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Efficacy and safety of omeprazole in Japanese patients with nonerosive reflux disease

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Background. There is increasing awareness of non-erosive reflux disease (NERD) as a disease requiring treatment in Japan. This randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy and safety of omeprazole 10 mg and 20 mg once daily in Japanese patients with NERD. ***Methods.*** Patients with heartburn for at least 2 days a week during the month before entry into the study and no endoscopic signs of a mucosal break (grade M or N according to Hoshihara's modification of the Los Angeles classification) were randomly assigned to one of three groups (omeprazole 10 mg or 20 mg, or placebo) once daily for 4 weeks. ***Results.*** Overall, 355 patients were enrolled, of whom 284 were randomly assigned to one of the three groups (omeprazole 10 mg, $n = 96$; omeprazole 20 mg, $n = 93$; placebo, $n = 95$). The rate of complete resolution of heartburn in week 4 was significantly higher in patients treated with omeprazole 10 mg [32.3%, 95% confidence interval (CI), 22.9%–41.6%] or 20 mg (25.8%, 95% CI, 16.9%–34.7%) than in the placebo group (12.0%, 95% CI, 5.3%–18.6%). No significant difference between the two omeprazole groups was observed. The rate of complete resolution of heartburn by omeprazole was similar between patients with grade M and those with grade N esophagus. Omeprazole also increased the rate of sufficient relief from heartburn. Omeprazole was well tolerated.

Conclusions. Omeprazole 10 mg or 20 mg once daily is effective and well tolerated in patients with NERD regardless of their endoscopic classification.

Key words: nonerosive reflux disease (NERD), heartburn, omeprazole

Introduction

The prevalence of gastroesophageal reflux disease (GERD) in Japanese subjects is approximately 6.6%.[1] The major symptom of GERD is heartburn, which is caused primarily by the reflux of acidic gastric contents into the esophagus. GERD is classified into erosive esophagitis and nonerosive reflux disease (NERD) on the basis of endoscopic findings. NERD is a symptomatic disease with no mucosal break in the esophagus according to the Los Angeles (LA) classification. In Japan, NERD is further subdivided into grade M (minimal change in endoscopic findings) or grade N (endoscopically normal mucosa) based on the appearance of the esophageal mucosa, in accordance with Hoshihara's modified version of the LA classification.[2]

Recently, the increasing prevalence of NERD[3,4] and awareness of its impact on the quality of life[5,6] have led to growing acceptance of NERD as a disease requiring treatment in Japan.

Proton pump inhibitors (PPIs) such as omeprazole are the most effective agents currently available for the treatment of NERD in Western countries.[7] Controlled

studies in Europe, North America, and Australia have consistently shown that PPIs produce significantly greater relief of NERD symptoms than H₂-receptor antagonists (H₂RAs) in Caucasian patients.[8–11] However, few reports are available for Japanese patients.[12] Moreover, the response to the treatment in relation to the endoscopic classification of NERD is unknown.

In clinical practice, it is not feasible to perform 24-h intraesophageal pH monitoring[13,14] or a PPI test[15] on every patient with heartburn to determine whether the symptoms are acid-related. Another practical tool for identifying responders to PPIs is their efficacy during early treatment.

In this paper, we present results from a randomized, double-blind, placebo-controlled, parallel-group study on the efficacy and safety of omeprazole 10 mg or 20 mg once daily in Japanese patients with NERD. Efficacy in patients with grade M or N NERD was also investigated in the study.

Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 33 centers in Japan. The study was conducted in compliance with good clinical practice, and the study protocol was approved by the institutional review board at each study center. Written informed consent to participate in the study was obtained from every patient before study entry.

Subjects

The inclusion criteria of the study were (1) provision of written informed consent, (2) female or male, aged 20 years or more, (3) patients who identified their predominant symptom as heartburn, (4) patients with a history of moderate or severe heartburn episodes for 2 days or more each week for at least a month just before the screening, and (5) patients who were classified as having a grade M or N esophagus according to Hoshihara's modified version of the LA classification[2] by endoscopy at the screening. Patients with erosive esophagitis or those with a history of this condition were excluded from the study.

Study design and procedures

At the initial visit, patient eligibility and the severity of heartburn were determined, and endoscopy was performed to classify the esophagus according to Hoshihara's modified version of the LA classification[2] into grade M or N and to confirm the presence or absence of a hiatal hernia (absent, none or shorter than

2 cm; present, 2 cm or longer). The result of an endoscopy obtained before the informed consent was used if that endoscopy was performed 7 to 14 days before randomization. To exclude patients who did not need treatment with PPIs, patients were then enrolled in an observation period during which they received antacid (dried aluminum hydroxide gel–magnesium hydroxide; Towa Pharmaceutical, Osaka, Japan) three times daily for 7 days (up to 14 days). Patients experiencing heartburn on 2 or more days during the final 7 days of the observation period were randomly assigned to omeprazole 10 mg or 20 mg or to placebo for 4 weeks of treatment. All study medication was administered once daily after breakfast.

Efficacy assessments

The primary objective of the study was to compare the efficacy of omeprazole 10 mg or 20 mg to placebo in patients with NERD in terms of the complete resolution of heartburn (defined as no heartburn for 7 consecutive days) during the fourth week of treatment. Secondary efficacy variables were the rate of sufficient relief from heartburn (defined as no heartburn or no more than 1 day with mild heartburn for 7 consecutive days) during the fourth week of treatment.

Heartburn was recorded by patients on diary cards. Heartburn was defined as a burning feeling, rising from the stomach or lower part of the chest toward the neck. The severity of heartburn was assessed on a four-point scale: none (no heartburn), mild (awareness of heartburn but easily tolerated), moderate (discomforting heartburn sufficient to cause interference with daily activities), or severe (incapacitating heartburn, causing inability to perform daily activities).

Safety assessments

Safety was assessed by monitoring adverse events throughout the study period and by clinical laboratory tests (clinical chemistry, hematology, and urinalysis) at the start and end of the study.

Genotyping of CYP2C19

Samples for genetic analysis were collected during the study period. The *CYP2C19*2* allele was identified by polymerase chain reaction (PCR)-based allele-specific amplification of exon 5 of *CYP2C19* followed by digestion with the restriction enzyme *SmaI*. Similarly the *CYP2C19*3* allele was analyzed by PCR amplification of exon 4 of *CYP2C19* followed by digestion with the restriction enzyme *Bam*HI.[16] On the basis of the results of these assays, patients were classified as being a homozygous extensive metabolizer (EM), a heterozygous

EM, or a poor metabolizer. Samples were collected and assayed by Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

Helicobacter pylori *tests*

During the study period, the *Helicobacter pylori* status of each patient was determined by IgG antibody testing of a blood serum sample using an Eiken serum *H. pylori* antibody test (E Plate; Eiken Chemical, Tokyo, Japan). These tests were performed by Mitsubishi Chemical Medience Corporation.

Statistical analyses

Statistical analyses were performed with the full analysis set (FAS). Within each treatment group, the rate of complete resolution of heartburn or sufficient relief from heartburn during the fourth week and the corresponding two-sided 95% confidence interval (CI) were calculated. Comparisons of binary variables between treatment groups were made by χ-squared tests. For the primary efficacy variable, the effects of patient demographics and other characteristics were evaluated by logistic regression analysis. Additional statistical analyses were performed for the primary variable for the subgroups of patients classified as having a grade M or grade N esophagus. All statistical tests were two-sided with a significance level of 5%.

Results

Patient disposition and demography, and treatment compliance

A total of 355 patients were enrolled, of whom 284 were randomly assigned to one of three groups: 96 patients, omeprazole 10 mg; 93, omeprazole 20 mg; and 95, placebo (Fig. 1). All randomized patients received the study treatment, and 271 completed it. Overall, 281 patients were included in the FAS population, whereas safety was evaluated in 283 patients. Two patients who violated the patient selection criteria were excluded from the FAS population, and one was excluded from both the FAS and safety analysis populations for failure to adhere to the study schedule. The demographic and other characteristics of the patients at baseline are summarized in Table 1.

Compliance with treatment was generally good in this study. The proportion of patients taking more than 75% of the study medication doses was 99.0% in the omeprazole 10 mg group, 97.8% in the omeprazole 20 mg group, and 96.8% in the placebo group.
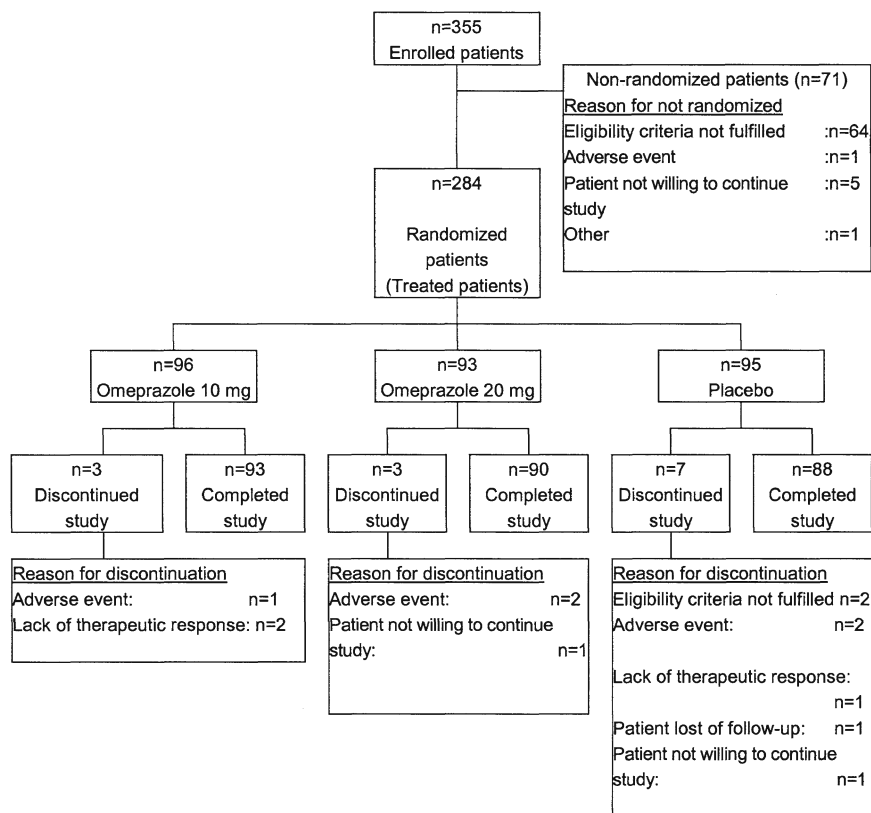

Fig. 1. Disposition of patients during the study

Table 1. Patient characteristics at baseline (FAS)

	Omeprazole 10 mg ($n = 96$) n (%)	Omeprazole 20 mg ($n = 93$) n (%)	Placebo ($n = 92$) n (%)
Sex			
Male	47 (49.0)	53 (57.0)	43 (46.7)
Female	49 (51.0)	40 (43.0)	49 (53.3)
Age (years)			
Mean ± SD (range)	44.4 ± 16.2 (21–80)	43.8 ± 16.4 (21–80)	42.4 ± 15.4 (21–80)
Hoshihara grade			
Grade N	63 (65.6)	57 (61.3)	63 (68.5)
Grade M	33 (34.4)	36 (38.7)	29 (31.5)
Helicobacter pylori			
Negative	59 (61.5)	44 (47.3)	50 (54.3)
Positive	37 (38.5)	49 (52.7)	42 (45.7)
Hiatus hernia			
Absent	91 (94.8)	84 (90.3)	90 (97.8)
Present	5 (5.2)	9 (9.7)	2 (2.2)
Severity of investigator-reported heartburn at beginning of treatment			
Mild	54 (56.3)	43 (46.2)	39 (42.4)
Moderate	33 (34.4)	41 (44.1)	41 (44.6)
Severe	4 (4.2)	1 (1.1)	4 (4.3)
Maximum severity of heartburn in the observation period			
Mild	36 (37.5)	32 (34.4)	33 (35.9)
Moderate	46 (47.9)	52 (55.9)	47 (51.1)
Severe	14 (14.6)	9 (9.7)	12 (13.0)
Number of days with heartburn in the observation period			
2 days	4 (4.2)	4 (4.3)	5 (5.4)
3 days	6 (6.3)	5 (5.4)	5 (5.4)
4 days	12 (12.5)	12 (12.9)	5 (5.4)
5 days	15 (15.6)	16 (17.2)	12 (13.0)
6 days	15 (15.6)	16 (17.2)	11 (12.0)
7 days	44 (45.8)	40 (43.0)	54 (58.7)
Mean	5.7	5.7	6.0

FAS, full analysis set

Efficacy

The rate of complete resolution of heartburn during the fourth week of treatment was 32.3% (95% CI, 22.9%–41.6%) in the omeprazole 10 mg group and 25.8% (95% CI, 16.9%–34.7%) in the omeprazole 20 mg group, compared with 12.0% (95% CI, 5.3%–18.6%) in the placebo group (Table 2). The rate of complete resolution in each omeprazole group was significantly higher than that in the placebo group, $P < 0.001$ for omeprazole 10 mg versus placebo, and $P = 0.016$ for omeprazole 20 mg versus placebo, whereas no significant difference was found between omeprazole 10 mg and omeprazole 20 mg (Table 3).

In the logistic regression analysis, sex, maximum severity of heartburn in the observation period, and number of days with heartburn in the observation period were significantly associated with the complete resolution of heartburn (Table 4). More frequent heartburn events during the observation period were associated

Table 2. Rate of complete resolution of heartburn during the fourth week of treatment (FAS)

Treatment	Estimate	95% CI Lower	95% CI Upper
Omeprazole 10 mg	32.3% (31/96)	22.9%	41.6%
Omeprazole 20 mg	25.8% (24/93)	16.9%	34.7%
Placebo	12.0% (11/92)	5.3%	18.6%

CI, confidence interval

with a lower rate of complete resolution. The analysis did not find any significant difference according to omeprazole dose, age, *CYP2C19* genotype, *H. pylori* infection status, or NERD grade (Hoshihara's modified version of the LA classification).

A further subgroup analysis was performed to evaluate the rate of complete resolution of heartburn in patients with a grade M or grade N esophagus. In each treatment group, the 95% CI of patients with grade M

Table 3. Differences in the rate of complete resolution of heartburn during the fourth week of treatment between all pairs of treatment groups (FAS)

| Treatment | Estimate | 95% CI | | P (χ-square test) |
		Lower	Upper	
Omeprazole 20 mg – placebo	13.8%	2.8%	24.9%	0.016
Omeprazole 10 mg – placebo	20.3%	8.9%	31.8%	<0.001
Omeprazole 20 mg – omeprazole 10 mg	−6.5%	−19.4%	6.4%	0.326

Table 4. Logistic regression analysis of the complete resolution of heartburn during the fourth week of treatment (FAS)

| Effect | | Odds ratio | | | P |
| | | Estimate | 95% CI | | |
			Lower	Upper	
Treatment	Omeprazole 10 mg vs. 20 mg	1.554	0.759	3.181	0.228
Sex	Female vs. male	0.379	0.182	0.793	0.010
Age	<65 years vs. ≥65 years	1.245	0.444	3.489	0.676
CYP2C19 status	Hetero EM vs. PM	0.536	0.196	1.465	0.470
	Homo EM vs. PM	0.686	0.248	1.897	
Hoshihara classification	Grade M vs. grade N	1.201	0.576	2.508	0.625
H. pylori status	Negative vs. positive	0.682	0.329	1.415	0.304
Maximum severity of heartburn in the observation period	Mild vs. severe	0.797	0.263	2.416	0.034
	Moderate vs. severe	0.328	0.110	0.976	
Number of days with heartburn in the observation period	Days of heartburn increased by 1	0.629	0.492	0.804	<0.001

Hetero EM, heterozygous extensive metabolizer; Homo EM, homozygous extensive metabolizer; PM, poor metabolizer

or grade N esophagus with complete resolution of heartburn were broad and overlapped greatly (Fig. 2). Thus, there was no substantial difference between patients with a grade M or grade N esophagus in the rate of complete resolution of heartburn.

The rate of sufficient relief from heartburn during the fourth week of treatment was 45.8% (95% CI, 35.9%–55.8%) in the omeprazole 10 mg group, 46.2% (95% CI, 36.1%–56.4%) in the omeprazole 20 mg group, and 23.9% (95% CI, 15.2%–32.6%) in the placebo group (Table 5). Thus, rates of sufficient relief from heartburn showed a similar pattern among groups to those of complete resolution of heartburn.

Safety and tolerability

Both omeprazole treatments were well tolerated. Adverse events were reported by 21 patients (21.9%) in the omeprazole 10 mg group, 34 (36.6%) in the omeprazole 20 mg group, and 29 (30.9%) in the placebo group. Of these, five patients (5.2%) in the omeprazole 10 mg group, four (4.3%) in the omeprazole 20 mg group, and one (1.1%) in the placebo group experienced a drug-related adverse event. There were no serious adverse events. Five patients (two each in the placebo and omeprazole 20 mg groups and one in the omeprazole 10 mg groups) discontinued treatment

Table 5. Rate of sufficient relief from heartburn during the fourth week of treatment (FAS)

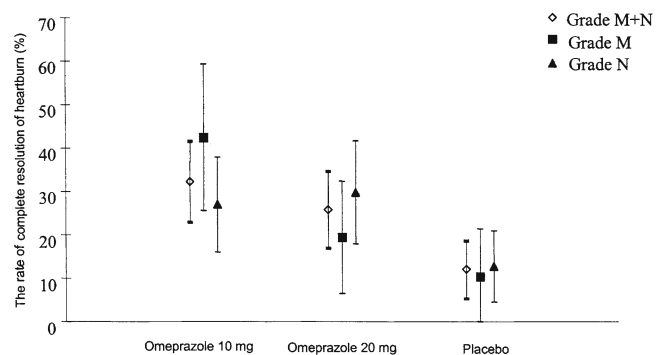| Treatment | Estimate | 95% CI | |
		Lower	Upper
Omeprazole 10 mg	45.8%	35.9%	55.8%
Omeprazole 20 mg	46.2%	36.1%	56.4%
Placebo	23.9%	15.2%	32.6%

Fig. 2. Rate of patients with a grade M or N esophagus with complete resolution of heartburn during the fourth week of treatment (estimate and 95% confidence interval, full analysis set)

Table 6. Most commonly reported adverse events[a]

	Number of patients (%)		
	Omeprazole 10 mg ($n = 96$)	Omeprazole 20 mg ($n = 93$)	Placebo ($n = 94$)
Nasopharyngitis	4 (4.2)	5 (5.4)	9 (9.6)
Diarrhea	4 (4.2)	7 (7.5)	2 (2.1)
Overdose[b]	1 (1.0)	3 (3.2)	2 (2.1)
Loose stools	2 (2.1)	3 (3.2)	0
Constipation	1 (1.0)	1 (1.1)	2 (2.1)
Upper respiratory tract infection	0	1 (1.1)	2 (2.1)
Pharyngolaryngeal pain	0	2 (2.2)	0

[a] ≥2 patients in any treatment group are shown
[b] Overdose was defined as higher than the intended dose; these patients did not show any adverse reactions

because they took a higher than intended dose. None of these patients showed any adverse drug reaction to the higher dose. The most commonly reported adverse events are summarized in Table 6. No clinically important changes in hematology, clinical chemistry, or urinalysis results were observed during the study.

Discussion

The present study demonstrated that treatment with omeprazole 10 mg or 20 mg once daily is effective for Japanese patients with NERD. Both doses resulted in a significantly higher rate of complete resolution of heartburn compared with placebo. The rate of complete resolution of heartburn in the present study (32.3% for omeprazole 10 mg and 25.8% for omeprazole 20 mg) is comparable to rates reported in Western studies of patients with NERD. In Western studies, the rate of complete resolution of heartburn is 31%–49% in patients treated with omeprazole 10 mg, 41%–68% in patients treated with omeprazole 20 mg,[8–11] and 32% in patients treated with rabeprazole 20 mg.[17] This suggests that omeprazole treatment is as effective in Japanese patients with NERD as in Western patients with NERD.

Curiously, the rate of complete resolution of heartburn by omeprazole in the present study was low compared with the efficacy of omeprazole for other indications. Similarly, clinical studies have shown that patients with NERD respond poorly to treatment with PPIs when compared with patients with erosive esophagitis.[18] There are three possible reasons for the observed lower efficacy.

First, patients with an attenuated response to PPIs (e.g., functional heartburn) might have been included in the present study. Functional heartburn is characterized clinically by burning retrosternal discomfort or pain without pathologic GERD.[19] Although the definition of heartburn was carefully determined in the present study, recruitment of patients without acid-related reflux might have influenced the result.

Second, patients with frequent heartburn episodes were included in the present study. The frequency of heartburn at baseline in the present study (5.7–6.0 days per week) was higher than that in the Western studies (3–4 days per week).[8–11] The inability of omeprazole to achieve complete resolution might be related to the increased frequency of heartburn in the patients chosen for the present study. In fact, the logistic regression analysis in the present study showed that the frequency of heartburn at baseline affected the rate of complete resolution of heartburn. Interestingly, patients received antacids before administration of the study treatment but still had frequent heartburn at baseline. This finding suggests that antacids may have limited efficacy for heartburn in NERD patients or that responders to antacids were excluded after the antacid dosing in the observation period.

Third, the use of complete resolution of heartburn as the primary end point might be a rather strict efficacy variable. The definition of complete resolution of heartburn required no heartburn for 7 consecutive days, which might be difficult to achieve in a study with patients having heartburn episodes at high frequency. However, sufficient relief from heartburn, which requires either no heartburn or no more than 1 day with mild heartburn for 7 consecutive days, showed better study results (45.8% for omeprazole 10 mg; 46.2% for omeprazole 20 mg; 23.9% for placebo). In medical practice, disease control that gives at least sufficient relief is considered an appropriate goal for treatment of NERD.[20]

A combination of these three factors may have affected the primary end point in the present study. Nevertheless, omeprazole showed acceptable efficacy in

bringing about sufficient relief from heartburn. Thus, we conclude that omeprazole is an effective option for treatment of NERD in medical practice.

In Hoshihara's modification of the LA classification, the esophagus of patients with NERD is graded according to the appearance of the esophageal mucosa, but it is not known whether the response to therapy differs between grades. The present study found no substantial difference between patients with a grade M or N esophagus in the rate of complete resolution of heartburn by logistic regression and subgroup analysis. The overall similarity in results between the two grades is consistent with the results of a pharmacodynamic study[21] in which omeprazole produced a comparable reduction in the acidity (i.e., pH < 4) in the esophagus and in the number of heartburn episodes in both patients with grade M and those with grade N NERD. It appears, therefore, that the treatment benefit achieved with omeprazole applies irrespective of grade M or N. On the other hand, a study that evaluated interobserver variance and diagnostic agreement for NERD (grades M and N) showed that the degree of interobserver agreement was too low to be of clinical value.[22] Consequently, since it may be considered unnecessary to classify patients as having grade M or grade N for treatment purposes, omeprazole can be a useful treatment option to relieve symptoms of heartburn and to improve the quality of life of patients with NERD irrespective of its endoscopic classification as grade M or grade N.

CYP2C19 displays a gene polymorphism that influences the pharmacokinetics and pharmacodynamics of omeprazole. In the present study, however, logistic regression analysis showed no significant influence of *CYP2C19* genotype on the rate of complete resolution of heartburn. This result is congruent with the results of a study of patients with reflux esophagitis that also showed no influence of *CYP2C19* genotype on efficacy of omeprazole.[23] The proportions of patients classified as poor metabolizers in both studies were comparable to the proportion in the Japanese population, suggesting that omeprazole is effective for NERD treatment regardless of the *CYP2C19* genotype of the patient.

The prevalence of *H. pylori* infection, which affects acid secretion, is particularly high in the Japanese population. We also investigated whether the efficacy of omeprazole was affected by infection with *H. pylori*. In the present study, logistic regression analysis showed that *H. pylori* infection had no significant influence on the rate of complete resolution of heartburn during the 4-week treatment with omeprazole. This finding is in line with the result of another Japanese study, which reported that omeprazole was effective for treatment of NERD regardless of *H. pylori* infection status.[12] Thus, omeprazole is considered to be effective for NERD treatment irrespective of *H. pylori* infection, although

famotidine is less effective in relieving GERD symptoms in *H. pylori*-negative patients. Since eradication therapy is one of the treatments of choice for *H. pylori*-positive patients, PPIs such as omeprazole can be recommended to relieve acid-related symptoms in patients with NERD.

It is unclear why PPIs are less effective in a subset of patients. NERD is a heterogeneous disease with multiple pathological mechanisms of heartburn. In addition to acid reflux, other hypotheses have emerged to explain nonacid reflux, such as functional heartburn (e.g., hypersensitive esophagus and abnormal esophageal motility).[24] It is not easy to clearly distinguish NERD from functional heartburn by using the Montreal definition[25] or the Rome III criteria[26] because in clinical practice both diseases are diagnosed mainly by symptoms. However, considering the nature of the two diseases, it is important to focus on acid for their diagnosis and treatment. Although a PPI test and 24-h intraesophageal pH monitoring are useful procedures for identifying acid reflux,[24] it is not feasible to routinely conduct these tests in clinical practice. However, identifying responders to PPIs by using more conventional procedures would be beneficial in medical practice. In the present study, we conducted an exploratory analysis to assess whether the treatment response (i.e., improved, unchanged, or aggravated) at week 2 could be used to predict efficacy at week 4. Treatment response was evaluated based on the number of days with heartburn and the maximum intensity of heartburn at week 4 compared with those at the time of study entry. Overall assessment of treatment response was classified as YES (improved) or NO (unchanged or aggravated) for further estimation (Table 7). Among the 93 patients who completed 4 weeks of treatment with omeprazole 10 mg, 74 showed a YES response and 19 showed a NO response at week 2. Among the 74 patients with the YES response at week 2, 73 (98.6%) achieved a YES response at week 4 (Fig. 3). In addition, 31 (41.9%) and 42 (56.8%) of these patients showed complete resolution of heartburn and sufficient relief, respectively, at week 4. By contrast, of the 19 patients with a NO response at week 2, only two (10.5%) achieved sufficient relief at week 4 and no patients achieved complete resolution of heartburn. Thus, the majority of patients who showed a positive treatment response to omeprazole at week 2 achieved complete relief or sufficient relief at week 4 in the present study. These findings indicate an early treatment response at week 2 can accurately predict efficacy at week 4 in patients with NERD.

Omeprazole was well tolerated in the present study. The adverse event profile in the two omeprazole groups was comparable to that in the placebo group, and there were no drug-related serious adverse events or clinically

Table 7. Criteria for an overall assessment of treatment response based on changes in the individual measures, number of days with heartburn, and maximum intensity of heartburn

Change in days with heartburn	Change in maximum intensity of heartburn		
	Improved	Unchanged	Aggravated
Decreased	YES (Improved)	YES (Improved)	NO (Unchanged)
Unchanged	YES (Improved)	NO (Unchanged)	NO (Aggravated)
Increased	NO (Unchanged)	NO (Aggravated)	NO (Aggravated)
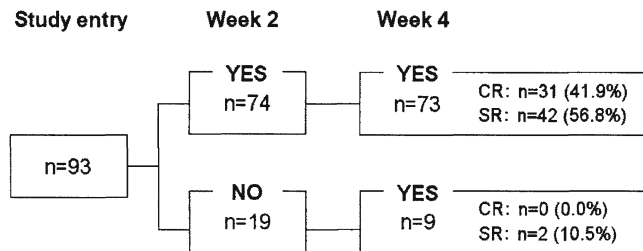
Fig. 3. Summary of treatment responses at weeks 2 and 4 among the patients who completed 4 weeks of treatment with omeprazole 10 mg. *CR*, complete resolution of heartburn; *SR*, sufficient relief; *YES*, categorized as Improved (see Table 7); *NO*, categorized as Unchanged or Aggravated (Table 7). The percentages in the week 4 boxes were calculated in relation to the number of patients in the corresponding week 2 therapeutic response group (YES or NO)

significant abnormalities in the clinical laboratory test results. This favorable safety profile is similar to that reported in studies outside Japan[27] and in a study of long-term omeprazole maintenance therapy in Japanese patients with reflux esophagitis.[23]

In conclusion, treatment with omeprazole 10 mg or 20 mg once daily is effective in Japanese patients with NERD. The classification of the esophagus as grade M or grade N does not affect the response to omeprazole. Omeprazole was well tolerated throughout the study period. Thus, omeprazole 10 mg or 20 mg is effective and well tolerated in Japanese patients with NERD, regardless of their endoscopic classification.

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