INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Randomized Trial Comparing Esomeprazole and Rabeprazole in First-line Eradication Therapy for *Helicobacter pylori* Infection based on the Serum Levels of Pepsinogens

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Abstract

Objective *CYP2C19* metabolic activity influences the efficacy of *Helicobacter pylori* eradication therapies comprising PPIs. Rabeprazole (RPZ) and esomeprazole (EPZ) are PPIs not extensively metabolized by *CYP2C19*. The aim of this study was to elucidate whether or not first-line triple therapies using RPZ or EPZ are equally effective in Japanese patients with different *CYP2C19* genotypes.

Methods Two-hundred patients infected with *H. pylori* were randomized to receive one of the following regimens: amoxicillin (750 mg), clarithromycin (200 mg), and either esomeprazole (20 mg) (EAC group) or rabeprazole (10 mg) (RAC group), twice a day for one week. The *CYP2C19* polymorphisms were determined by polymerase chain reaction and the serum level of pepsinogens was measured.

Results The eradication rates of the EAC and RAC regimens were 79.8% (95% confidential interval: 71.7-89.0%) and 74.7% (66.0-83.4%), respectively, in a per protocol (PP) analysis (p=0.488). The eradication rates of the EAC and RAC regimens were not significantly different between patients with the homo EM genotype (p=0.999) or hetero IM or PM genotypes (p=0.286). A lower PG I/II ratio was associated with lower eradication rates (p=0.025).

Conclusion Although the eradication rate was less than 80%, the EAC and RAC regimens were equally effective in each *CYP2C19* genotype group. The PG I/II ratio was associated with the results of EAC and RAC therapy in this series of patients.

Key words: *Helicobacter pylori*, eradication, CYP2C19, pepsinogen

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Introduction

Helicobacter pylori infection has been associated with gastro-duodenal and systematic diseases, and the eradication of *H. pylori* infection has been shown to reduce the risk of gastric cancer (1, 2). In 2014, the International Agency for Research on Cancer suggested that the eradication of *H. pylori* should be considered as a strategy for preventing gastric cancer (3). The Japanese health insurance system approved efforts to eradicate *H. pylori* for all infected patients to eliminate gastric cancer in 2013 (4), and the number of patients receiving eradication therapy is on the rise.

Since the approval of *H. pylori* eradication in November

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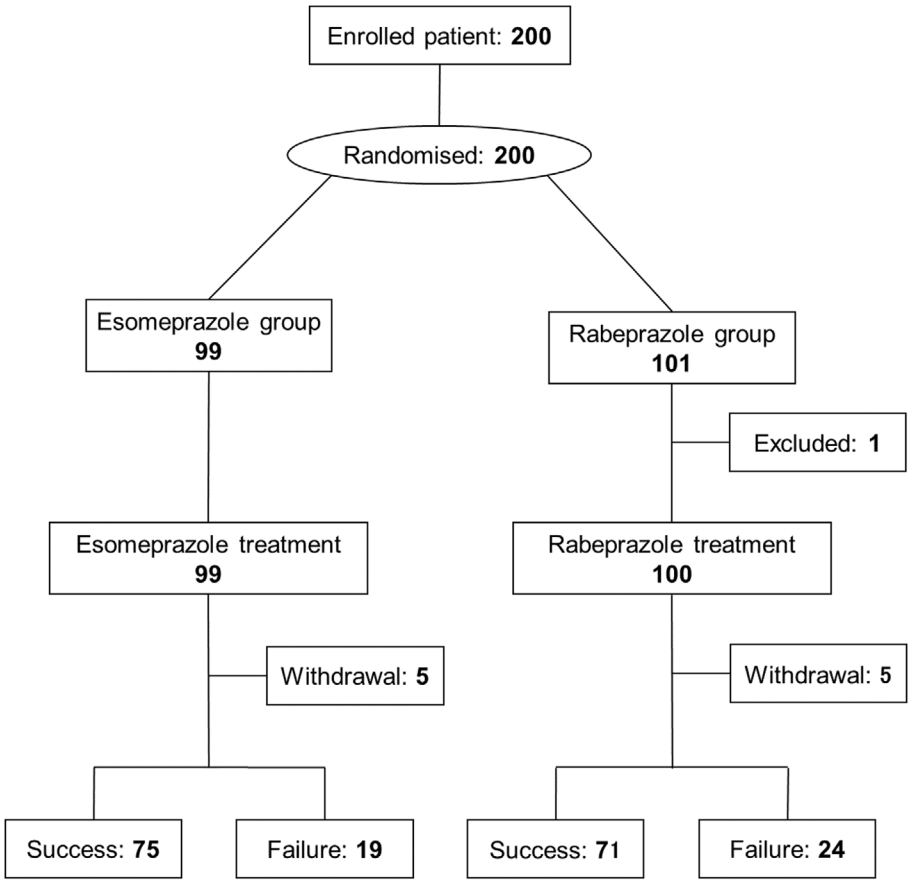

Figure 1. Assignment of patients and subsequent study flow. The study enrolled 200 patients at 8 medical institutes in Aomori Prefecture. The patients were randomly assigned to either the EAC group (n=99) or the RAC group (n=100).

2000, first-line eradication therapy has consisted of one week of triple therapy with a proton pump inhibitor (PPI), amoxicillin (AMOX) and clarithromycin (CLA) (5). In this therapy, the role of the PPI is to achieve a high intragastric pH for acid-labile antibiotics. PPIs are known to stabilize AMOX in the gastric mucus and the eradication rates of regimens containing AMOX are affected by the dose of PPI (6). The effect of PPIs such as omeprazole (OPZ) or lansoprazole (LPZ) are affected by the metabolic activity of the hepatic enzyme, cytochrome *P450* (*CYP*) *2C19* (7). Indeed, some previous reports have shown lower eradication rates of triple therapy with OPZ or LPZ in patients with wild-type *CYP2C19* compared to that in patients with a mutated genotype (8, 9). In contrast, later PPIs such as rabeprazole (RPZ) and esomeprazole (EPZ) have less *CYP2C19*-mediated metabolism than OPZ or LPZ (10, 11), and a meta-analysis showed that EPZ and RPZ had higher eradication rates than LPZ or OPZ in the treatment of *H. pylori* infection (12). However, in Japan, the efficacy of triple therapy with RPZ or EPZ in association with *CYP2C19* genetic polymorphism has never been compared in a prospective, randomized trial.

In the present study, we conducted a prospective, open, randomized multi-center trial to elucidate whether or not triple therapies using RPZ or EPZ are equally effective in patients with different *CYP2C19* genotypes. We also examined the association between several factors, including serum level of pepsinogens, and the results of triple therapy using EPZ or RPZ.

Materials and Methods

Patients

Patients who received upper GI endoscopy at any of eight institutes in Aomori Prefecture were enrolled in the study from May through September 2014. The presence of *H. pylori* was confirmed with a rapid urease test, ^{13}C-urea breath test (UBT), stool antigen test or serum or urine antibody. Patients who met any of the following criteria were excluded from the study: [1] age under 16 years or over 70 years; [2] received antibiotic and/or PPI treatment(s) within 2 weeks of study commencement; [3] active peptic ulcer(s); [4] a history of gastric surgery; [5] a history of *H. pylori* eradication therapy; or [6] suspected of having malignant disease(s).

A total of 200 patients were registered and 1 patient in the RPZ group was excluded due to severe heart disease (Fig. 1). The characteristics of the patients who completed the study are shown in Table 1. All patients gave their writ-

Table 1. Characteristics of the Patients who Completed the Regimen.

		EAC	RAC	Total	p value
Number		94	95	189	
Sex	Men	43 (45.7)	47 (49.5)	90 (47.6)	0.663
	Women	51 (54.3)	48 (50.5)	99 (52.4)	
Age (years)	<40	8 (8.5)	7 (7.4)	15 (7.9)	0.800
	≥40	86 (91.5)	88 (92.6)	174 (92.1)	
Smoking	Non	73 (77.7)	75 (78.9)	148 (78.3)	0.861
	Current	21 (22.3)	20 (21.1)	41 (21.7)	
Drinking	Non	43 (45.7)	46 (48.4)	89 (47.1)	0.771
	Current	51 (54.3)	49 (51.6)	100 (52.9)	
PG I (ng/mL)	<49.0	23 (24.2)	26 (27.7)	49 (25.9)	0.753
	49.0≤<69.0	24 (25.3)	25 (26.6)	49 (25.9)	
	69.0≤<89.0	17 (17.9)	19 (20.2)	36 (19)	
	89.0<	31 (32.6)	24 (25.5)	55 (29.2)	
PG II (ng/mL)	<15.0	17 (17.9)	26 (27.7)	43 (22.8)	0.270
	15.0≤<23.0	29 (30.5)	30 (31.9)	59 (31.2)	
	23.0≤<31.0	19 (20.0)	18 (19.1)	37 (19.6)	
	31.0<	30 (31.6)	20 (21.3)	50 (26.4)	
PG I/II ratio	<2.2	25 (26.3)	19 (20.2)	44 (23.3)	0.370
	2.2≤<2.9	25 (26.3)	19 (20.2)	44 (23.3)	
	2.9≤<3.6	16 (16.8)	23 (24.5)	39 (20.6)	
	3.6<	29 (30.6)	33 (35.1)	62 (32.8)	
CYP2C19	homo EM	30 (31.9)	30 (31.6)	60 (31.7)	
	hetero IM/PM	64 (68.1)	65 (68.4)	129 (68.3)	0.999
anti-Hp antibody (U/mL)	<24	34 (36.2)	28 (29.5)	62 (32.8)	0.514
	24≤<46	29 (30.9)	36 (37.9)	65 (34.4)	
	≥46	31 (33.0)	31 (32.6)	62 (32.8)	

N, (%)

ten informed consent before receiving eradication therapy. Peripheral blood was obtained and leukocytes were used for the *CYP2C19* genotype analysis. Genotyping procedures for identifying the *CYP2C19* wild-type gene and two mutated alleles, *CYP2C19m1* and *CYP2C19m2*, were performed by a PCR-restriction fragment length polymorphism (PCR-RFLP) method with allele-specific primers (13). Serum samples were stored at -20℃ and the titer of IgG antibody to *H. pylori* was determined by an enzyme immunoassay (E-plate; Eiken, Tokyo, Japan) and the levels of pepsinogen (PG) I and PG II by a radioimmunoassay.

Eradication therapy

Patients were randomly assigned to one of the following eradication therapy groups: [1] EAC group: EPZ (20 mg) twice a day (bid), AMPC (750 mg) bid, and CLA (200 mg) bid for one week; or [2] RAC group: RPZ (10 mg) bid, AMPC (750 mg) bid, and CLA (200 mg) bid for one week. After completing the treatment, any PPIs and other anti-ulcer agents that might affect the viability of *H. pylori* or urease activity were not used. Eradication assessment using a UBT (14) or stool antigen test (15) was performed 6 (±2) weeks after the completion of eradication therapy.

One patient in the RAC group could not complete the regimen due to severe itching. During the treatment, eruption was observed in three patients, loose stool was recorded in two patients, and one patient complained of a metallic taste. However, these patients completed their regimens. Five patients in the EAC group and four patients in the RAC group did not visit the hospital and dropped out.

Ethics assignment

The unit of randomization was the individual, and the allocation sequence was generated by an unaffiliated person at the Hirosaki University Hospital who was blinded to the details of the study. This study was approved by Hirosaki University Medical Ethics Committee and registered to UMIN Clinical Trials Registry (UMIN000014366).

Statistical analysis

Differences between the groups were compared using the χ^2 test. A p value of <0.05 was considered significant.

Results

The eradication rates of the EAC and RAC regimen groups were 79.8% [95% confidential interval (CI): 71.7-89.0%] and 74.7% (66.0-83.4%) for the per protocol (PP) analysis and 75.8% (67.4-84.2%) and 71.0% (62.1-79.9%) for the intention-to-treat (ITT) analysis, respectively (Fig. 2A). No significant differences were observed between the two regimens.

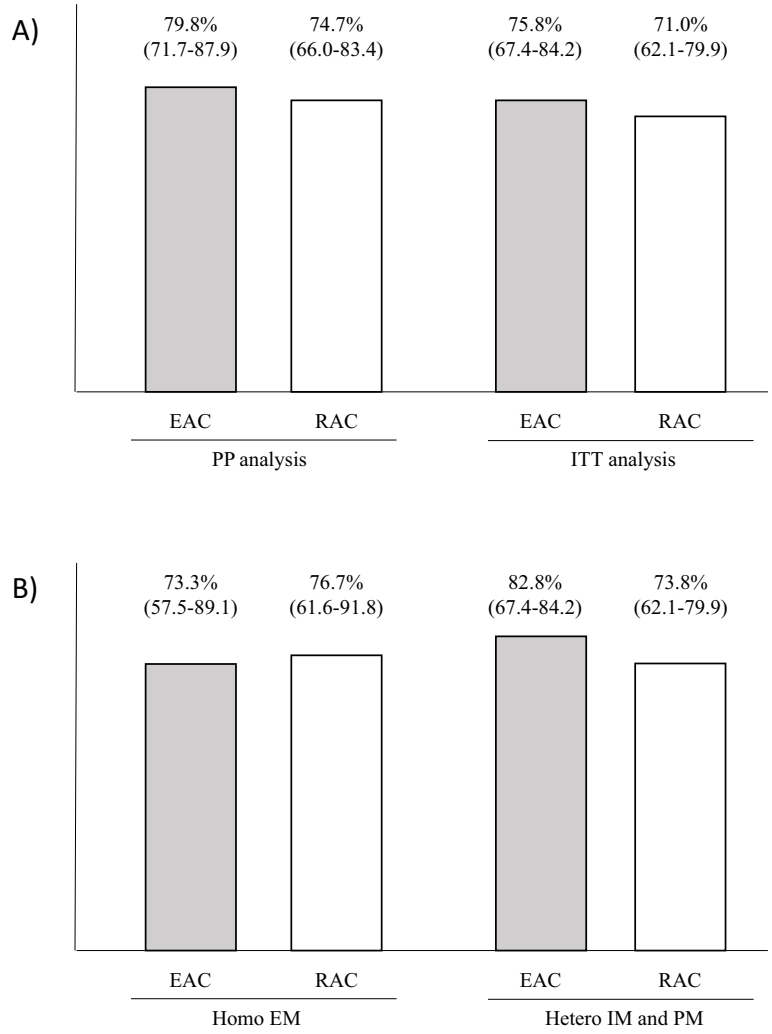

Figure 2. **(A) The eradication rates of EAC and RAC therapy by a per-protocol (PP) analysis or intention-to-treat analysis. (B) The eradication rates of EAC and RAC therapy by a PP analysis in patients with homo EM versus those with hetero IM or PM.**

Regarding the *CYP2C19* genetic polymorphism status, 62 patients were assigned to the homozygous extensive metabolizer (homo EM) group, 102 patients with 1 mutation were assigned to the heterozygous intermediate metabolizer group (hetero IM), and 35 patients with 2 mutations were assigned to the poor metabolizer (PM) group. Fig. 2B shows the PP-based eradication rates in relation to the *CYP2C19* polymorphism. The eradication rate of the EAC and RAC regimens in the homo EM patients was 73.3% (CI: 57.5-89.1%) and 76.7% (CI: 61.6-91.8%), respectively. In the hetero IM and PM patients, the eradication rate of the EAC regimen was 82.8% (73.6-92.0%), and that of the RAC regimen was 73.8% (63.1-84.5%). The eradication rates of the EAC and RAC regimen groups were not significantly different between the patients with homo EM genotype and those with hetero IM or PM genotype. The eradication rates of homo EM patients were not markedly different from those of the hetero IM or PM patients in the EAC (p=0.287) or RAC (p=0.999) regimen groups.

Table 2 shows the association between the patients' characteristics and the results of eradication therapy in 189 patients who completed the protocol. No factors were associated with the results of eradication therapy. Table 3 shows the association between the serum pepsinogen levels and the results of eradication therapy. Although the levels of PG I and II were not significantly associated with the treatment results, the eradication rates tended to increase with an increasing PG I/II ratio (p=0.025). The eradication rate was 68.2% in the 44 patients with a PG I/II ratio lower than 2.2 and 84.2% in those with a PG I/II ratio higher than 2.9.

Discussion

EPZ has been the most popular PPI worldwide for more than 10 years. However, in Japan, the use of EPZ was only just approved in September 2011, and thus relatively few studies have examined the efficacy of EPZ in *H. pylori* eradication therapy compared with other PPIs in a Japanese population. The present study is the first prospective randomized study to compare the efficacy of EPZ and RPZ in first-line eradication therapy for *H. pylori* infection among Japanese patients with different *CYP2C19* genotypes.

Table 2. Patients' Characteristics and the Results of Eradication Therapy.

		Eradication		p value
		failure	success	
Sex	Men	19 (21.1)	71 (78.9)	0.729
	Women	24 (24.2)	75 (75.8)	
Age (years)	<40	4 (26.7)	11 (73.3)	0.749
	≥40	39 (22.4)	135 (77.6)	
Smoking	Non	34 (23)	114 (77)	0.999
	Current	9 (22)	32 (78)	
Drinking	Non	17 (19.1)	72 (80.9)	0.299
	Current	26 (26)	74 (74)	
CYP2C19	homo EM	15 (25)	45 (75)	0.710
	Hetero IM+PM	28 (21.7)	101 (78.3)	
anti-Hp antibody (U/mL)	<24	14 (22.6)	48 (77.4)	0.997
	24≤<46	15 (23.1)	50 (76.9)	
	≥46	14 (22.6)	48 (77.4)	

N, (%)

Table 3. Level of Pepsinogens and the Results of Eradication Therapy.

		eradication			p value
		success (N)	failure (N)	rate (%)	
PG I (ng/mL)	<49.0	35	14	71.4	0.177
	49.0≤<69.0	37	12	75.5	
	69.0≤<89.0	29	7	80.6	
	89.0<	45	10	81.8	
PG II (ng/mL)	<15.0	35	8	81.4	0.573
	15.0≤<23.0	46	13	78.0	
	23.0≤<31.0	26	11	70.3	
	31.0<	39	11	78.0	
PG I/II ratio	<2.2	30	14	68.2	0.025
	2.2≤<2.9	31	13	70.5	
	2.9≤<3.6	33	6	84.6	
	3.6<	52	10	83.9	

Suppression of gastric acid is important for the eradication therapy of *H. pylori* infection (6, 16). Better eradication rates have been observed in PM patients undergoing PPI-based triple therapies using OPZ or LPZ than in EM patients (7, 8). Similarly, a recent meta-analysis showed that *CYP2C19* loss-of-function variants are associated with increased *H. pylori* eradication rates in patients receiving these therapies (17). In this study, the eradication rates in EM patients were not significantly different from those in IM and PM patients receiving the EAC and RAC regimens. Therefore, the genotyping of CYP2C19 is not necessary for first-line eradication therapy when EPZ or RPZ are used with AMOX and CLA. However, even the highest eradication rate, which was observed in the IM and PM patients treated with EAC regimen, remained 82.8%. Generally, regimens with >90% eradication rate are recognized as effective (18). The results of this study indicate that 7-days of EAC and RAC regimens both had an insufficient effect without testing susceptibility to antibiotics. Indeed, the European guideline suggests that EAC and RAC regimens should last 10-14 days and PPIs should be administered at high dose (19). Furthermore, EAC and RAC regimens containing higher doses of EPZ or RPZ had higher eradication rates (20). To use EAC and RAC regimens as the first-line therapy, a longer duration and higher dose of EPZ or RPZ as well as testing for CLA resistance should be approved by the Japanese health insurance system.

The most common cause of failure of first-line therapy is bacterial resistance to CLA (3). Determining CLA resistance is important for predicting the results of triple therapy. However, bacterial culture is not always available. Therefore, it would be useful to determine other factors associated with the results of first-line therapy using RPZ or EPZ. Recently, ABC classification for the risk of gastric cancer has been introduced by many health surveys (21). In this classification, patients are tested serum antibody to *H. pylori* with the serum levels of PGs. Therefore, information about the serum level of PGs is available for these patients before starting eradication therapy. The results of the present study showed that a lower PG I/II ratio was associated with failure of

EAC or RAC therapy. Generally, low levels of PG I reflect mucosal atrophy of the gastric corpus, while higher levels of PG II reflect more severe gastric mucosal inflammation. The PG I/II ratio increases after successful eradication (22) and is usually high in patients not infected by *H. pylori* (23). Therefore, the present results suggest that failure of *H. pylori* eradication by EAC or RAC therapy might be more frequent in stomachs with advanced mucosal atrophy and persistent inflammation. However, a previous study showed that a low pepsinogen I/II ratio was associated with successful eradication in a different eradication regimen (24). Further studies are required to determine whether or not the serum level of PGs is associated with the results of eradication therapy and to elucidate whether or not alternative therapy is required for patients who have a lower level of PG I/II.

The limitation of this study is the lack of information about bacterial susceptibility to antibiotics. As already mentioned, resistance to CLA is the most common cause for the failure of first-line therapy (5). However, bacterial culture is not always successful, and it takes more than 10 days to obtain the results of susceptibility to antibiotics in most medical institutions. Furthermore, at present, the tests for neither the susceptibility of *H. pylori* to antibiotics nor the detection of the point mutation of bacterial 23S rRNA gene are covered by the Japanese health insurance system. For many patients, the extra cost and longer duration before starting treatment are not acceptable. In addition, AMOX-resistant *H. pylori* is very rare in Japan (5). We therefore did not examine bacterial susceptibility to antibiotics in this study. Since this study is a prospective randomized trial, the influence of bacterial susceptibility on the differential eradication rates between EAC and RAC therapies would be minimal. However, we cannot exclude the possibility that a higher CLA resistance rate caused the lower eradication rate in patients with a lower PG I/II ratio.

In conclusion, both the EAC and RAC regimens were safe and similarly effective as first-line eradication therapies for *H. pylori* infection, regardless of *CYP2C19* genotype. However, the eradication rates of both therapies were insufficient under the current approval of the Japanese health insurance system. The PG I/II ratio seems to be associated with the results of EAC or RAC therapy.

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

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