Characteristics of Refractory Gastroesophageal Reflux Disease (GERD) Symptoms—Is Switching Proton Pump Inhibitors Based on the Patient's CYP2C19 Genotype an Effective Management Strategy?

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Abstract

Objective We investigated factors related to proton pump inhibitor (PPI) -refractory gastroesophageal reflux disease (GERD) symptoms, particularly with respect to acid, the CYP2C19 genotype and psychological aspects.

Methods Patients with an Frequency Scale for the Symptoms of GERD (FSSG) score of ≥ 8 after the initial treatment were switched to therapy with rabeprazole at a dose of 20 mg once daily for eight weeks. We investigated the rate of improvement in PPI-refractory GERD symptoms, background factors, the Hospital Anxiety and Depression Scale (HADS) score and the CYP2C19 genotype.

Patients Sixty patients endoscopically diagnosed with reflux esophagitis within the past six months who had received omeprazole at a dose of 20 mg once daily for eight weeks or longer were enrolled.

Results In 71.6% of the patients, the FSSG score decreased to < 8 after treatment with omeprazole at a dose of 20 mg once daily for ≥ 8 weeks, resulting in improvements in their GERD symptoms. Significant factors related to omeprazole-refractory GERD symptoms included a longer disease duration ($p=0.0004$) and higher HADS score ($p=0.01$). Among the omeprazole-refractory cases, only 23.5% of the patients showed symptom improvement after switching to rabeprazole. There were no significant differences in the average scores for FSSG ($p=0.089$) or HADS ($p=0.182$), before or after the drug change. A total of 92% of the rabeprazole poor responders were homo/hetero extensive metabolizers for the CYP2C19 genotype.

Conclusion Our findings suggest that switching the PPI from omeprazole (20 mg once daily) to rabeprazole (20 mg once daily) is not a significant effective therapeutic strategy for improving PPI-refractory GERD symptoms, taking into consideration possible psychometric factors and patients who require stronger acid suppression than that achieved with a double dose of PPIs for PPI-refractory GERD symptoms.

Key words: omeprazole, rabeprazole, CYP2C19 genotype, gastroesophageal reflux disease, PPI-refractory GERD symptoms

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Introduction

Gastroesophageal reflux disease (GERD) is a condition that damages the esophageal mucosa via the regurgitation of stomach contents, primarily gastric acid, into the esophagus. Global attention has been focused on GERD as a disease since the 1980's, and the Montreal Definition (1) was released in 2006 as an international consensus on this disorder. Subsequently, the Asian-Pacific Consensus (2) in the Asia-Pacific region, and ACG Guidelines (3) of the American College of Gastroenterology (ACG) in the USA were formulated as international treatment guidelines for GERD.

The incidence of reflux esophagitis (RE) is increasing (4) in Japan in association with aging of the population, Westernization of the diet, a decrease in the rate of *Helicobacter pylori* (*H. pylori*) infection, etc. As in the overseas guidelines, the GERD treatment guidelines (5) compiled by the Japanese Society of Gastroenterology recommend the use of proton pump inhibitors (PPIs) as the first choice drug both for RE and non-erosive reflux disease (NERD).

The standard dose of PPIs is administered in most patients with GERD; however, GERD symptoms do not exhibit remission in some patients, and several treatment methods may be applied in cases in which the therapeutic effect of standard-dose PPI therapy is insufficient. Concerning drug therapy, several investigations have been published regarding the efficacy of changing the dose or dividing the administration of PPIs (6-8), as well as the concomitant use of other drugs, including histamine H₂-receptor antagonists (H₂RAs) (9) and prokinetic agents (10). In addition, switching between PPI medications is another treatment choice.

Currently, four PPIs are clinically available in Japan, including omeprazole, lansoprazole, rabeprazole and esomeprazole. However, the findings of reports of differences in clinical effect between PPIs vary, and the choice of drug and dose depend on the clinical experience of the physician. As a result, there is currently no established evidence supporting a standard treatment regimen.

In this study, we investigated the background factors of PPI-refractory patients with GERD symptoms who did not respond sufficiently to treatment with omeprazole at a dose of 20 mg once daily, the standard drug and dose of PPI therapy in Japan, and evaluated the therapeutic effect of switching to rabeprazole at a dose of 20 mg once daily, double the recommended dose in Japan. In addition, psychometric factors were considered as a cause of a treatment refractory status, as an association between GERD symptoms and anxiety or depression has been reported in some studies (11, 12).

Materials and Methods

Patients

Of the patients who visited institutions from August 2010

to August 2012, those 20 years of age or older who were endoscopically diagnosed with RE associated with erosion of grade A to D according to the LA classification within the past six months and had received omeprazole at a dose of 20 mg once daily for eight weeks or longer were enrolled consecutively at each site.

Patients were excluded based on the following criteria: (i) a history or complications of Zollinger-Ellison syndrome, inflammatory bowel disease or irritable bowel syndrome, (ii) a history of gastroenterectomy or vagotomy, (iii) complications of peptic ulcers, (iv) serious hepatic, renal or cardiac disease, (v) a history of *H. pylori* eradication therapy within two months prior to the start of the study, (vi) treatment with the continuous administration of any drugs known to interact with the study drugs.

The study protocol was conducted according to the Helsinki Declaration, with written informed consent obtained from the patients after sufficiently explaining the purpose, methods, merits and possible risks of the study. Approval of the Institutional Review Board of each hospital was obtained prior to initiation of the study.

Study design and method

This study was designed as a multicenter, single-arm, open label study.

Fig. 1 shows the study procedure. Patients who satisfied the inclusion criteria completed the following questionnaires: the Frequency Scale for the Symptoms of GERD (FSSG) (13) and Hospital Anxiety and Depression Scale (HADS) (14). The HADS has been previously validated and consists of seven questions for anxiety and seven questions for depression. Each item is answered on a 4-point (0-3) scale. The score for each subcategory (anxiety and depression) ranges from 0-21, as follows: without anxiety/depression (0-7), suspected anxiety/depression (8-10), with anxiety/depression (11<).

Excluding PPIs, the concomitant use of drugs for the digestive system was allowed only in cases in which the treatment had been initiated prior to the switch to rabeprazole; no changes in the dose or agent were allowed during the study period.

Endpoints

The primary endpoint was the identification of background factors related to the therapeutic effect of the oral administration of omeprazole at a dose of 20 mg once daily for ≥ 8 weeks. The rate of symptom improvement was defined as an FSSG score of < 8 points. The secondary endpoint was the identification of factors of a poor response to rabeprazole treatment based on the same definition for the FSSG score. Furthermore, the CYP2C19 genotype and changes in the FSSG and HADS scores from before to after the oral administration of rabeprazole were investigated.

Statistical methods

The rate of symptom improvement was presented descrip-

Figure 1. Study design. Factors related to the therapeutic response to therapy with orally administered omeprazole (20 mg once daily) were investigated in the RE patients receiving treatment with omeprazole at a dose of 20 mg once daily for ≥ 8 weeks and who satisfied the enrollment criteria. In addition, changes in the FSSG and HADS scores were investigated. Patients with an FSSG score of ≥ 8 points were managed as being omeprazole-refractory, and the treatment regimen was changed to the oral administration of rabeprazole at a dose of 20 mg once daily for eight additional weeks. CYP2C19 gene tests were conducted during the rabeprazole treatment period, and the same factors as those investigated during the treatment period with omeprazole (20 mg once daily) were again investigated, as well as changes in the FSSG and HADS scores after the completion of rabeprazole therapy.

tively. Background factors related to an unsuccessful response to omeprazole and/or rabeprazole were analyzed according to the χ^2 test, with a significance level of 5%.

Changes in the mean FSSG and HADS scores were analyzed according to the two-sided paired *t*-test, with a significance level of 5%.

Sample size

A sample size of approximately 100 patients was determined to be required for the investigation of background factors (approximately 10 factors) with respect to the primary endpoint (the treatment response to omeprazole at a dose of 20 mg once daily for ≥ 8 weeks) (15). Regarding the required number of patients for the secondary endpoint (the assessment of the rate of improvement in the FSSG scores from before to after treatment with rabeprazole at a dose of 20 mg once daily), the proportion of subjects demonstrating a treatment response to therapy with omeprazole at a dose of 20 mg once daily for ≥ 8 weeks (proportion of those with a comprehensive FSSG score of < 8 points) was assumed to be 60%. Meanwhile, a total of 93 patients was required for the estimation of the confidence interval within a range of $\pm 10\%$. Accordingly, the target number of patients was set at 100.

Results

Patient background factors and flowchart

A total of 60 patients, including 32 men and 28 women, were enrolled in this study. The mean patient age was 61.9 ± 11.2 years. A total of 17 patients smoked and 19 drank alcohol. Thirty patients had a disease duration between ≥ 2 and < 12 months.

Fifty patients were negative for *H. pylori* infection. With respect to RE, 29 patients had Grade A disease, 25 patients had Grade B disease, five patients had Grade C disease and one patient had Grade D disease according to the LA classification.

Fig. 2 shows the patient flowchart. A total of 17 patients were switched from omeprazole (20 mg once daily) to rabeprazole (20 mg once daily) due to a lack of therapeutic effect.

Primary endpoint

Table 1 shows the therapeutic effect of treatment with omeprazole at a dose of 20 mg once daily for ≥ 8 weeks according to the patients' background factors. The longer the duration of disease ($p=0.0004$, χ^2 test), the larger the number of patients found to be refractory to omeprazole therapy

Figure 2. Patient flowchart. The therapeutic effect was investigated based on an FSSG score of <8 and ≥8 points following the administration of oral omeprazole at a dose of 20 mg once daily for ≥8 weeks as being present (treatment response cases) or absent (treatment refractory cases), respectively, with a symptom improvement rate of 71.6%. The oral administration of rabeprazole at a dose of 20 mg once daily for eight weeks in 17 patients whose treatment with omeprazole (20 mg once daily) was judged to be ineffective (poor responders) did not show any improvements in symptoms.

at a dose of 20 mg once daily. The subjects who tested negative for *H. pylori* infection (*NS*, $p=0.159$, χ^2 test) and did not have any complications (*NS*, $p=0.076$, χ^2 test) tended to be more refractory to treatment; however, no other factors exhibited a significant difference.

Based on the results for the HADS score, the more severe the anxiety and/or depression, the greater the likelihood of being refractory to treatment with omeprazole at a dose of 20 mg once daily ($p=0.01$, χ^2 test) (Fig. 3). In addition, a significant positive correlation was observed between the FSSG and HADS score ($p=0.00002$, $R=0.562$, Spearman's rank correlation coefficient) (Fig. 4).

Among the patients with an FSSG score of <8 points, defined as achieving remission of GERD symptoms, the rate of symptom improvement associated with treatment with omeprazole at a dose of 20 mg once daily was 71.6% (43/60 patients), while that associated with treatment with rabeprazole at a dose of 20 mg once daily for eight weeks was 23.5% (4/17 patients).

Secondary endpoint

Treatment with rabeprazole at a dose of 20 mg once daily did not correlate with any significant differences in the therapeutic effect when assessed according to the severity of anxiety and/or depression. In this regard, 92% (12/13) of the rabeprazole treatment poor responders were homo/hetero extensive metabolizers (EM) of the CYP2C19 genotype (Table 2). Furthermore, no significant differences were observed in the FSSG or HADS score before or after the administration of rabeprazole (20 mg once daily) ($p=0.089$, $p=0.182$, respectively, paired *t*-test) (Fig. 5).

Discussion

In this study, the percentage of patients with an FSSG score of ≥8 and omeprazole-refractory symptoms was 28.3% (17/60 patients), and, even after switching to the double dose of rabeprazole of 20 mg once daily, no improvements in symptoms were observed in more than 75% of the patients.

Some reports have demonstrated that 10% to 20% of RE patients display resistance to PPI treatment (16-18); however, this finding is based on the rate of endoscopic healing, and it has also been reported that the number of patients with persistent symptoms is greater than recognized (19).

In a systematic review of seven trials comparing PPIs with a placebo, the rate of GERD symptom improvement after four weeks of treatment with a PPI was found to be 55.5% in patients with RE and 36.7% in patients with NERD, with a significant difference ($p<0.0001$) (20). Therefore, RE patients, who experience a longer duration of exposure to esophageal acid, obtain a higher symptom improvement rate with PPI treatment than NERD patients and that a higher percentage of NERD patients are refractory to PPI therapy.

The present study included patients with RE, which develops due to acid regurgitation, and therefore differs from studies of NERD patients in terms of background factors. Few reports have evaluated the degree of symptom improvement achieved by switching PPIs in patients whose symptoms persist after PPI treatment for ≥8 weeks, as in this study. In order to fully evaluate the treatment effects, we switched to rabeprazole at a dose of 20 mg once daily (double dose), which has a stronger acid-suppressing effect.

Comparing rabeprazole with omeprazole and lansoprazole, there were fewer differences in metabolic ability between the poor metabolizer (PM) and EM groups, and CYP2C19 contributed less to metabolic clearance. Therefore, rabeprazole is considered to be affected by CYP2C19 to a lower degree. In one study that evaluated the rate of recurrence of GERD symptoms in RE patients receiving maintenance therapy with omeprazole (20 mg once daily), lansoprazole (15 mg once daily) or rabeprazole (10 mg once daily) for six months, the recurrence rate was 25% in the omeprazole group, 30.8% in the lansoprazole group and 4.4% in the rabeprazole group; the recurrence rate in the rabeprazole group was significantly lower than that observed in the other two groups (21). In addition, the rate of recurrence according to the CYP2C19 genotype was 10.9% in the heterozygous EM group and 5.6% in the PM group, compared to 38.5% in the homozygous EM group. The authors pointed out that the presence of homozygous EM patients in the Japanese population reduces the clinical effects of PPIs.

In the present study, an improvement in symptoms was observed after switching to the double dose of rabeprazole (20 mg once daily) in 23.5%, less than one-quarter, of the patients. Two possibilities may be considered based on this

Table 1. Therapeutic Effect by Background Factor after Treatment with Omeprazole at a Dose of 20 mg Once Daily for ≥ 8 Weeks

Background factors		Omeprazole responders (n=43)	Omeprazole refractory cases (n=17)	Total (n=60)	p value (unknown excluded)
Gender	Male	23	9	32	NS
	Female	20	8	28	
Age	30s	1	1	2	NS
	40s	4	5	9	
	50s	8	1	9	
	60s	16	7	23	
	70s	12	3	15	
	80s	2	0	2	
	Mean	63.5 $\pm$ 10.5	57.8 $\pm$ 12.4	61.9 $\pm$ 11.2	
Age	< 65 years	21	10	31	NS
	≥ 65 years	22	7	29	
Smoking	No	31	12	43	NS
	Yes	12	5	17	
Alcohol drinking	No	28	13	41	NS
	Yes	15	4	19	
<i>H. pylori</i> infection	Negative	34	16	50	NS
	Positive	9	1	10	
LA classification	A	18	11	29	NS
	B	20	5	25	
	C	4	1	5	
	D	1	0	1	
GERD duration	≤ 2 months	13	2	15	p=0.0004
	≤ 6 months	14	1	15	
	≤ 12 months	1	5	6	
	> 12 months	4	6	10	
	Unknown	11	3	14	
Hernia	No	29	9	38	NS
	Yes	14	8	22	
Extent of hernia	≤ 1 cm	15	5	20	NS
	1-3 cm	10	4	14	
	> 3 cm	4	0	4	
	Unknown	14	8	22	
Complication	No	25	14	39	NS
	Yes	18	3	21	

χ^2 test
(n=60)

result. 1) The acid-suppressing effects of rabeprazole (20 mg once daily) did not differ from those of omeprazole (20 mg once daily), as has been reported and may also have been affected by the CYP2C19 genotype, meaning that the drug was unable to produce an additional acid-suppressing effect. Contrary to expectations, our findings suggest that switching from omeprazole (20 mg once daily) to rabeprazole (20 mg once daily, the double dose), is not very effective as a therapeutic strategy for improving GERD symptoms. In this study, 92% of the patients refractory to treatment with rabeprazole at a dose of 20 mg once daily exhibited an EM status, with an equal number of subjects being homo- and heterozygous EM; thus, the rabeprazole treatment may have been affected by the CYP2C19 genotype in terms of symptom improvement. 2) Taking into account the findings of past reports of the acid-suppressing effects of rabeprazole

(20 mg once daily), acid regurgitation may be involved to a minor extent in the condition of patients with symptoms lasting after the administration of omeprazole at a dose of 20 mg once daily for ≥ 8 weeks. That is to say, factors other than acid, such as psychometric factors, as discussed below, may play a significant role.

The results of the FSSG and HADS questionnaires showed that the patients with persistent GERD symptoms had specific background factors, including a longer disease duration and more severe anxiety and/or depression. Two studies in Japan used the FSSG alone to evaluate background factors related to PPI-refractory symptoms. In one study, 101 GERD patients (28 RE patients, 73 NERD patients) were treated with rabeprazole at a dose of 10 mg once daily for four weeks, and, if their symptoms were not relieved, the rabeprazole dose was doubled every two

Figure 3. Therapeutic effect of treatment with omeprazole at a dose of 20 mg once daily according to the presence/absence of psychometric factors. The more severe the anxiety and/or depression, the larger the number of patients found to be refractory to treatment with omeprazole at a dose of 20 mg once daily.

Figure 4. Relationship between the FSSG score and HADS score following treatment with omeprazole at a dose of 20 mg once daily. A significant correlation was observed between the FSSG and HADS scores: the higher the FSSG score, the higher the HADS score.

weeks. Background factors related to heartburn relief or persistence were subsequently assessed over a total of eight weeks (22). Consequently, the rate of complete heartburn relief in the RE patients was 67.9%, 84.0% and 91.7% after

Table 2. Background Factors of Patients Treatment with Rabeprazole at a Dose of 20 mg Once Daily

Background factors		Rabeprazole responders (n=4)	Rabeprazole poor responders (n=13)	Total (n=17)	p value
CYP2C19 genotype	EM	2	12	14	NS
	PM	2	1	3	
Degree of anxiety/depression	With/ Suspected	3	9	12	NS
	Without	1	4	5	

 χ^2 test
(n=17) **Figure 5.** Changes in the FSSG and HADS scores from before to after treatment with rabeprazole at a dose of 20 mg once daily. No significant differences were noted in the FSSG or HADS scores from before to after the administration of rabeprazole at a dose of 20 mg once daily.

four, six and eight weeks, respectively, and more than 90% of the patients achieved complete symptom relief following the administration of rabeprazole 40 mg once daily. In contrast, the rate of complete heartburn relief in the NERD patients was 42.5%, 61.5% and 68.9%, respectively. Furthermore, background factors associated with resistance to rabeprazole (10 mg once daily, the standard dose in Japan) were a female sex, non-smoking, frequent heartburn, low FSSG Q4 score (a question about acid reflux: “subconsciously rubbing the chest”), high Q7 score (“unusual sensation in the throat”) and high Q3 score (a question about dysmotility: “a heavy stomach after a meal”). Meanwhile, background factors associated with resistance to rabeprazole (20 mg once daily, a double dose in Japan) included frequent heartburn and a high Q7 score. In the other study, the PPI non-response rate and background factors were assessed among 467 GERD patients (118 RE patients, 349 NERD patients), including RE patients who received rabeprazole at a dose of 10 mg once daily, lansoprazole at a dose of 30 mg once daily or omeprazole at a dose of 20 mg once daily and

NERD patients who received a half dose of lansoprazole or omeprazole for two weeks (23). Consequently, the PPI non-response rates in the RE and NERD patients were 42.4% and 52.7%, respectively, and factors for PPI non-response in both patient groups were a younger age and higher score on the FSSG dysmotility question Q8 (“fullness while eating”).

The HADS is a self-administered questionnaire developed to evaluate states of depression and anxiety independently from physical symptoms (24). We searched PubMed for studies that used the HADS alone in GERD patients and we found none conducted in Japan and two performed outside Japan. One study had evaluated GERD patients with sleep disturbances and emotional dysfunction (25), while the other had assessed GERD patients with asthma (26). Both studies described a relationship between symptoms and psychometric factors; however, the analyses were conducted in GERD patients with other diseases and thus cannot be directly compared with our findings. The present study is the first to report a significant correlation between the FSSG and HADS in RE patients with PPI-refractory GERD symptoms.

In our study, the mean HADS total score before and after switching to rabeprazole (20 mg once daily) was 10.3 and 9.7, respectively, both of which are lower than that reported in the two studies discussed above. In addition, the level of anxiety and/or depression in this study was assessed as mild based on the HADS score, and no changes in the scores were observed as a result of switching the PPI treatment. Therefore, there is a possibility that psychometric factors were strongly involved in producing PPI-refractory symptoms in our study population. Our results suggest that the use of both FSSG and HADS to evaluate the level of anxiety and depression in RE patients makes it easier to predict whether a patient will be PPI-refractory due to psychometric factors. In addition, the fact that the PPI-refractory patients had higher HADS scores suggests the possibility that some of these patients also had a preexisting functional gastrointestinal disorder, such as functional dyspepsia, which is strongly associated with psychological stress.

These observations suggest the possibility that, even in patients diagnosed with RE, switching to treatment with a double dose of a PPI does not show promise in subjects with persistent PPI-refractory symptoms. Potential reasons for this result include 1) the presence of patients in whom psychometric factors play a major role, as evaluated according to the HADS, and 2) the presence of cases that require stronger acid suppression than that achieved with a double dose of PPI therapy. In addition, we cannot rule out alkaline reflux or hyperesthesia as a cause of persistent symptoms. However, in this study, endoscopic examinations and alkaline reflux tests were not performed following the administration of omeprazole or the switch to rabeprazole. Therefore, we were not able to determine the causes of the remaining symptoms in individual PPI-refractory patients. The limitations of our study include the fact that the sample of patients considered to be PPI-refractory and who switched drugs was small and that CYP2C19 genotyping was performed only in this small subset.

Conclusion

The results of this study indicate that switching from omeprazole (20 mg once daily) to rabeprazole (20 mg once daily) is not an effective therapeutic strategy for improving PPI-refractory GERD symptoms, taking into consideration possible psychometric factors and the presence of patients who require stronger acid suppression than that achieved with a double dose of PPIs for PPI-refractory GERD symptoms.

The authors state that they have no Conflict of Interest (COI).

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