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ORIGINAL ARTICLE

Clinical Trials Study

First-line eradication for *Helicobacter pylori*-positive gastritis by esomeprazole-based triple therapy is influenced by *CYP2C19* genotype

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Abstract

AIM: To evaluate the effect of first line esomeprazole (EPZ)-based triple therapy on *Helicobacter pylori* (*H. pylori*) eradication.

METHODS: A total of 80 Japanese patients with gastritis who were diagnosed as positive for *H. pylori* infection by endoscopic biopsy-based or ^{13}C-urea breath tests were included in this study. The average age of the patients was 57.2 years (male/female, 42/38). These patients were treated by first-line eradication therapy with EPZ 40 mg/d, amoxicillin 1500 mg/d, and clarithromycin 400 mg/d for 7 d. All drugs were given twice per day. Correlations between *H. pylori* eradication, *CYP2C19* genotype, and serum pepsinogen

(PG) level were analyzed. This study was registered with the UMIN Clinical Trials Registry (UMIN000009642).

RESULTS: The *H. pylori* eradication rates by EPZ-based triple therapy evaluated by intention-to-treat and per protocol were 67.5% and 68.4%, respectively, which were similar to triple therapies with other first-generation proton pump inhibitors (PPIs). The eradication rates in three different *CYP2C19* genotypes, described as extensive metabolizer (EM), intermediate metabolizer, and poor metabolizer, were 52.2%, 72.1%, and 84.6%, respectively. The *H. pylori* eradication rate was significantly lower in EM than non-EM ($P < 0.05$). The serum PG Ⅰ level and PG Ⅰ/Ⅱ ratio were significantly increased after eradication of *H. pylori* ($P < 0.01$), suggesting that gastric atrophy was improved by *H. pylori* eradication. Thus, first-line eradication by EPZ-based triple therapy for patients with *H. pylori*-positive gastritis was influenced by *CYP2C19* genotype, and the eradication rate was on the same level with other first-generation PPIs in the Japanese population.

CONCLUSION: The results from this study suggest that there is no advantage to EPZ-based triple therapy on *H. pylori* eradication compared to other first-generation PPIs.

Key words: *CYP2C19*; Esomeprazole; *Helicobacter pylori*; Pepsinogen; Proton pump inhibitor

Core tip: Esomeprazole (EPZ) is considered to be more effective for inhibition of gastric acid secretion than other first-generation proton pump inhibitors (PPIs) because its metabolism is not influenced by *CYP2C19* genotype. In the present study, however, first-line eradication by EPZ-based triple therapy for patients with *Helicobacter pylori* (*H. pylori*)-positive gastritis was influenced by *CYP2C19* genotype, and the eradication rate was on the same level with triple therapies with other first-generation PPIs in the Japanese population. Unlike previous studies, our results suggest that there is no advantage for EPZ-based triple therapy on *H. pylori* eradication in comparison with other first-generation PPIs.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most prevalent bacterial pathogens and is associated with upper gastrointestinal disorders, such as gastritis, peptic ulcers, functional dyspepsia, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer[1-3]. Eradication of *H. pylori* infection is reported to be an effective approach to curing or preventing these *H. pylori*-associated diseases[4,5]. One-week of triple therapy with a proton pump inhibitor (PPI), amoxicillin (AMPC), and clarithromycin (CAM) is recommended as first-line *H. pylori* eradication therapy and covered under the national health insurance system in Japan. However, the eradication rates for *H. pylori* have declined to approximately 70%[6].

The use of PPIs combined with antibiotics in *H. pylori* eradication therapy has been demonstrated to not only protect the stomach, but also increase the eradication rate. As antibiotics are more stable in higher pH gastric environments, strong gastric acid inhibition increases the efficacy of *H. pylori* eradication. The metabolism of first-generation PPIs such as omeprazole (OPZ) is influenced by genetic polymorphism of *CYP2C19*[7]. Based on the wild-type allele (*1) and the two mutated alleles (*2 and *3) of the *CYP2C19* gene, patients can be categorized into three groups: extensive metabolizer (EM; *1/*1), intermediate metabolizer (IM; *1/*2 or *1/*3), and poor metabolizer (PM; *2/*2, *2/*3, or *3/*3). As EM metabolizes OPZ rapidly, the success rate of *H. pylori* eradication by OPZ-based therapy in EM is lower than that of PM[7-9].

Esomeprazole (EPZ), the S-isomer of OPZ, is the most recent member of the PPI family and is a more potent acid inhibitor than other first-generation PPIs[10,11]. The metabolism of EPZ is considered to be unaffected by *CYP2C19* genotype. Indeed, recent studies have reported that there were no significant differences in *H. pylori* eradication by EPZ-based therapy among EM, IM, and PM of the *CYP2C19* genotype, and that EPZ showed better overall *H. pylori* eradication rates than first-generation PPIs[9,12-14]. However, Nishida *et al*[15] demonstrated that the *H. pylori* eradication rate of EPZ-based triple therapy was lower than lansoprazole (LPZ) in the Japanese population. Thus, the effect of *H. pylori* eradication by EPZ-based therapy is controversial. To evaluate the effect of first line EPZ-based triple therapy on *H. pylori* eradication, we investigated eradication rate, *CYP2C19* genotype, and serum pepsinogen (PG) level in Japanese patients with *H. pylori*-positive gastritis.

MATERIALS AND METHODS

Patients and study design

A total of 80 Japanese patients with gastritis who were diagnosed as positive for *H. pylori* infection by a ^{13}C-urea breath test (UBT) or endoscopic biopsy-based test (*i.e.,* histologic examination and *H. pylori* culture) were included in this study. Patients were recruited between January and September 2013 at the Kitasato

Table 1 Serum pepsinogen level and *Helicobacter pylori* eradication in the extensive metabolizer group (*CYP2C19* genotype: *1/*1)

Case	Age	Sex	PG Ⅰ/Ⅱ				UBT	Eradication
			Before eradication		After eradication			
E1	45	F	3.6	-	5.0	-	0.1	○
E2	39	M	3.3	-	6.7	-	0.4	○
E3	59	M	3.1	-	5.2	-	0.5	○
E4	58	M	2.9	-	7.1	-	0.4	○
E5	50	F	2.2	1+	5.1	-	0.3	○
E6	43	F	2.2	1+	4.9	-	0.3	○
E7	63	F	1.6	1+	4.1	-	0.0	○
E8	56	F	2.8	2+	4.1	-	0.3	○
E9	36	F	2.2	2+	4.6	-	0.0	○
E10	75	F	2.5	2+	4.8	-	0.9	○
E11	67	M	3.7	-	2.2	2+	0.0	○
E12	64	M	0.8	3+	2.2	2+	1.3	○
E13	48	M	3.4	-	3.1	-	12.7	×
E14	50	F	4.3	-	6.4	-	12.7	×
E15	67	M	3.5	-	3.7	-	41.6	×
E16	34	F	3.0	-	3.4	-	19.5	×
E17	63	M	3.1	-	3.0	-	26.8	×
E18	71	F	1.2	3+	3.1	-	11.0	×
E19	55	M	2.4	1+	2.6	1+	24.6	×
E20	56	M	2.0	2+	2.2	1+	24.9	×
E21	80	M	1.7	2+	1.8	2+	20.9	×
E22	53	M	2.2	2+	2.2	2+	26.6	×
E23	43	F	2.2	2+	2.3	2+	11.5	×

(-), PG Ⅰ ≥ 70 ng/mL and PG Ⅰ/PG Ⅱ ratio ≥ 3.0; (1+), PG Ⅰ < 70 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (2+), PG Ⅰ < 50 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (3+), PG Ⅰ < 30 ng/mL and PG Ⅰ/PG Ⅱ ratio < 2.0. Eradication (○) rate = 12/23 (52.2%). M: Male; F: Female; PG: Pepsinogen; UBT: ^{13}C-urea breath test.

Institute Hospital (Tokyo, Japan). The average age of the patients was 57.2 years (male/female, 42/38).

These patients were treated by first-line eradication therapy with EPZ 40 mg/d, AMPC 1500 mg/d, and CAM 400 mg/d for 7 d. All drugs were given twice per day. Three months after eradication, *H. pylori* infection was validated by UBT. Correlations between *H. pylori* eradication, *CYP2C19* genotype, and serum PG level were analyzed. The study was approved by the ethics committee of the Kitasato Institute Hospital, and written informed consent was obtained from all patients prior to examinations. This study was registered with the UMIN Clinical Trials Registry, number UMIN000009642.

CYP2C19 genotyping

Blood samples were collected from the patients before eradication therapy. The *CYP2C19* genotyping for wild-type allele (*1) and two mutated alleles (*2 and *3) was conducted by SRL (Tokyo, Japan). The patients were categorized into three groups based on the *CYP2C19* genotype, EM (*1/*1), IM (*1/*2 or *1/*3), and PM (*2/*2, *2/*3, or *3/*3).

Serum PG level

Serum PG Ⅰ and Ⅱ levels were measured before and after eradication therapy. Gastric atrophy was evaluated as described previously[16,17]: (-), PG Ⅰ ≥ 70 ng/mL and PG Ⅰ/PG Ⅱ ratio ≥ 3.0; (1+), PGI < 70 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (2+), PG Ⅰ < 50 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (3+), PG Ⅰ < 30 ng/mL and PG Ⅰ/PG Ⅱ ratio < 2.0.

Statistical analysis

Data were analyzed using the SPSS statistics version 22 software package (IBM Corp., Armonk, NY, United States). The data were also analyzed using χ^2 test and multiple logistic regression analysis. *H. pylori* eradication rate was evaluated by intention-to-treat (ITT) and per protocol (PP). Differences at $P < 0.05$ were considered significant.

RESULTS

Influence of CYP2C19 genotype on H. pylori eradication by EPZ-based triple therapy

Among 80 patients who were treated by first-line eradication therapy with EPZ, AMPC, and CAM, one patient did not return for a UBT after the therapy. The *H. pylori* eradication rates of this first-line therapy evaluated by ITT and PP were 67.5% and 68.4%, respectively, which were similar to first-line therapy with LPZ, AMPC, and CAM (67.5%) in the Kitasato Institute Hospital. The results of *CYP2C19* genotype and serum PG level in association with *H. pylori* eradication are shown in Tables 1-3. The eradication rates of first-line therapy with EPZ in the three *CYP2C19* genotypes, EM, IM, and PM, were 52.2% (12/23), 72.1% (31/43), and 84.6% (11/13), respectively. The *H. pylori* eradication rate of EM was significantly lower than that of non-EM ($P = 0.048$).

Table 2 Serum pepsinogen level and *Helicobacter pylori* eradication in the intermediate metabolizer group (*CYP2C19* genotype: *1/*2, *1/*3)

Case	Age	Sex	*CYP2C19* genotype	PG Ⅰ/Ⅱ				UBT	Eradication
				Before eradication		After eradication			
I1	61	F	*1/*2	2.6	-	4.5	-	1.1	○
I2	66	M	*1/*2	3.6	-	6.0	-	0.0	○
I3	65	F	*1/*2	2.5	-	4.1	-	0.2	○
I4	71	F	*1/*2	3.5	-	7.4	-	0.9	○
I5	59	M	*1/*3	2.2	-	5.3	-	1.1	○
I6	62	M	*1/*3	3.3	-	8.3	-	0.0	○
I7	67	M	*1/*2	4.9	-	5.0	-	0.3	○
I8	64	F	*1/*2	2.8	-	5.2	-	0.5	○
I9	64	F	*1/*2	3.2	-	5.4	-	0.1	○
I10	34	M	*1/*2	3.1	-	6.9	-	0.3	○
I11	52	M	*1/*2	3.7	-	4.9	-	0.8	○
I12	64	M	*1/*2	3.6	-	4.5	-	0.2	○
I13	55	M	*1/*3	2.0	-	4.7	-	1.1	○
I14	58	M	*1/*2	3.8	-	9.4	-	0.6	○
I15	66	F	*1/*3	1.4	-	3.7	-	1.0	○
I16	47	M	*1/*2	4.0	-	5.4	-	0.0	○
I17	42	M	*1/*3	2.8	1+	5.3	-	0.4	○
I18	53	M	*1/*2	2.3	1+	3.7	-	0.8	○
I19	56	M	*1/*3	2.0	1+	4.0	-	2.4	○
I20	51	F	*1/*2	1.1	1+	3.3	-	0.0	○
I21	62	F	*1/*2	2.3	1+	4.1	-	0.3	○
I22	39	F	*1/*2	2.7	2+	6.0	-	0.4	○
I23	63	F	*1/*3	2.1	2+	4.0	-	0.1	○
I24	53	F	*1/*2	2.3	2+	4.1	-	0.3	○
I25	45	M	*1/*2	2.4	2+	4.9	-	0.6	○
I26	55	M	*1/*2	2.6	2+	4.2	-	0.5	○
I27	50	M	*1/*2	1.8	2+	3.9	-	0.6	○
I28	55	M	*1/*2	1.3	3+	3.6	-	0.0	○
I29	53	F	*1/*2	1.7	2+	2.9	2+	0.4	○
I30	64	M	*1/*2	1.2	3+	2.5	2+	1.5	○
I31	66	F	*1/*2	0.8	3+	0.8	3+	1.4	○
I32	53	M	*1/*3	4.1	-	4.5	-	49.8	×
I33	61	M	*1/*2	4.2	-	3.2	-	24.8	×
I34	44	F	*1/*2	3.2	-	3.2	-	44.5	×
I35	51	F	*1/*2	2.4	2+	3.1	-	21.7	×
I36	28	F	*1/*3	2.2	-	2.2	1+	43.6	×
I37	70	M	*1/*3	2.7	1+	2.7	1+	9.3	×
I38	70	F	*1/*2	2.5	1+	2.0	1+	39.2	×
I39	65	M	*1/*3	3.1	-	3.0	2+	28.0	×
I40	45	F	*1/*3	2.8	-	2.5	2+	13.0	×
I41	78	F	*1/*2	0.8	3+	1.4	3+	4.1	×
I42	45	F	*1/*2	1.5	3+	1.6	3+	17.0	×
I43	70	M	*1/*3	1.1	3+	1.1	3+	37.4	×

(-), PG Ⅰ ≥ 70 ng/mL and PG Ⅰ/PG Ⅱ ratio ≥ 3.0; (1+), PG Ⅰ < 70 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (2+), PG Ⅰ < 50 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (3+), PG Ⅰ < 30 ng/mL and PG Ⅰ/PG Ⅱ ratio < 2.0. Eradication (○) rate = 31/43 (72.1%). M: Male; F: Female; PG: Pepsinogen; UBT: ^{13}C-urea breath test.

Influence of PG level on H. pylori eradication by EPZ-based triple therapy

In addition to *H. pylori* infection, serum PG level is associated with gastric mucosal atrophy and gastric cancer risk, which is used for gastric cancer screening[17-19]. Serum PG Ⅰ level and PG Ⅰ/Ⅱ ratio in association with *H. pylori* eradication are shown in Tables 1, 2, and 3. Table 4 is a summary of PG Ⅰ/Ⅱ ratio and *H. pylori* eradication. Serum PG Ⅰ level and PG Ⅰ/Ⅱ ratio were significantly increased after eradication of *H. pylori* (P = 0.007), suggesting that gastric atrophy was improved by *H. pylori* eradication therapy. We performed a multiple logistic regression analysis to identify independent predictors associated with *H. pylori* eradication. As shown in Table 5, only *CYP2C19* genotype was statistically significant as an independent predictor associated with *H. pylori* eradication.

DISCUSSION

EPZ is a second-generation PPI that is broadly used for the treatment of acid-peptic diseases. It is believed that EPZ is more effective for inhibition of gastric acid secretion than other first-generation PPIs, because it is the S-isomer of OPZ and its metabolism is not affected by *CYP2C19* genotype. Recent studies have also shown that *H. pylori* eradication by EPZ-based

Table 3 Serum pepsinogen level and *Helicobacter pylori* eradication in the poor metabolizer group (*CYP2C19* genotype: *2/*2, *2/*3, *3/*3)

Case	Age	Sex	*CYP2C19* genotype	PG Ⅰ/Ⅱ				UBT	Eradication
				Before eradication		After eradication			
P1	64	F	*2/*2	3.6	-	5.8	-	0.2	○
P2	46	M	*2/*2	4.0	-	5.5	-	1.2	○
P3	64	F	*2/*2	2.2	1+	3.8	-	1.1	○
P4	63	F	*2/*2	2.1	2+	3.9	-	0.0	○
P5	62	F	*2/*3	2.3	2+	4.2	-	0.2	○
P6	64	M	*2/*3	2.2	2+	5.0	-	0.0	○
P7	63	M	*2/*2	2.7	2+	4.9	-	1.2	○
P8	77	F	*3/*3	1.7	3+	2.9	2+	0.1	○
P9	68	M	*2/*2	1.3	2+	1.9	3+	1.2	○
P10	60	M	*2/*2	0.6	3+	1.4	3+	0.8	○
P11	57	M	*2/*2	4.1	-	ND	ND	0.2	○
P12	65	F	*2/*2	2.0	1+	2.0	1+	30.2	×
P13	38	F	*2/*2	2.3	2+	2.5	1+	63.8	×

(-), PG Ⅰ ⩾ 70 ng/mL and PG Ⅰ/PG Ⅱ ratio ⩾ 3.0; (1+), PG Ⅰ < 70 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (2+), PG Ⅰ < 50 ng/mL and PG Ⅰ/PG Ⅱ ratio < 3.0; (3+), PG Ⅰ < 30 ng/mL and PG Ⅰ/PG Ⅱ ratio < 2.0. Eradication (○) rate = 11/13 (84.6%). M: Male; F: Female; ND: Not detected; PG: Pepsinogen; UBT: ^{13}C-urea breath test.

Table 4 Correlation between pepsinogen Ⅰ/Ⅱ ratio and *Helicobacter pylori* eradication

Eradication	PG Ⅰ/Ⅱ ratio			Total
	Increase	No change	Decrease	
Success	26	26	1	53
Failure	4	18	3	25
Total	30	44	4	78

Serum PG Ⅰ level and PG Ⅰ/Ⅱ ratio were significantly increased after eradication of *Helicobacter pylori* ($P < 0.01$). PG: Pepsinogen.

Table 5 Multiple logistic regression analysis to identify independent predictors associated with *Helicobacter pylori* eradication

Variable	*P* value
CYP2C19 genotype (EM *vs* non-EM)	0.048
Age	0.603
Sex	0.637
Pepsinogen Ⅰ/Ⅱ before eradication	0.809

EM: Extensive metabolizer.

therapy is not influenced by *CYP2C19* genotype, and that overall *H. pylori* eradication rates of EPZ-based therapy was better than first-generation PPIs[9,12-14]. On the other hand, Hunfeld *et al*[11] revealed that the acid-inhibitory effect of EPZ was influenced by *CYP2C19* genotype. Nishida *et al*[15] demonstrated that the *H. pylori* eradication rate of EPZ-based triple therapy was lower than LPZ in the Japanese population. Thus, the effect of EPZ-based therapy on *H. pylori* eradication is controversial.

In this study we evaluated the influence of *CYP2C19* genotype in patients with *H. pylori*-positive gastritis treated by EPZ-based triple therapy. Our results demonstrated that the *H. pylori* eradication rate was significantly lower in EM phenotype patients having the wild-type *CYP2C19* genotype, compared to the non-EM patients with at least one mutant allele (*2 and *3). The result of multiple logistic regression analysis also showed that *CYP2C19* genotype is an independent predictor associated with *H. pylori* eradication. These findings suggest that EM metabolizes EPZ more rapidly, and therefore plasma concentrations of EPZ become lower, resulting in a lower *H. pylori* eradication rate than that of non-EM. Nishida *et al*[15] conducted a multicenter, randomized, open-label, non-inferiority trial comparing EPZ and LPZ in triple therapy for *H. pylori* eradication in Japan. They reported that the *H. pylori* eradication rates of EPZ-based triple therapy (69.4%/76.9%, ITT/PP) were lower than LPZ-based triple therapy (73.9%/79.8%, ITT/PP). In this study, the overall *H. pylori* eradication rates of EPZ-based triple therapy were 67.5%/68.4% (ITT/PP), which were similar to the previous report. A recent study with a Japanese population has also shown that the *H. pylori* eradication rates by the regimen with rabeprazole, AMPC, and CAM were 73.3%/77.2% (ITT/PP)[6]. Thus, these findings indicate that the *H. pylori* eradication rate by EPZ-based triple therapy is at the same level with triple therapies with other first-generation PPIs.

Serum PG level is associated with gastric mucosal atrophy and gastric cancer risk[17-19]. In the present study, the serum PG Ⅰ level and PG Ⅰ/Ⅱ ratio were significantly increased after eradication of *H. pylori*, suggesting that gastric atrophy was improved by *H. pylori* eradication. Serum PG level and PG Ⅰ/Ⅱ ratio can be noninvasive biomarkers for screening of gastric atrophy and gastric cancer. *H. pylori* eradication has clinical benefit for improvement of gastric mucosal atrophy and prevention against gastric cancer.

In conclusion, first-line *H. pylori* eradication by EPZ-based triple therapy was influenced by *CYP2C19*

genotype, and the overall eradication rate was on the same level with triple therapies with other first-generation PPIs in Japanese patients with *H. pylori*-positive gastritis. Unlike previous reports, the results in this study suggest that there is no advantage to EPZ-based triple therapy on *H. pylori* eradication in comparison to other first-generation PPIs. Further studies are needed in a large population of patients in different countries before an accurate correlation between the EPZ-based therapy and *CYP2C19* genotype is completed. Evaluation of *CYP2C19* genotype and serum PG level is important to develop more effective personalized *H. pylori* eradication therapy with EPZ.

COMMENTS

Background

Esomeprazole (EPZ) is a second-generation proton pump inhibitor (PPI) that is broadly used for the treatment of acid-peptic diseases. Recent studies have shown that EPZ is more effective for inhibition of gastric acid secretion than other first-generation PPIs because its metabolism is not influenced by *CYP2C19* genotype. However, the effect of *Helicobacter pylori* (*H. pylori*) eradication by EPZ-based therapy is controversial.

Research frontiers

First-line eradication by EPZ-based triple therapy for patients with *H. pylori*-positive gastritis was influenced by *CYP2C19* genotype, and the eradication rate was at the same level found with other first-generation PPIs in the Japanese population.

Innovations and breakthroughs

Unlike previous reports, the results in this study suggest that there is no advantage to EPZ-based triple therapy on *H. pylori* eradication in comparison to other first-generation PPIs.

Applications

Evaluation of *CYP2C19* genotype and serum pepsinogen level is important to develop more effective personalized *H. pylori* eradication therapy with EPZ.

Terminology

EPZ is the most recent member of the PPI family and is a more potent acid inhibitor than other first-generation PPIs. The metabolism of first-generation PPIs is influenced by genetic polymorphism of *CYP2C19*. Based on *CYP2C19* genotype, patients can be categorized into three groups: extensive metabolizer, intermediate metabolizer, and poor metabolizer.

Peer-review

This study reports that the second-generation PPI inhibitor, EPZ, has no apparent advantage over triple therapies utilizing other first-generation PPIs for overall eradication of *H. pylori* in patients with gastritis. The EPZ-based therapy was influenced by the *CYP2C19* genotype of the studied Japanese patients.

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