 (3.34)
	Not measured	902 (54.40)	748 (55.04)	154 (51.51)
Endoscopic findings at baseline	Grade A	715 (39.81)	623 (42.61)	92 (27.54)
	Grade B	602 (33.52)	522 (35.70)	80 (23.95)
	Grade C	349 (19.43)	245 (16.76)	104 (31.14)
	Grade D	130 (7.24)	72 (4.92)	58 (17.37)
Duration of RE (years)	<1	536 (29.84)	452 (30.92)	84 (25.15)
	1≤ <5	700 (38.98)	576 (39.40)	124 (37.13)
	≥5	316 (17.59)	232 (15.87)	84 (25.15)
	Unknown	244 (13.59)	202 (13.82)	42 (12.57)
H. pylori infection test result	Positive	165 (9.19)	140 (9.58)	25 (7.49)
	Negative	533 (29.68)	449 (30.71)	84 (25.15)
	Unknown	1,098 (61.14)	873 (59.71)	225 (67.37)
Complications of RE	No	882 (49.11)	767 (52.46)	115 (34.43)
	Yes	894 (49.78)	679 (46.44)	215 (64.37)
	Hiatus hernia	843 (46.94)	638 (43.64)	205 (61.38)
	Barrett's esophagus	92 (5.12)	74 (5.06)	18 (5.39)
	Stenosis	23 (1.28)	12 (0.82)	11 (3.29)
	Unknown	20 (1.11)	16 (1.09)	4 (1.20)
Other complications	No	707 (39.37)	609 (41.66)	98 (29.34)
	Yes	1,089 (60.63)	853 (58.34)	236 (70.66)
	Osteoporosis	177 (9.86)	143 (9.78)	34 (10.18)
	Kyphosis	138 (7.68)	103 (7.05)	35 (10.48)
	Hypertension	543 (30.23)	431 (29.48)	112 (33.53)
	Hyperlipidemia (Dyslipidemia)	346 (19.27)	283 (19.36)	63 (18.86)
	Diabetes mellitus	123 (6.85)	102 (6.98)	21 (6.29)
	Other	709 (39.48)	555 (37.96)	154 (46.11)
Prior drug (PPI) use	PPI monotherapy	1,107 (61.64)	951 (65.05)	156 (46.71)
	PPI+other drug	689 (38.36)	511 (34.95)	178 (53.29)

All values are expressed as n (%).

*Patients with kyphosis as a comorbidity were excluded from this analysis.

counting, were: no treatment with a PPI prior to starting RPZ b.i.d. in 131 patients; unable to evaluate the efficacy because of a lack of data on the HRQOL, FSSG, or endoscopic evaluation in 118 patients; and lost to follow-up after starting b.i.d. therapy in 62 patients. The efficacy was analyzed in 1,796 patients (RPZ 10 mg b.i.d.: 1,462 patients, RPZ 20 mg b.i.d.: 334 patients) (Table 1).

Fig. 1 shows the results of a multivariate logistic analysis performed to explore the patients' characteristics. The factors that affected the selection of the RPZ b.i.d. dose by physicians were evaluated, and as expected, "endoscopic findings when treatment was started" had a strong effect on the selection of the RPZ dose. There were also significant differences in "*H. pylori* infection", "RE complications (hiatal hernia, Barrett's esophagus, perforation)", "prior treatment drugs", and "dose of prior PPI" between the 10 mg and 20 mg b.i.d. groups. Because of these large differences in patients' characteristics between the 2 groups, separate analyses were performed for the 10 mg and 20 mg b.i.d. groups.

Efficacy of RPZ 10 mg b.i.d. treatment

Fig. 2 shows the HRQOL scores (a), FSSG scores (b), and endoscopic healing rates (c) in patients treated with RPZ 10 mg b.i.d. Before starting RPZ 10 mg b.i.d., the HRQOL PCS was 41.7±9.1 (mean ± standard deviation

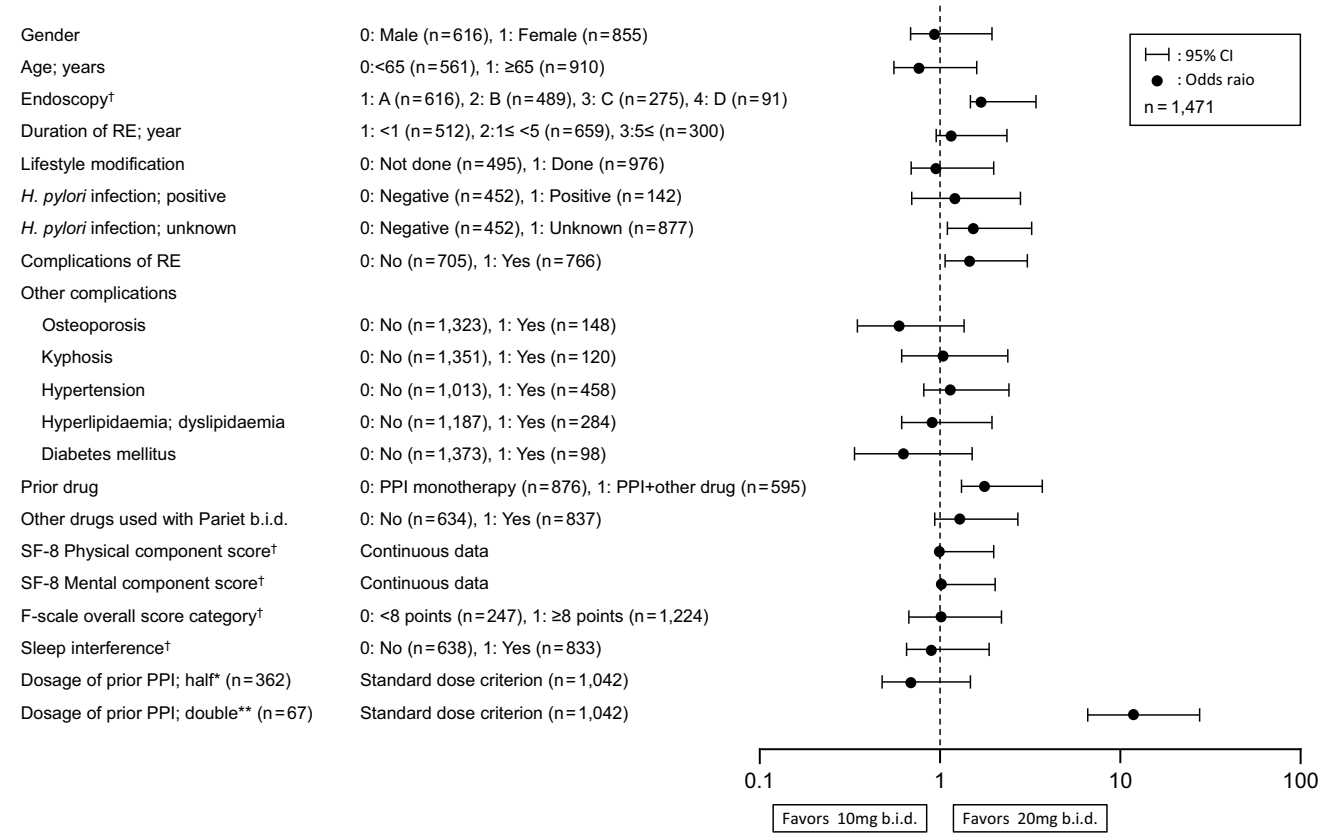

Figure 1. **Multivariate logistic analyses were performed to explore the patients' characteristics with regard to selection of the RPZ b.i.d. dose. Treatment: 0: 10 mg b.i.d., 1: 20 mg b.i.d. †At baseline. *half: omeprazole 10 mg q.d., lansoprazole 15 mg q.d., esomeprazole 10 mg q.d., **double: rabeprazole 20 mg q.d.**

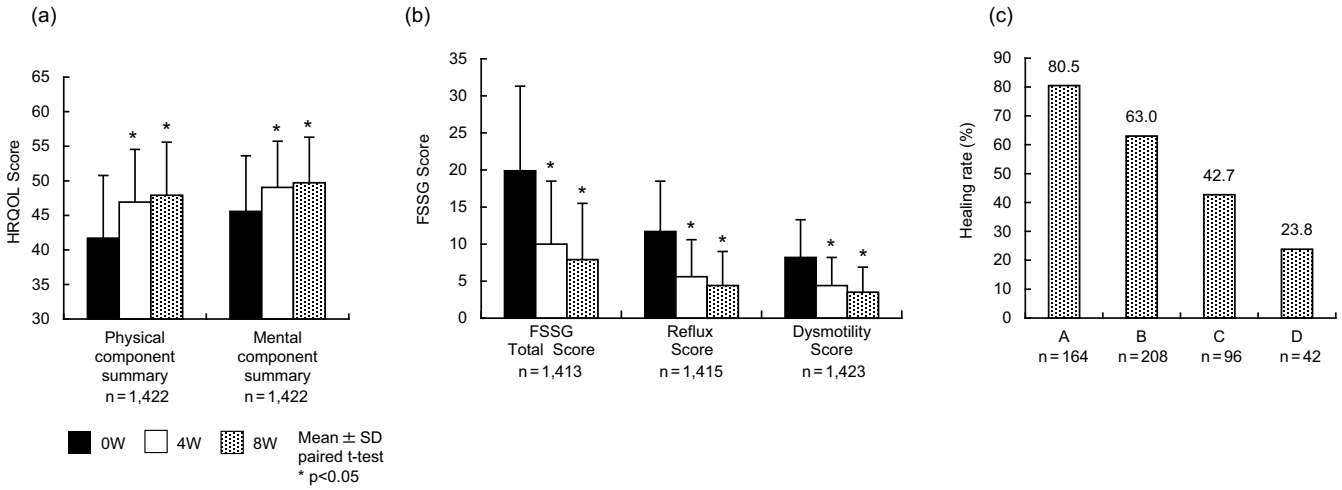

Figure 2. **Efficacy of rabeprazole 10 mg b.i.d. (a) Changes in the health-related quality of life (HRQOL) after beginning rabeprazole 10 mg b.i.d. treatment. (b) Changes in the frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score after beginning rabeprazole 10 mg b.i.d. treatment. (c) Endoscopically confirmed healing of reflux esophagitis after 8-week rabeprazole 10 mg b.i.d. treatment based on the Los Angeles Classification at baseline. W: week**

[SD]), and the MCS was 45.6±8.0. After 4 weeks of RPZ 10 mg b.i.d., the PCS was 46.9±7.6, and the MCS was 49.0 ±6.7; after 8 weeks, the PCS was 47.9±7.7, and the MCS was 49.7±6.6. These two scores were significantly improved compared to baseline (both $p<0.001$, paired *t*-test). In addition, all 8 subscale scores were significantly improved at 4

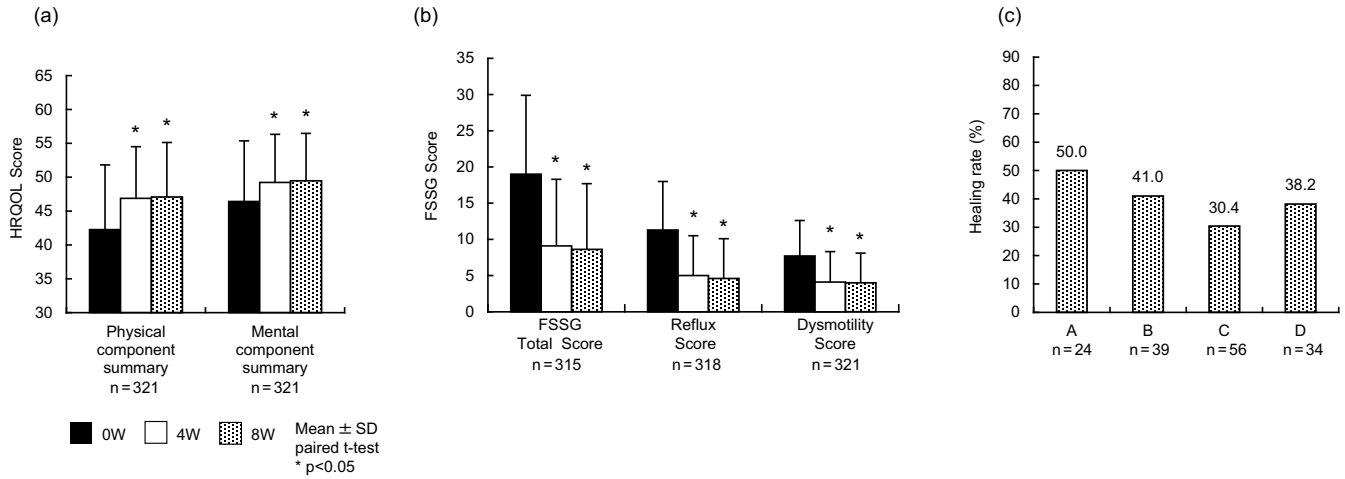

Figure 3. **Efficacy of rabeprazole 20 mg b.i.d. (a) Changes in the health-related quality of life (HRQOL) after beginning rabeprazole 20 mg b.i.d. treatment. (b) Changes in the frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score after beginning rabeprazole 20 mg b.i.d. treatment. (c) Endoscopically confirmed healing of reflux esophagitis after 8-week rabeprazole 20 mg b.i.d. treatment based on the Los Angeles Classification at baseline. W: week**

and 8 weeks (all p<0.001, paired *t*-test).

Before starting RPZ 10 mg b.i.d., the FSSG total score was 19.9±11.4 (mean ± SD), the acid reflux score was 11.7 ±6.8, and the dysmotility score was 8.2±5.1. After 4 weeks of RPZ 10 mg b.i.d. administration, the total, acid reflux, and dysmotility scores were 10.0±8.5, 5.6±5.0, and 4.4±3.8, respectively, and after 8 weeks, they were 7.9±7.6, 4.4±4.6, and 3.5±3.4, respectively. There were significant improvements in these three scores compared to baseline (all p< 0.001, paired *t*-test).

Endoscopic examinations were performed after 8-week b.i.d. treatment in 26.3% (164/623) of patients with Grade A esophagitis, 39.8% (208/522) with Grade B, 39.2% (96/245) with Grade C, and 58.3% (42/72) with Grade D. The endoscopic healing rates at week 8 were 80.5% (132/164) in patients with Grade A, 63.0% (131/208) in Grade B, 42.7% (41/96) in Grade C, and 23.8% (10/42) in Grade D.

Efficacy of RPZ 20 mg b.i.d. treatment

Fig. 3 shows the HRQOL scores (a), FSSG scores (b), and endoscopic healing rates (c) in patients treated with RPZ 20 mg b.i.d.

Before starting RPZ 20 mg b.i.d., the HRQOL PCS was 42.3±9.6 (mean ± SD), and the MCS was 46.4±8.9. After 4 weeks of RPZ 20 mg b.i.d., the PCS was 46.9±7.6, and the MCS was 49.2±7.1; after 8 weeks, the PCS was 47.1±8.0, and the MCS was 49.5±7.0. These two scores were significantly improved compared to baseline (all p<0.001, paired *t*-test). In addition, all 8 subscale scores were significantly improved at 4 and 8 weeks (all p<0.001, paired *t*-test).

Before starting RPZ 20 mg b.i.d., the FSSG total score was 19.0±10.9 (mean ± SD), the acid reflux score was 11.3 ±6.7, and the dysmotility score was 7.7±4.9. After 4 weeks of RPZ 20 mg b.i.d., the total, reflux, and dysmotility scores were 9.1±9.2, 5.0±5.5, and 4.1±4.2, respectively, and after 8 weeks, they were 8.6±9.1, 4.6±5.5, and 4.0±4.1, respectively. There were significant improvements in these three scores compared to baseline (all p<0.001, paired *t*-test).

Endoscopic examinations were performed after 8-week b.i.d. treatment in 26.1% (24/92) of patients with Grade A esophagitis, 48.8% (39/80) with Grade B, 53.8% (56/104) with Grade C, and 58.6% (34/58) with Grade D. The endoscopic healing rates at week 8 were 50.0% (12/24) in patients with Grade A, 41.0% (16/39) with Grade B, 30.4% (17/56) with Grade C, and 38.2% (13/34) with Grade D.

Long-term treatment after 8-week RPZ b.i.d. treatment

Fig. 4 (a) shows the selected long-term treatment after 8-week RPZ 10 mg b.i.d. and RPZ 20 mg b.i.d. therapy combined. Fig. 4 (b) shows the recurrence rates of erosive lesions at week 32 in the RPZ b.i.d. and q.d. treatment groups, although only some of the enrolled cases were investigated by the endoscopic study at this time point. During the follow-up period from week 8 to week 32, the majority of the enrolled cases were treated by q.d. administration of a PPI.

Among 335 patients with endoscopic healing at the end of 8-week RPZ b.i.d. treatment, only 117 were re-examined endoscopically at week 32. The recurrence rate of erosive esophagitis at week 32 was 9.7% in RPZ b.i.d.-treated patients and 28.4% in PPI q.d.-treated patients.

In all patients after 8 weeks of b.i.d. treatment, regardless of whether the attending physician continued a PPI b.i.d., switched to a PPI q.d., did not treat, or selected some other treatment, the HRQOL and symptoms at 16 and 32 weeks were not markedly different from those at 8 weeks (data not shown).

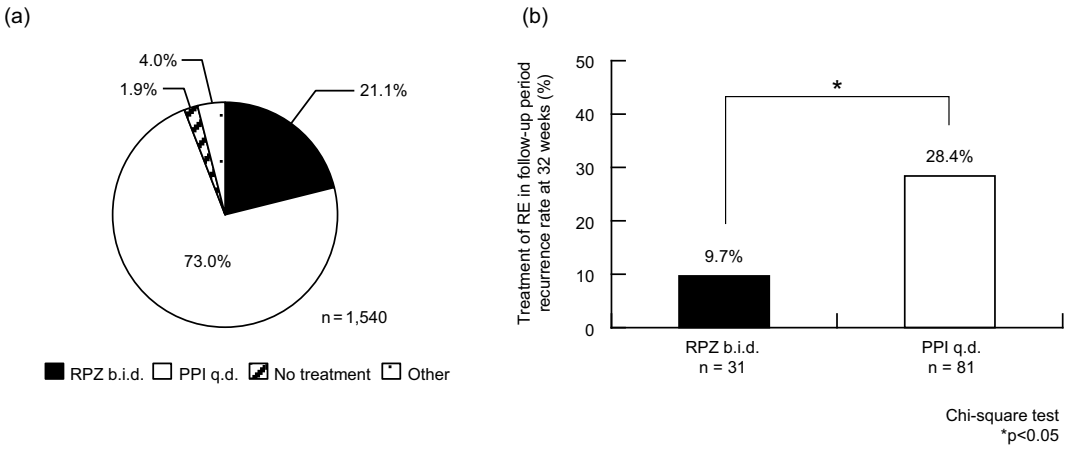

Figure 4. **Follow-up and recurrence of RE during maintenance therapy. (a) RE treatment status after 8 weeks of rabeprazole b.i.d. (b) RE recurrence rate after 32 weeks. RPZ b.i.d. includes both rabeprazole 10 mg b.i.d. and rabeprazole 20 mg b.i.d. PPI q.d. includes any PPI q.d. prescribed by attending physician.**

Table 2. **Adverse Drug Reactions.**

	10 mg b.i.d. (n=1,666)	20 mg b.i.d. (n=378)
All adverse drug reactions*	7 (0.42)	4 (1.06)
System organ class Preferred term		
Immune system disorders	0 (0.00)	1 (0.26)
Hypersensitivity	0 (0.00)	1 (0.26)
Vascular disorders	1 (0.06)	0 (0.00)
Hypertension	1 (0.06)	0 (0.00)
Gastrointestinal disorders	3 (0.18)	1 (0.26)
Abdominal pain	0 (0.00)	1 (0.26)
Diarrhea	2 (0.12)	0 (0.00)
Enterocolitis	1 (0.06)	0 (0.00)
Skin and subcutaneous tissue disorders	3 (0.18)	1 (0.26)
Dermatitis allergic	1 (0.06)	0 (0.00)
Pruritus	2 (0.12)	1 (0.26)
General disorders and administration site conditions	0 (0.00)	1 (0.26)
Edema peripheral	0 (0.00)	1 (0.26)

All values are expressed as n (%).

*Patients with adverse drug reactions each experienced only one adverse drug reaction.

Safety

Table 2 summarizes the adverse drug reactions. There were 7 adverse drug reactions in 7 patients during 8-week RPZ 10 mg b.i.d treatment. The incidence of adverse drug reactions was 0.4% (7/1,666 patients). There were 4 adverse drug reactions in 4 patients during 8-week RPZ 20 mg b.i.d treatment. The incidence of adverse drug reactions was 1.1% (4/378 patients). Only 1 serious adverse drug reaction (peripheral edema) occurred in a patient (0.3%) taking RPZ 20 mg b.i.d.

Discussion

The present study found that RPZ 10 mg b.i.d. and RPZ 20 mg b.i.d. improved the HRQOL and subjective symptoms in patients with RE refractory to PPI q.d. treatment.

Lack of an apparent correlation between the severity of esophageal erosions and symptoms has been reported (17). Patients with RE have been reported to show a decreased HRQOL because of the unpleasant symptoms, and their HRQOL is considered to be lower than in cases with angina pectoris or duodenal ulcers (18). Observational studies in Japan (19, 20) investigating HRQOL in patients with RE have reported HRQOL scores below the standard of the general

Japanese population.

GERD clinical practice guidelines (6) by the JSGE strongly recommend a PPI as a first-line treatment, not only for preventing complications (Grade A: Strongly recommended), but also for improving the HRQOL. For the initial treatment of RE, no significant differences in the efficacy among different PPIs have been reported (21, 22). The endoscopic healing rates after 8-week treatment were 88.3% (1) with RPZ, 89.8% (2) with lansoprazole, and 87.3% (3) with esomeprazole. Thus, PPI resistance is found in about 10% of cases after PPI first-line therapy, irrespective of the type of PPI used.

The present prospective observational study investigated changes in the HRQOL with RPZ 10 mg b.i.d. or 20 mg b.i.d. in patients with unhealed RE despite initial standard treatment with a PPI q.d. (omeprazole 10 mg or 20 mg, lansoprazole 15 mg or 30 mg, RPZ 10 mg or 20 mg, and esomeprazole 10 mg or 20 mg).

A review of 25 reports grading Japanese RE patients according to the Los Angeles Classification showed that the grades of RE were as follows: Grade A 54.6%, Grade B 32.4%, and Grades C and D 13.0% (23). The grades of RE in the present study after standard PPI q.d. treatment were: Grade A 39.8%, Grade B 33.5%, and Grades C and D 26.7%. Therefore, the cases enrolled in this study were considered to have high-grade RE with possible resistance to PPI treatment.

A 20 mg RPZ b.i.d. regimen is approved by the Japanese regulatory agency only for the treatment of PPI-resistant patients with high-grade RE, and the attending physicians are expected to follow this regulation. However, despite the recommendation by the Japanese regulatory committee, only one-third of high-grade patients with grade C or D esophagitis were treated by the RPZ 20 mg b.i.d regimen, and two-thirds were treated by the 10 mg b.i.d regimen, as shown in Table 1. In contrast, as many as 13% of cases with grade A or B low-grade esophagitis were treated by the high-dose regimen with RPZ 20 mg b.i.d.

When the factors affecting the dose selection of the RPZ b.i.d. regimen were evaluated, the presence of RE complications and stronger initial treatment with double-dose PPIs or combination therapy including PPIs and other therapeutic agents such as prokinetics were also found to be important factors in this study. Gastric acid reflux occurs more frequently in cases with hiatal hernia and is a factor in recurrent RE (24). Therefore, stronger suppression of acid secretion must be considered when selecting a PPI dose. Doubling the dose of a PPI has been effective in patients who fail to respond to a standard PPI dose (11, 12). The addition of another drug, such as an HR2A, to PPI treatment may also be effective in symptom improvement (25). Although these factors affecting dose selection of an RPZ b.i.d. regimen were evaluated in this study, there was still a large amount of data that could not be assessed. Therefore, further investigation is necessary. Although the healing rates in patients with higher grade RE (LA Classification grade C and D) with 40-mg split doses were not markedly different from those in patients with 20-mg split doses in this study, the 40-mg split dose may still be more effective in patients with endoscopically confirmed LA Classification grade C or D RE after PPI q.d. treatment, in those with RE complications, and in those previously treated with a combination a PPI and other drug.

The endoscopic healing rates after 8-week treatment with RPZ 10 mg b.i.d. were higher in cases with low-grade esophagitis but lower in cases with more severe baseline esophagitis. The HRQOL and subjective symptoms, on the other hand, improved significantly after 4-week treatment with RPZ 10 mg b.i.d. After 8-week treatment with RPZ 20 mg b.i.d., the HRQOL and subjective symptoms improved significantly as well, irrespective of the relatively low esophagitis healing rates. This lower endoscopic healing rate was considered to be caused by the larger number of difficult-to-treat cases in the 20 mg b.i.d.-treated group.

Endoscopy rates after 8-week treatment with RPZ b.i.d. were higher in patients with higher-grade LA Classification at the time of treatment initiation. In many cases, an endoscopic examination was not performed if symptoms were relieved by treatment. Therefore, patients with a higher chance of having uncured esophageal mucosal lesions might have been more frequently investigated by endoscopy after 8-week b.i.d. RPZ treatment.

Few patients with Grade A or B esophagitis progress to more severe RE (26). Therefore, the therapeutic priority in cases with low-grade esophagitis should be given to improving the symptoms and HRQOL. In Grade C and D patients, on the other hand, because of the risk of serious complications (27), complete healing of RE is also considered important. Therefore, b.i.d. treatment with RPZ, although very effective for the resolution of symptoms and for improving the HRQOL, may not be sufficient to achieve endoscopic healing in some cases with high-grade esophagitis.

The evaluation of the endoscopic healing rates in RE, both during initial treatment and during second-line therapy with RPZ b.i.d., has been performed after 8-week treatment worldwide. In reports of serial evaluations of endoscopic healing rates (3, 28), rapidly increasing endoscopic healing rates have been reported each week. Therefore, if the treatment duration is prolonged further, the endoscopic healing rates may increase further, even with the same treatment regimen (28). In patients with PPI-resistant RE, treatment for longer than 8 weeks may need to be evaluated in a future study.

The healing rates with RPZ b.i.d. in PPI q.d.-refractory RE were lower than those with PPI q.d. for the initial treatment of RE. Because the causes of refractory RE were not specified and varied among patients, specifying these factors in this study was very difficult. Gastric acid secretion in healthy Japanese adults has not changed in recent years (29, 30), and there is no evidence that gastric acid secretion in the RE patients enrolled in the present study was markedly different from that of previous RE patients. Gas-

tric acid reflux occurs more frequently and gastric acid clearance from the esophagus is lower in patients with hiatal hernia, thus leading to relapse of RE (24). Approximately half of the cases enrolled in this study had hiatal hernia as a complication of RE. Thus, hiatal hernia is a factor in RE relapse and probably accounts for a lower healing rate.

The majority of refractory RE patients enrolled in the present study were treated with various forms of maintenance therapy with RPZ b.i.d. or a PPI q.d. even after 8-week RPZ b.i.d. treatment. The recurrence rates of mucosal breaks after 24 weeks of maintenance therapy were significantly lower with the RPZ b.i.d regimen (9.7%) than with the PPI q.d. regimen (28.4%). Therefore, in patients with PPI q.d.-resistant RE, long-term subsequent maintenance therapy with RPZ b.i.d. after 8-week remission induction therapy should also be evaluated in the future.

Author's disclosure of potential Conflicts of Interest (COI).

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Institutional review board statement

This research was part of post-marketing surveillance conducted in accordance with the Japanese Good Post-marketing Study Practice (GPSP) ordinance provided by the Japanese Ministry of Health and Welfare. The GPSP ordinance specifies items that are to be strictly complied with in order to perform appropriate post-marketing studies of drugs. According to this ordinance, a post-marketing study is to be conducted in accordance with the approved indications and in daily practice.

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