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Clinical Characteristics of Patients with Gastroesophageal Reflux Disease Refractory to Proton Pump Inhibitors and the Effects of Switching to 20 mg Esomeprazole on Reflux Symptoms and Quality of Life

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Background: Refractory gastroesophageal reflux disease (GERD) may deteriorate patient quality of life (QOL) despite proton pump inhibitor (PPI) therapy.

Material/Methods: Nineteen Japanese institutions were surveyed to determine the clinical characteristics and QOL of patients with refractory GERD. Those patients treated with a conventional PPI were switched to 20 mg esomeprazole for 4 weeks. Symptoms and QOL were assessed using Global Overall Symptom and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires at baseline and at 2 and/or 4 weeks of esomeprazole treatment.

Results: Of 120 patients who completed the survey, 58 (48.3%) had refractory GERD. Of these, 69.0% were aged ≥65 years, 79.3% were prescribed a PPI at a standard or high dose, and 22.4% were prescribed a PPI together with another drug. After switching to esomeprazole, patients reported significant improvements in heartburn, acid regurgitation, and excessive belching at 2 weeks using a symptom diary, as well as the total score, reflux, abdominal pain, and indigestion, which were assessed using the GSRS at 4 weeks.

Conclusions: About half of Japanese patients with GERD may be refractory to conventional PPIs. Their reflux-related symptoms are often severe and may impair QOL. Switching to esomeprazole could be used to improve their symptoms and QOL.

MeSH Keywords: Esomeprazole • Gastroesophageal Reflux • Proton Pump Inhibitors • Quality of Life

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Background

The symptoms of gastroesophageal reflux disease (GERD), such as heartburn and acid regurgitation, are serious problems that cause discomfort, impair quality of life (QOL) [1], and affect the mental state and social activities of patients. Although proton pump inhibitors (PPIs) are the first-line therapy for reflux esophagitis [2], some cases are refractory to these drugs. The Japanese guidelines for the diagnosis and treatment of GERD recommend adjusting the dose of the PPI, switching the type of PPI, or adding a prokinetic agent in refractory cases [2]. Because the proton pump-binding and pharmacokinetic properties of PPIs vary [3–6], switching to another PPI may be an effective treatment strategy.

Esomeprazole, a PPI, is an *S*-enantiomer of omeprazole that was approved in July 2011 in Japan. Because esomeprazole has greater inhibitory effects on gastric secretion than other PPIs [7], it is expected to become a therapeutic option for refractory GERD. In prior studies of Japanese patients, switching to esomeprazole was associated with improvements in symptoms [8,9]. Although several studies have examined the improvements in symptoms, no study in English with Japanese patients examined the changes in QOL. Because QOL is an important component of clinical care of patients with GERD, it is essential to determine the effects of changing the PPI on QOL as well as symptoms.

To address this limitation of prior studies, we first conducted a survey of patients with GERD treated with conventional PPIs (omeprazole, lansoprazole, or rabeprazole) to identify those with refractory disease, and recorded the clinical characteristics of these patients. After obtaining informed consent, these patients were switched to oral esomeprazole at a dose of 20 mg once daily for 4 weeks to examine the effects of switching the PPI on the QOL of these patients.

Material and Methods

This study was conducted at 19 institutions between February 2012 and March 2013, and complied with the Declaration of Helsinki (World Medical Association) and the Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare, Japan). The study protocol was approved by the medical ethics committee of Nagasaki University. The patients were given a description of the study and provided written informed consent before enrollment. This study was registered with the University Hospital Medical Information Network (identifier: UMIN000013708).

Patients

Participating investigators searched their medical records to identify patients who had visited any of the participating institutions between February 2012 and March 2013, were aged ≥20 years, and who had been diagnosed with Grade A or worse reflux esophagitis according to the Los Angeles Classification of endoscopic findings. Patients were eligible for the switching study if they had refractory GERD, which was defined as disease with scores of ≥4 (moderate or higher) for question 2 (heartburn) or question 3 (acid regurgitation) in the Global Overall Symptom (GOS) questionnaire after treatment with a conventional PPI (omeprazole, lansoprazole, or rabeprazole) for ≥8 weeks. Patients with any of the following were excluded from the switching study: history of gastric resection or vagotomy; presence of vomiting, gastrointestinal bleeding (including hematemesis, melena, and anemia), or sudden weight loss; history of structural brain disorders, schizophrenia, or a predisposition to schizophrenia; known addiction to alcohol or drugs; presence of serious cardiac, hepatic, renal, or hematopoietic disorders; or a history of hypersensitivity to the ingredients of the study drug.

Clinical survey of patients with GERD

First, we asked patients to complete the GOS to identify patients with refractory GERD. The questionnaire objectively assesses the severity and improvements in overall gastroenterological symptoms by grading a range of general digestive and reflux-related symptoms, which include acid-related and non-acid-related symptoms [10]. The GOS questionnaire recorded eight symptoms (epigastric pain, heartburn, acid regurgitation, heavy stomach feeling, nausea, excessive belching, early satiety, and upper abdominal bloating), which were graded using a 7-point scale, where 1=no problems; 2=minimal problems (can be easily ignored without effort); 3=mild problems; 4=moderate problems; 5=moderately severe problems; 6=severe problems; and 7=very severe problems (cannot be ignored and markedly limit daily activities and often require rest) [10]. This questionnaire has been used in Japanese studies [11,12], although the Japanese version of the GOS has not yet been validated. Patients on a conventional PPI with reflux-related symptoms and scores of ≥4 for question 2 (heartburn) or question 3 (acid regurgitation) were classified as having refractory GERD. We chose this objective questionnaire because it allowed us to ask about the onset and severity of symptoms other than acid-related symptoms in patients whose symptoms persisted despite PPI therapy for >8 weeks.

Switching study

We next conducted a prospective, nonrandomized, open-label, uncontrolled study in which patients with refractory

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GERD who required maintenance therapy were switched to oral esomeprazole at a dose of 20 mg once daily for 4 weeks. The patients enrolled in this phase of the study completed the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire [13] and GOS questionnaire before and at 2 and 4 weeks after starting esomeprazole therapy. The GSRS questionnaire was used to evaluate changes in QOL. It consists of 15 items that assess the following general gastrointestinal symptoms: pain or discomfort in the upper abdomen or in the pit of the stomach; heartburn; acid reflux; hunger pains; nausea; rumbling; bloating; belching; breaking wind; constipation; diarrhea; loose stools; hard stools; urgent need to have a bowel movement; and the sensation of not completely emptying the bowels. Each item is graded on a 7-point scale in which higher scores indicate worse QOL. The Japanese version of the GSRS has not yet been validated. The patients also recorded symptom diaries during the study, and the changes in the severity of heartburn and acid regurgitation were evaluated at 2 weeks after starting esomeprazole based on the information in these diaries. The patients were instructed to assess their symptoms using a 7-point scale similar to the GOS and GSRS. Treatment compliance was also confirmed using the patients' diaries. The efficacy of esomeprazole was prospectively evaluated based on the response rates and changes in GOS scores at 2 and 4 weeks after starting esomeprazole and GSRS scores at 4 weeks after starting esomeprazole. Regarding the doses of conventional PPIs, patients could use half, standard, or double doses.

Prohibited and permitted concomitant drugs

During the study, patients were prohibited from using drugs that may affect efficacy evaluations (e.g., prokinetic drugs, antiulcer drugs, and anticholinergic drugs) and drugs that may interact with esomeprazole. However, these drugs were permitted if they were used throughout the study period without changes in their dose and administration frequency. Concomitant use of therapeutic drugs for comorbid diseases was permitted if the dose of these drugs was not reduced or administration suspended during the study period, and if the investigator expected the drugs to have no effects on the efficacy evaluations.

Endpoints

The clinical survey data, including the GOS questionnaire, were used to determine the proportion of patients with refractory GERD and investigate their clinical characteristics, including patient characteristics (e.g., sex, age, and body mass index), details of prior therapy (e.g., type, dose, and duration of the prior drug), type and severity of symptoms, and clinical factors that might explain resistance to the prior PPI.

The primary endpoint in the switching study was the proportion of patients who reported an improvement in reflux-related symptoms evaluated by the GOS questionnaire at 4 weeks after switching to esomeprazole. Secondary endpoints included the proportion of patients with improvements in QOL evaluated by the GSRS questionnaire at 4 weeks; the proportion of patients with resolution of reflux-related symptoms evaluated by the GOS questionnaire at 2 and 4 weeks; the proportion of patients with improvements in reflux-related symptoms evaluated by the GOS questionnaire at 2 weeks after switching to esomeprazole; and the changes in reflux-related symptoms evaluated by patients' diaries at 2 weeks after switching to esomeprazole.

Statistical analysis

In two prior studies of Japanese patients, it was reported that 70.6% and 71.0% of patients reported improvements in symptoms at 4 weeks after switching from a conventional PPI to 20 mg esomeprazole [8,9]. Based on these results, we assumed that 70% of patients would have improvements in symptoms after 4 weeks of treatment with esomeprazole. Based on a standard deviation of 15% and a 95% confidence interval, we needed to enroll 36 patients into this study. Assuming a dropout rate of 10%, we needed to enroll 40 patients into the switching study. Based on previous reports, we estimated that 40% of patients with GERD would be refractory to a PPI [14,15] and would be eligible for the initial survey. On the assumption that 70% of these patients would be willing to enroll in the switching study, we planned to enroll 140 patients for the survey.

The full analysis set and the per-protocol set were used for the primary and secondary analyses, respectively. The full analysis set included all of the patients except for those who did not receive the study drug at all and those who did not visit the hospital after providing informed consent. Differences in the distribution of patient characteristics at baseline were compared between patients with refractory GERD and the total cohort of patients using the χ^2 test.

An improvement in dyspepsia symptoms was defined as GOS scores of 1 or 2 for individual questions after 4 weeks of treatment with esomeprazole. Symptom resolution was defined as a score of 1 at 4 weeks. The proportions of patients with GOS scores of 1 or 2 for each symptom were compared between baseline and after 2 and 4 weeks of treatment with esomeprazole using McNemar's test.

The changes in the mean GSRS scores from baseline to 4 weeks and the changes in the severity of reflux-related symptoms from baseline to 2 weeks after switching to esomeprazole were compared using Wilcoxon's signed rank-sum test. The proportions

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of patients with resolution of reflux-related symptoms (GSRS scores of 1 or 2; considering the mean value in European patients of 1.53 [16]) at 2 and 4 weeks after switching to esomeprazole and the proportions of patients with improvements of reflux-related symptoms at 2 weeks after switching to esomeprazole were evaluated using McNemar's test.

In all tests, the significance level was set at $P<0.05$.

Results

Clinical characteristics of patients with refractory GERD

Overall, 120 patients with GERD treated with conventional PPIs provided informed consent and completed the GOS questionnaire within the study period. Of these, 58 (48.3%) were refractory to PPI therapy based on GOS scores of ≥4 points for heartburn or acid regurgitation. Table 1 shows the clinical characteristics of all 120 patients with GERD and 58 patients with refractory GERD.

In the total cohort of 120 patients, about 52% were male, and the mean age and body mass index were 67.1 years and 24.1 kg/m^2, respectively. The Los Angeles classification was grade A in 39.2%, grade B in 14.2%, and grade C or worse in 3.3% of patients. The prior PPI was administered at a half dose, standard dose, and double dose/higher in 31.7%, 63.3%, and 5.0% of patients, respectively. The most common PPI was 10 mg rabeprazole (30.8% of patients), followed by 20 mg omeprazole (25.8%), 10 mg omeprazole (17.5%), and 15 mg lansoprazole (14.2%). Most of the patients (75.0%) had been treated with a PPI for ≥1 year, while 15.0% had been treated with a PPI for 2–6 months. Figure 1A shows the distribution of GOS scale scores for each question. Figure 1B shows the proportions of patients with scores ≥4 for each symptom. As might be expected, heartburn and acid regurgitation were the major symptoms, with about 40% of patients reporting scores of ≥4 for these symptoms.

Most patients with refractory GERD were aged ≥65 years (69.0%; 40/58). The majority of patients with refractory GERD were prescribed a PPI at a standard or higher dose (79.3%;

Table 1. Patient characteristics.

Characteristic		Total cohort	Patients with refractory GERD	Patients without refractory GERD	P*
N		120	58	62	
Sex	Male	62 (51.7)	26 (44.8)	36 (58.1)	0.147
	Female	58 (48.3)	32 (55.2)	26 (41.9)	
Age (years)	Mean ±SD (range)	67.1±11.2 (37–92)	69.4±9.12 (47–89)	65.0±12.6 (37–92)	0.035
	<65	45 (37.8)	17 (29.8)	28 (45.2)	0.085
	≥65	74 (62.2)	40 (70.2)	34 (54.8)	
	Unknown	1	1	–	
BMI (kg/m^2)	Mean ± SD	24.1±5.3	24.0±3.36	24.1±3.61	0.86
	<25	64 (55.7)	31 (55.4)	33 (55.9)	0.951
	≥25	51 (44.3)	25 (44.6)	26 (44.1)	
	Unknown	5	2	3	
Current smoking	No	91 (75.8)	44 (75.9)	47 (75.8)	0.922
	Yes	17 (14.2)	8 (13.8)	9 (14.5)	
	Smoking history	12 (10.0)	6 (10.3)	6 (9.7)	
Alcohol intake	Never	62 (52.1)	33 (56.9)	29 (47.5)	0.565
	Sometimes	26 (21.8)	12 (20.7)	14 (23.0)	
	Almost every day	31 (26.1)	13 (22.4)	18 (29.6)	
	Unknown	1	–	1	
H. pylori infection	Negative	40 (80.0)	26 (78.8)	14 (82.4)	0.765
	Positive	10 (20.0)	7 (21.2)	3 (17.6)	
	Unknown	70	25	45	

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Table 1 continued. Patient characteristics.

Characteristic		Total cohort	Patients with refractory GERD	Patients without refractory GERD	*P**
Los Angeles classification	N	17 (16.3)	4 (7.4)	13 (26.0)	0.086
	M	19 (18.3)	13 (24.1)	6 (12.0)	
	A	47 (45.2)	27 (50.0)	20 (40.0)	
	B	17 (16.3)	8 (14.8)	9 (18.0)	
	C	3 (2.9)	2 (3.7)	1 (2.0)	
	D	1 (1.0)	0 (0.0)	1 (2.0)	
	Unknown	16	4	12	
Hiatus hernia	Absent	37 (41.6)	19 (40.4)	18 (42.9)	0.816
	Present	52 (58.4)	28 (59.6)	24 (57.1)	
	Unknown	31	11	20	
PPI dose	Half dose	38 (31.7)	12 (0.7)	26 (41.9)	0.017
	Standard dose	76 (63.3)	41 (70.7)	35 (56.5)	
	≥Double dose	6 (5.0)	5 (8.6)	1 (1.6)	
Dose/type of PPI	10 mg omeprazole	21 (17.5)	6 (10.3)	15 (24.2)	0.017
	15 mg lansoprazole	17 (14.2)	6 (10.3)	11 (17.7)	
	20 mg omeprazole	31 (25.8)	21 (36.2)	10 (16.1)	
	30 mg lansoprazole	8 (6.7)	2 (3.4)	6 (9.7)	
	10 mg rabeprazole	37 (30.8)	18 (31.0)	19 (30.6)	
	10 mg ×2/20 mg rabeprazole	6 (5.0)	5 (8.6)	1 (1.6)	
Frequency of administration	Every day	109 (92.4)	51 (91.1)	58 (93.5)	0.787
	4–6 days/week	6 (5.1)	3 (5.4)	3 (4.8)	
	As necessary	3 (2.5)	2 (3.6)	1 (1.6)	
	Unknown	2	2	–	
Duration of administration	≥2–6 months	18 (15.3)	9 (15.8)	9 (14.8)	0.958
	≥6–12 months	10 (8.5)	4 (7.0)	6 (9.8)	
	≥12 months	90 (76.3)	44 (77.2)	46 (75.4)	
	Unknown	2	1	1	
Concomitant use of other stomach drugs	No	81 (67.5)	45 (77.6)	36 (58.1)	0.023
	Yes	37 (30.8)	13 (22.4)	26 (41.9)	
Complications	No	25 (21.0)	14 (24.6)	11 (17.7)	0.362
	Yes	94 (79.0)	43 (75.4)	51 (82.3)	
	Unknown	1	1	–	
Concomitant drugs	No	30 (25.0)	17 (29.3)	13 (21.0)	0.292
	Yes	90 (75.0)	41 (70.7)	49 (79.0)	

Values are presented as the n (%) or mean ±SD. * *P*-values were calculated using the χ^2 test. BMI – body mass index; GERD – gastroesophageal reflux disease, PPI – proton pump inhibitor.

46/58). Only 13/58 patients (22.4%) were using a PPI together with other stomach drugs. The Los Angeles classification was grade A in about half of the patients with refractory GERD.

Efficacy of esomeprazole

A total of 38 patients with refractory GERD were switched to 20 mg esomeprazole; their clinical characteristics are presented in

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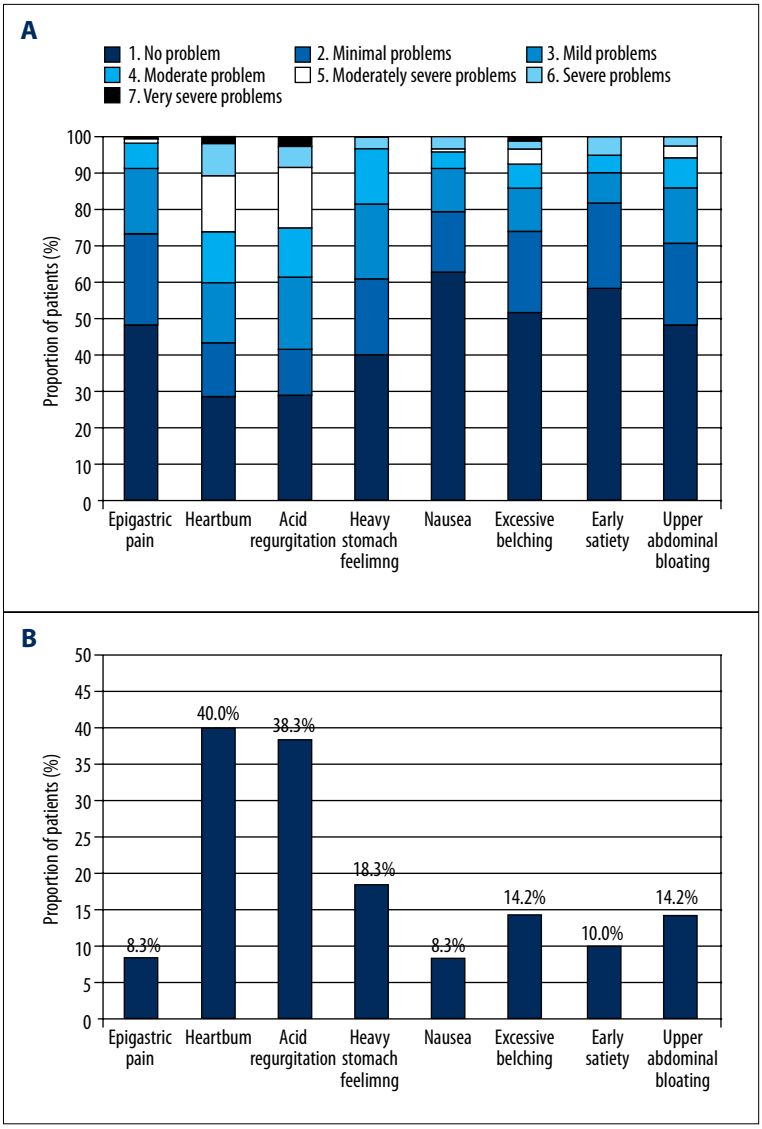

Figure 1. Severity of dyspepsia symptoms measured by the Global Overall Symptom (GOS) scale in the total cohort of 120 patients with gastroesophageal reflux disease (**A**) and proportion of patients with GOS scale scores ≥4 for individual symptoms (**B**).

Table 2. There were 25 females (65.8%) and the mean age was 71.5 years. The Los Angeles classification immediately before switching to esomeprazole was grade A in 13 patients (34.1%), grade B in 4 patients (10.5%), and grade C in 1 patient (2.6%). The most frequently used PPI was 20 mg omeprazole (19 patients), followed by 10 mg rabeprazole (10 patients), and 15 mg lansoprazole (4 patients).

Table 3 shows the proportions of patients with improvements or resolution of symptoms at 2 or 4 weeks after switching to esomeprazole. As shown, significant numbers of patients had improvements or resolution of heartburn and acid regurgitation after 2 and 4 weeks of treatment compared with baseline values.

Of the 38 patients with refractory GERD who were switched to esomeprazole, 6 were excluded because of protocol deviations. Therefore, the changes in GSRS as an index of QOL were calculated for 32 patients (i.e., per-protocol set). Table 4 shows the changes in the GSRS total score and individual symptom scores in these patients. The reference values for the GSRS in a general population of European individuals were 1.53 for the total score, 1.39 for reflux, 1.56 for abdominal pain, 1.78 for indigestion, 1.38 for diarrhea, and 1.55 for constipation [16], with similar values in a prior Japanese study [17]. As shown in Table 4, the GSRS significantly decreased from before (1.88±0.52) to 4 weeks after switching to esomeprazole (1.33±0.53) ($P<0.001$). Likewise, there were significant reductions (i.e., improvements) in scores for reflux, abdominal pain, and indigestion. There were significant improvements in the GSRS total score and in the scores for reflux, abdominal pain, and indigestion in 29 patients whose prior PPI was administered at a standard dose or higher (Table 4). In three patients who were administered a PPI at a half dose, the GSRS total

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Table 2. Clinical characteristics of patients with refractory gastroesophageal reflux disease who participated in the prospective switching study (n=38).

Characteristic		Value	
Sex	Male	13	(34.2)
	Female	25	(65.8)
Age (years)	Mean ±SD	71.5±8.36	
BMI (kg/m^2)	<25	19	(50.0)
	≥25	19	(50.0)
	Mean ± SD	24.3±3.7	
Current smoking	No	32	(84.2
	Yes	3	(7.9)
	Smoking history	3	(7.9)
Alcohol intake	Never	24	(63.2)
	Sometimes	4	(10.5)
	Almost every day	10	(26.3)
H. pylori infection	Negative	19	(50.0)
	Positive	7	(18.4)
	Unknown	12	(31.6)
Los Angeles classification (immediately before switching to esomeprazole)*	N	4	(10.5)
	M	12	(31.6)
	A	13	(34.2)
	B	4	(10.5)
	C	1	(2.6)
	Unknown	3	(7.9)
Hiatus hernia	Absent	14	(36.8)
	Present	17	(44.7)
	Unknown	7	(18.4)
PPI dose	Half dose	4	(10.5)
	Standard dose	31	(81.6)
	≥ Double dose	3	(7.9)
Dose/type of PPI	15 mg lansoprazole	4	(10.5)
	20 mg omeprazole	19	(50.0)
	30 mg lansoprazole	2	(5.3)
	10 mg rabeprazole	10	(26.3)
	10 mg ×2/20 mg rabeprazole	1 (2.6)/2 (5.3)	

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Table 2 continued. Clinical characteristics of patients with refractory gastroesophageal reflux disease who participated in the prospective switching study (n=38).

Characteristic		Value	
Frequency of administration	Every day	36	(94.7)
	4–6 days/week	1	(2.6)
	As necessary	1	(2.6)
Duration of administration	≥2–6 months	5	(13.2)
	≥6–12 months	2	(5.3)
	≥12 months	31	(81.6)
Concomitant use of other stomach drugs	No	29	(76.3)
	Yes	9	(23.7)
Complications	No	10	(26.3)
	Yes	27	(71.1)
	Unknown	1	(2.6)
Concomitant drugs	No	11	(28.9)
	Yes	27	(71.1)

Values are presented as the n (%) or mean ±SD. * The Los Angeles classification was determined immediately before switching to esomeprazole. BMI – body mass index; PPI – proton pump inhibitor.

Table 3. Proportions of patients with an improvement or resolution of symptoms at 2 or 4 weeks after switching to esomeprazole.

Symptom*	After 2 weeks of treatment				After 4 weeks of treatment			
	Symptom improvement†	*P*‡	Symptom resolution§	*P*‡	Symptom improvement†	*P*‡	Symptom resolution§	*P*‡
Epigastric pain	66.7% (2/3)	nd#	33.3% (1/3)	nd#	66.7% (2/3)	nd#	66.7% (2/3)	nd#
Heartburn	75.8% (25/33)	<0.001	54.5% (18/33)	<0.001	90.9% (30/33)	<0.001	57.6% (19/33)	<0.001
Acid regurgitation	71.4% (20/28)	<0.001	46.4% (13/28)	<0.001	82.1% (23/28)	<0.001	46.4% (13/28)	<0.001
Heavy stomach feeling	70.0% (7/10)	<0.05	40.0% (4/10)	ns	70.0% (7/10)	ns	40.0% (4/10)	ns
Nausea	66.7% (4/6)	nd#	50.0% (3/6)	nd#	100.0% (6/6)	nd#	50.0% (3/6)	nd#
Excessive belching	81.8% (9/11)	<0.01	72.7% (8/11)	<0.05	100.0% (11/11)	<0.01	72.7% (8/11)	<0.05
Early satiety	83.3% (5/6)	nd#	83.3% (5/6)	nd#	100.0% (6/6)	nd#	83.3% (5/6)	nd#
Upper abdominal bloating	100.0% (5/5)	nd#	80.0% (4/5)	nd#	80.0% (4/5)	nd#	60.0% (3/5)	nd#

* Symptom scores are reported for subjects with a score of ≥4 for at least one symptom. † Symptom score ≤2 at 2 or 4 weeks. ‡ McNemar's test (*vs.* before switching to esomeprazole). § Symptom score=1 at 2 or 4 weeks. # *P*-values were not determined because of the small numbers of subjects. nd – not determined; ns – not significant.

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Table 4. Changes in Gastrointestinal Symptom Rating Scale total scores and scores for individual symptoms.

Variable	All patients (n=32)			Patients whose prior PPI was administered at a standard or high dose (n 29)		
	Before	4 weeks	*P**	Before	4 weeks	*P**
Total score	1.88±0.52	1.33±0.53	<0.001	1.85±0.51	1.30±0.50	<0.001
Reflux	4.23±1.41	1.66±0.84	<0.001	4.33±1.43	1.62±0.85	<0.001
Abdominal pain	1.66±0.80	1.28±0.55	0.018	1.62±0.80	1.22±0.50	<0.001
Indigestion	1.70±0.65	1.27±0.40	<0.001	1.66±0.63	1.24±0.37	0.002
Diarrhea	1.31±0.95	1.25±0.85	ns	1.22±0.76	1.18±0.76	ns
Constipation	1.34±0.71	1.33±0.72	ns	1.34±0.73	1.34±0.75	ns

Values are presented as the mean ±SD. * Wilcoxon signed rank-sum test. PPI – proton pump inhibitor; ns – not significant.

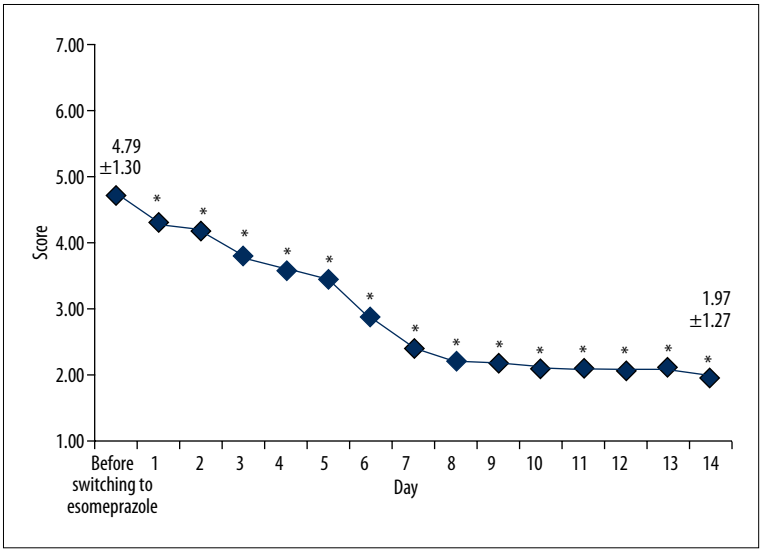

Figure 2. Changes in the severity of reflux-related symptoms (heartburn or acid regurgitation) for the first 2 weeks after switching to esomeprazole (n=36) in patients who reported scores of ≥4 for either symptom on the Global Overall Symptom (GOS) scale. The severity of each symptom was rated using a 7-point scale and recorded in a daily diary, similar to that used in the GOS and Gastrointestinal Symptom Rating Scale. * *P*<0.01 *vs.* before switching to esomeprazole (Wilcoxon signed rank-sum test).

score decreased from 2.13±0.50 to 1.69±0.64, and the reflux syndrome score decreased from 3.33±0.62 to 2.00±0.71.

Figure 2 shows the changes in the severity score for reflux-related symptoms recorded for the first 2 weeks in a diary after switching to esomeprazole in 36 patients. As shown, the severity score for reflux-related symptoms decreased significantly (i.e., improved) as early as 1 day after switching to esomeprazole. The symptom score had decreased by 58.5% at 2 weeks after switching to esomeprazole.

Discussion

According to the Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease developed by the Japanese Society of Gastroenterology [2], the presence of GERD-related symptoms more than once per week decreases the QOL of patients. The Japanese Society of Gastroenterology guidelines also suggest that drugs that achieve quicker symptom resolution may improve QOL. It was also suggested that PPIs achieve greater improvements in QOL than H_2 receptor agonists or prokinetic agents.

Miwa conducted an internet-based survey between July and August, 2010, of 117 patients with GERD or patients prescribed PPIs to treat GERD-related symptoms to determine the frequency of GERD-related symptoms, such as heartburn, during PPI therapy [18]. The survey revealed that 12% and 26% of patients had GERD symptoms daily or 2–3 times per week, respectively. Thus, approximately one-third of patients with GERD experienced symptoms at least twice weekly despite PPI therapy. Additionally, in a study that performed endoscopy before and after PPI therapy in 541 Japanese patients with Los Angeles grade A–D reflux esophagitis, erosive esophagitis was unresolved in approximately 40% of patients treated with a PPI for a mean duration of 1.1 years [19].

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A systematic review suggested that, in about 30% of GERD patients, the symptoms remained despite standard doses of PPIs once daily, although the approved PPI doses in that review differed from those in Japan [20]. Likewise, in another systematic review on the use and adherence to PPIs in patients with GERD and reflux symptoms, it was reported that 19–44% of patients in secondary care had a partial or no response in a meta-analysis of randomized controlled studies [21]. It was also reported that reflux symptoms remained in 40–60% of patients in primary care in randomized controlled studies and in 50–60% of patients in observational studies [22].

Esomeprazole is an effective inhibitor of gastric acid secretion, and rapidly resolves the symptoms of GERD. It also has excellent effects in the context of endoscopic therapy. In past studies that measured the 24-h median intragastric pH, it was found that the duration of an intragastric pH ≥4 was significantly greater in patients treated with 20 mg esomeprazole than in patients treated with 20 mg omeprazole (12.7 *vs.* 10.5 h, $P<0.01$) [21], 15 mg lansoprazole (12.1 *vs.* 10.3 h, $P=0.026$) [7], or 10 mg rabeprazole (14.4 *vs.* 12.4 h, $P=0.011$) [9]. It was also reported that esomeprazole is less susceptible to hepatic metabolism by the cytochrome P450 family of enzymes. Therefore, its inhibition of gastric acid secretion is hardly affected by polymorphisms in *CYP2C19*, in particular [23].

In this study, we conducted a survey to determine the proportion of patients with GERD that is refractory to conventional PPIs, and to assess the clinical characteristics of these patients. We also conducted a prospective study to examine the effects of switching to 20 mg esomeprazole in patients with refractory GERD.

Intriguingly, we found that a large proportion of patients with refractory GERD were elderly, although the proportion was not significantly different to that in the cohort of 120 patients. The GOS questionnaire revealed that nearly half of the patients treated with a PPI had refractory GERD, even though about 70% were using a standard or high dose of the PPI. Regarding patient characteristics, the proportion of refractory patients was lower among patients with a low PPI dose and in patients who concomitantly used other drugs for stomach disorders. The higher proportion of refractory patients among patients using a high PPI dose may be related to the presence of severe symptoms in these patients. None of the other characteristics evaluated in this study were associated with the prevalence of refractory disease.

After switching from the conventional PPI to esomeprazole, patients reported significant improvements or resolution of acid regurgitation and excessive belching at 2 and 4 weeks after switching to esomeprazole. In terms of GSRS, which was used as an index of QOL, the patients reported significant improvements in the total score as well as the scores for reflux, abdominal pain, and indigestion at 4 weeks after switching to esomeprazole. Furthermore, the patients also reported significant improvements in the severity of reflux-related symptoms in the first 2 weeks after switching to esomeprazole, based on the scores reported in their diaries. Notably, the improvement in the reflux-related symptoms severity score was apparent as early as 1 day after switching to esomeprazole, and it decreased by 58.5% after 2 weeks of esomeprazole.

Several factors might contribute to the improvements in symptoms and QOL after switching from a conventional PPI to esomeprazole in patients with refractory GERD, including its strong inhibitory effects on gastric acid secretion [7,21,24] and the limited effect of *CYP2C19* polymorphisms on its metabolism [23]. It has also been suggested that the effectiveness of specific PPIs may differ among patients [20]. However, some aspects of the study design might contribute to the improvement in symptoms. First, participation in the study and recording symptoms in a diary might have increased the level of drug adherence and the patients might have experienced some improvements in symptoms if they continued or optimized their prior PPI rather than switching to esomeprazole. Second, we cannot exclude the possibility of a placebo effect associated with switching to a new drug, especially considering the relatively short observation time of 4 weeks. Thus, future studies should include a control arm in which patients continue their prior PPI or switch to an alternative comparator drug. Nevertheless, in an earlier study [12], 4 weeks of treatment with esomeprazole was associated with significant improvements in markers of quality of life and GERD symptoms. Finally, fewer patients were enrolled during the study period than originally planned, which might affect the statistical power of some analyses.

Conclusions

This study revealed that almost half of patients with GERD were refractory to conventional PPI therapy. Based on these results, we suggest that esomeprazole represents an alternative, effective treatment option for patients with GERD refractory to conventional PPIs.

Conflict of Interests

Dr. Takeshima has received medical writing services that were funded by AstraZeneca K.K. (Osaka, Japan) according to a publication support agreement.

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