

## The First-Line Eradication Rate for *Helicobacter pylori* Infection in Functional Dyspepsia Patients

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### ABSTRACT

**AIM:** The eradication rates of a first-line eradication regimen for *Helicobacter pylori* (*H. pylori*) infection in patients with functional dyspepsia (FD) and peptic ulcer disease (PUD) were compared. The eradication rates in distinction from proton pump inhibitors (PPIs) were also investigated.

**METHODS:** A total of 339 *H. pylori* infected patients were enrolled in this study. PPI [lansoprazole (L) 30 mg bid, omeprazole (O) 20 mg bid or rabeprazole (R) 10 mg bid] was randomly allocated along with amoxicillin (A) 750 mg bid and clarithromycin (C) 400 mg bid (L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub>, O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub>, or R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub>) by the envelope method.

**RESULTS:** Of 339 patients, 111 had PUD and 126 patients had FD. All patients underwent a gastrointestinal endoscopy for confirmation of the presence of gastroduodenal disease. The eradication rates of *H. pylori* in PUD patients obtained with the three regimens were similar. On the other hand, the eradication rate in FD patients was lower than that in the PUD patients (69.8%, 81.1%, respectively,  $P=0.0458$ ). The eradication rate with R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> was significantly lower in

the FD patients than in the PUD patients, according to both ITT and PP analysis ( $P=0.0458$ ,  $P=0.0161$ , respectively). Data analysis revealed that the lower eradication rate obtained in FD patients was attributable to the use of the R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> regimen. The overall frequency of adverse events was 32.9%.

**CONCLUSION:** The eradication rate in the first-line R-based regimen used for FD patients was very low (ITT: 54.1%, PP: 57.1%) compare with L-based regimen.

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**Key words:** The first-line eradication rate; *Helicobacter pylori*; PPI; Functional dyspepsia; Peptic ulcer disease

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### INTRODUCTION

According to a revised edition of the guideline for *Helicobacter pylori* (*H. pylori*) Infection Diagnosis and Treatment by the Japanese Society for *Helicobacter* Research in 2009, eradication of the organism is strongly recommended in all *H. pylori* infected-patients<sup>[1]</sup>. This is because it was confirmed in a Japanese multi-center, open-label, randomized controlled trial conducted in 2008 that preventive eradication of *H. pylori* after endoscopic resection of early gastric cancer can prevent the development of metachronous gastric cancer<sup>[2]</sup>. In February, 2013, eradication treatment for *H. pylori*-infected gastritis was authorized for use by the Japanese National Health Insurance system. This enabled us to conduct eradication treatment for all the patients infected with *H. pylori* as a health insurance treatment.

The first-line eradication regimen for *H. pylori* infection consists of

a proton pump inhibitor (PPI) + amoxicillin (A) + clarithromycin (C) in Japan. Any one of the four currently available PPIs, lansoprazole (L), omeprazole (O), rabeprazole (R) and esomeprazole (E) were originally used for the treatment of peptic ulcer disease (PUD) and reflux esophagitis, were authorized for use in *H. pylori* eradication regimens in November 2000, April 2002, January 2007, and September 2011, respectively.

The *H. pylori* eradication rates were compared between patients with functional dyspepsia (FD) and PUD, and among regimens including one of the three PPIs (L, O or R) in this prospective, open, randomized single-center study.

## METHODS

### Patients

This study was conducted from January 2008 to December 2013. A total of 339 patients with *H. pylori* infection who visited the out-patient clinic of the Department of Gastroenterology, Tama-Nagayama University Hospital, Nippon Medical School were enrolled in this study. The exclusion criteria included a history of previous *H. pylori* eradication, history of upper gastrointestinal tract surgery except for endoscopic treatment of gastric cancer, history of drug allergy to PPI, A or C, serious concomitant illness, pregnant or lactating women, and regular users of non-steroidal anti-inflammatory drugs (NSAIDs). Patients with a history of treatment with a PPI or histamine-2 receptor antagonist (H<sub>2</sub>RA), or treatment with any antibiotic within 4 weeks prior to the study commencement were also excluded. During the eradication treatment period, concomitant use of antibacterial or antiprotozoal agents, PPIs, H<sub>2</sub>RAs, NSAIDs, and corticosteroids was prohibited. Before the eradication therapy, gastrointestinal endoscopy was performed in all the patients to confirm the presence of gastroduodenal disease. Written informed consent for participation in this study was obtained from all the patients under the approval of Ethics Committee of Tama-Nagayama University Hospital.

The subjects were started on first-line triple therapy with a PPI (L 30 mg bid, O 20 mg bid or R 10 mg bid), A (750 mg bid), and C (400 mg bid) administered for 7 days (L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub>, O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub>, or R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub>) for eradication of *H. pylori* infection. All PPIs are double the doses of these drugs used in the treatment of PUD and reflux esophagitis. The LANSAP®800, packaged drugs set, was used in the L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub> group. As E was not brought out when this study started, it was not included in these groups. Using the envelope method, the patients were randomly allocated to one of the three treatment groups described above.

### Diagnosis of *H. pylori* infection

The diagnosis of *H. pylori* infection was made by the histological method, using biopsy specimens stained with hematoxylin-eosin and a Giemsa stain. *H. pylori* specific antibody immune staining was performed as appropriate for the histological diagnosis of *H. pylori* infection. Biopsy specimens for histological examination were obtained endoscopically in accordance with the triple-site gastric biopsy method as reported previously<sup>13,41</sup>. The pathologist examining the specimens was blinded to all clinical information. The <sup>13</sup>C-urea breath test (UBT) and/or *H. pylori* stool antigen test (HpSA) (Premier Platinum HpSA® PLUS) (Meridian Bioscience, Inc., Cincinnati, OH, USA) was also used for the diagnosis in some cases, when the histological diagnosis was negative, but *H. pylori* infection was, nevertheless, suspected. The Ubit tablet® (Otsuka Pharmaceuticals, Tokyo, Japan), containing 100 mg of <sup>13</sup>C-urea was used for the <sup>13</sup>C-UBT, and patients in whom the Δ<sup>13</sup>C value at 20 minutes after

ingestion was 2.5‰ or higher were deemed as *H. pylori* positive, and those with values lower than 2.5‰ deemed as *H. pylori* negative<sup>15</sup>.

### Diagnosis of *H. pylori* eradication

The <sup>13</sup>C-UBT, performed more than 6 weeks after the treatment, was used to confirm the eradication of *H. pylori* in response to the treatment. Δ<sup>13</sup>C values lower than 2.5‰ were deemed to represent successful eradication, values between 2.5 and 5.0‰ were considered as being in the gray zone, and values higher than 5.0‰ were considered as representing treatment failure<sup>16</sup>. In case of gray zone, the <sup>13</sup>C-UBT was performed again 2 to 3 months later.

### Statistical analysis

The eradication rates in each group were evaluated by intention-to-treat (ITT) analysis and per protocol (PP) analysis and compared using Fisher's exact test. The 95% confidence intervals (CIs) were also calculated. For continuous quantities (age, and body mass index), we performed an analysis of variance and for *P* values less than 0.05, performed t-tests among each group. For ratios (gender, smoker, drinker, and adverse events), Fisher's Exact test was performed using the cross table of 2×3. *P* values lesser than 0.05 were considered to be statistically significant.

An acceptable eradication rate is defined higher than 90% in the PP analysis<sup>17</sup>.

## RESULTS

### Patient profile

There were no differences in the mean age, the male/female ratio, the body mass index (BMI), smoking status, or alcohol drinking status among the patients receiving the three regimens (Table 1). 100% of the L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub> group, 100% of the O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub> group and 99.6% of the R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> group were compliant, resulting in a mean of 99.9%.

There were 5 histological *H. pylori* negative cases, which revealed *H. pylori* positive by UBT and/or HpSA. Three cases were UBT positive, 1 case was HpSA positive, and 1 case was HpSA negative and UBT positive. These cases were divided into L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub> (2 cases), O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub> (1 case), and R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> (2 cases) group.

Of the enrolled patients, 111 had PUD and the remaining 228 did not have PUD (non-PUD). The patients in the non-PUD group consisted of those with gastric erosion, gastric adenoma, gastric polyp, atrophic gastritis or FD. Patients with FD made up 126 of the non-FD group.

### Eradication rates

The overall eradication rate of *H. pylori* was 76.7% according to ITT analysis and 80.0% according to PP analysis (Table 2). There were no significant differences in the eradication rate among the three treatment groups in either the ITT or PP analysis (Table 2).

When the results were stratified according to the diagnosis of PUD and non-PUD, the eradication rates were 81.1% and 74.6%, respectively, according to the ITT analysis, and 84.7% and 78.0%, respectively, according to PP analysis (Table 2). There was no differences in the eradication rate between PUD and non-PUD (Table 2). There were no differences in the *H. pylori* eradication rate among the PUD patients receiving L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub>, O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub>, and R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub>, according to both ITT and PP analysis (Table 2). There was also no difference in the eradication rate among these groups of non-PUD patients (Table 2).

On the other hand, the overall eradication rate of *H. pylori* in the FD patients was significantly lower than that in the PUD patients, according to ITT analysis (*P*=0.0458) (Table 2). The eradication rate

with R20A1500C800 was significantly lower in the FD patients than in the PUD patients, according to both ITT and PP analysis ( $P=0.0482$ ,  $P=0.0161$ , respectively) (Table 2). There were no difference in the eradication rates between PUD and FD patients in L60A1500C800 and O40A1500C800 group. There was a significant difference in the eradication rate in FD patients between the L60A1500C800 and R20A1500C800 groups, according to both ITT and PP analysis ( $P=0.0360$ ,  $P=0.0287$ , respectively) (Table 2).

All eradication rates were lower than 85%, unacceptable, according to PP analysis (Table 2).

There were four, two, and two gray zone cases in the <sup>13</sup>C-UBT following treatment in the L60A1500C800, O40A1500C800, and R20A1500C800 treatment groups, respectively. In the L60A1500C800 treatment group, two cases were revealed to show treatment failure, and two cases were revealed to be in the gray zone again two months after the <sup>13</sup>C-UBT. Two cases in the O40A1500C800 treatment group and one case in the R20A1500C800 treatment group were found to be *H. pylori*-positive by two months after the <sup>13</sup>C-UBT. One patient from the R20A1500C800 treatment group did not come for the follow-up <sup>13</sup>C-UBT.

**Adverse events**

The number of cases included in the analysis of adverse events was 113, 112 and 109, respectively, from the L60A1500C800, O40A1500C800, and R20A1500C800 treatment groups, representing a total of 334 cases (Table 3). A total of 131 adverse events were reported from 110 patients. The overall frequency of adverse events was 32.9%. There were no differences in the occurred frequency of adverse events among the treatment groups (Table 3). Loose stools and diarrhea were the most frequent adverse events encountered with all the regimens

(18.6%, 25.0% and 13.8%, respectively). The frequency of dysgeusia and glossitis in the O40A1500C800 treatment group was significantly lower than that in the L60A1500C800 treatment group ( $P=0.0346$ ) (Table 3). Most of the adverse events were also mild to moderate in intensity and self-limiting. One patient from the R20A1500C800 treatment group discontinued the eradication therapy by the proposal from the patient because of the development of eruptions.

**DISCUSSION**

In Japan, eradication treatment for PUD became covered by the Japanese National Health Insurance system in November 2000, and since then the number of PUD patients has reduced drastically. In February 2013, eradication treatment for *H. pylori* infected gastritis began to be performed, and the number of eradication treatments increased approximately threefold. Before eradication treatment for *H. pylori* infected gastritis became covered by insurance, as we noticed that the eradication rate for some FD cases was lower than that of PUD cases, we examined the eradication rate divided into PUD and FD groups and compared the eradication rate in each regimen as a prospective, open, randomized single-center study.

Although the eradication rates obtained with three PPIs (L, O and R) by a Japanese multicenter study have been reported, all of the cases consisted of PUD patients<sup>[8-10]</sup>. These reported *H. pylori* eradication rates obtained with the three regimens, L60A1500C800, O40A1500C800, and R20A1500C800<sup>[8-10]</sup>, are consistent with the data of our present study. However, our eradication rate in FD patients (69.8%) was lower than that of PUD patients (81.1%). The lower eradication rate in the FD patients as compared with that in the PUD patients was only

**Table 1** Patient profile.

	L60A1500C800	O40A1500C800	R20A1500C800	Total	P value
Case number	113	113	113	339	
Mean age±SE <sup>1</sup> (range)	62.6 ± 1.2 (27-90)	62.3 ± 1.3 (19-88)	62.5 ± 1.2 (34-88)	62.5 ± 0.7 (19-90)	0.9496
Gender (male/female)	60/53	67/46	62/51	189/150	0.6186
Body mass index±SE <sup>1</sup>	21.8 ± 0.3	22.5 ± 0.3	22.8 ± 0.3	22.4 ± 0.2	0.0625
Smoker/non-smoker	64/49	59/54	68/45	191/148	0.5056
Drinker/non-drinker	27/86	20/93	27/86	74/265	0.4270

<sup>1</sup>SE: standard error. Fisher's exact test.

**Table 2** Eradication rate for peptic ulcer disease, non-peptic ulcer disease, and functional dyspepsia.

		L60A1500C800	95% CI	O40A1500C800	95% CI	R20A1500C800	95% CI	Total	95% CI
Total	ITT	78.8%	(89/113) 72.2-81.2	79.6%	(90/113) 71.2-86.3	71.7%	(81/113) 63.4-80.0	76.7%	(260/339) 67.4-80.2
	PP	82.4%	(89/108) 75.7-84.4	80.4%	(90/112) 75.2-89.6	77.1%	(81/105) 73.0-87.7	80.0%	(260/325) 69.1-85.2
PUD <sup>1</sup>	ITT	80.6%	(29/36) 67.6-93.5	84.2%	(32/38) 72.6-95.8	78.4% *	(29/37) 65.1-91.6	81.1% **	(90/111) 73.8-88.4
	PP	82.9%	(29/35) 70.4-95.3	84.2%	(32/38) 72.6-95.8	85.3% ***	(29/34) 73.4-97.2	84.7%	(90/107) 77.2-91.0
non-PUD	ITT	77.9%	(60/77) 68.7-87.2	77.3%	(58/75) 67.9-86.8	68.4%	(52/76) 58.0-78.9	74.6%	(170/228) 68.9-90.2
	PP	82.2%	(60/73) 73.4-91.0	78.4%	(58/74) 69.0-87.8	73.2%	(52/71) 62.9-83.5	78.0%	(170/218) 72.4-83.3
FD <sup>2</sup>	ITT	77.1% ****	(37/48) 65.2-89.0	75.6%	(31/41) 62.5-89.8	54.1% *****	(20/37) 38.0-70.1	69.8% *****	(88/126) 61.8-77.9
	PP	80.4% *****	(37/46) 69.0-91.9	77.5%	(31/40) 64.6-90.4	57.1% *****	(20/35) 40.8-73.5	72.7%	(88/121) 64.8-80.7

<sup>1</sup>PUD: peptic ulcer disease; <sup>2</sup>FD: functional dyspepsia. \* vs \*\*\*\*:  $P=0.0482$ , \*\* vs \*\*\*\*\*:  $P=0.0161$ , \*\* vs \*\*\*\*\*:  $P=0.0458$ , \*\*\*\* vs \*\*\*\*\*:  $P=0.0360$ , \*\*\*\*\* vs \*\*\*\*\*:  $P=0.0287$ . Fisher's exact test.

**Table 3** Adverse events.

Adverse events	L60A1500C800	O40A1500C800	R20A1500C800	Total	P value
None	72/113 63.3%	71/112 63.4%	81/109 74.3%	224/334 67.1%	0.1495
Occurred	41/113 36.7%	41/112 36.4%	28/109 25.7%	110/334 32.9%	0.1495
Loose stools, diarrhea	21/113 18.6%	28/112 25.0%	15/109 13.8%	64/334 19.2%	0.1033
Dysgeusia, glossitis	22/113 19.5%	10/112 8.9%	11/109 10.1%	43/334 12.9%	0.0443
Abdominal pain, epigastric discomfort	2/113 1.8%	1/112 0.9%	2/109 1.6%	5/334 1.5%	0.8111
Eruption	1/113 0.9%	2/112 1.8%	3/109 1.8%	6/334 1.8%	0.5880
Constipation	2/113 1.8%	4/112 3.6%	2/109 1.8%	8/334 2.4%	0.6071
Others	3/113 2.7%	1/112 0.9%	1/109 0.9%	5/334 1.5%	0.6253

Fisher's exact test.

noted in the patients treated with R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> (54.1%). There was no difference in the eradication rate between PUD and FD patients in the L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub> and O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub> treatment group.

We can find many different Japanese reports about eradication rates with PPI plus A and C<sup>[11-14]</sup>. Some reports consist of PUD or gastric ulcer patients only and some reports consist of PUD and FD patients. Miwa *et al* reported that in patients with PUD and FD there was no difference in the eradication rate yielded by R 10 mg bid plus A 500 mg tds and C 200 mg bid administered for 7 days (R<sub>20</sub>A<sub>1500</sub>C<sub>400</sub>) and R 20 mg bid plus A 500 mg tds and C 200 mg bid administered for 7 days (R<sub>40</sub>A<sub>1500</sub>C<sub>400</sub>) in either PUD or FD patients; the eradication rates (ITT, PP) were 87.0%, 89.7% in the R<sub>20</sub>A<sub>1500</sub>C<sub>400</sub> group, and 85.6%, 89.8% in the R<sub>40</sub>A<sub>1500</sub>C<sub>400</sub> group<sup>[14]</sup>. However, this is an eradication rate for PUD and FD combined together, and looking at the breakdown, the number of PUD patients is much more than that of FD patients (270 cases and 38 cases, respectively) and it is difficult to compare this with our study results. On the other hand, the eradication rate of FD yielded by R 20 mg bid plus A 1,000 mg bid and C 500 mg bid for 7 days (R<sub>40</sub>A<sub>2000</sub>C<sub>1000</sub>) was significantly higher than that yielded by R10 mg bid plus A 1,000 mg bid and C 500 mg bid for 7 days (R<sub>20</sub>A<sub>2000</sub>C<sub>1000</sub>) or O 20 mg bid plus A 1,000 mg bid and C 500 mg bid for 7 days (O<sub>40</sub>A<sub>2000</sub>C<sub>1000</sub>) (ITT analysis: 100%, 84.4%, 82.8%, respectively,  $P=0.007$ , PP analysis: 100%, 86.7%, 92.0%, respectively,  $P=0.035$ ) in Thai study<sup>[15]</sup>. They concluded that R<sub>40</sub>A<sub>2000</sub>C<sub>1000</sub> is necessary for successful *H. pylori* eradication in patients with FD<sup>[15]</sup>. It seems useful to use R 20 mg bid, seeing that our study with R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> resulted in a lower eradication rate.

Previous European studies have also reported higher eradication rates in PUD patients than FD patients<sup>[16-18]</sup>. Described in the background are the following points. Only one-half to two-thirds of Western-type isolates *H. pylori* possess the cytotoxin-associated gene (*cagA*), whereas nearly all East Asia-type isolates possess *cagA*<sup>[19]</sup>. In Japan, nearly 100% of the strains possess *cagA*<sup>[20]</sup>. The vacuolating cytotoxin gene (*vacA*) is present in all *H. pylori* strains. It is reported that the *vacA* s1/m1 and s1/m2 strains, which are mostly *cagA*-positive, seemed to be easier to eradicate than the *vacA* s2/m2 strain, which is mostly *cagA*-negative<sup>[21]</sup>. According to a European report, the *cagA*-positive strain is more prevalent in patients with PUD than in those with FD<sup>[22]</sup>. However, there are some counter-opinions to the report that presented a lower eradication rate for FD<sup>[23]</sup>. Almost all *H. pylori*-infected Japanese possess *cagA*, regardless of the presence of disease, e.g., PUD and FD<sup>[20]</sup>. Consequently we cannot accept these European concepts in Japan. Therefore, it seems that there are some other reasons for the lower eradication rate in FD patients administered with R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub>.

Among the many causes of eradication treatment failure, C resistance is the most frequent<sup>[24,25]</sup>. Miki *et al* reported that effective treatment of *H. pylori* depends on the susceptibility to CAM and that the odds ratio for failure in the CAM-resistant versus CAM-susceptible cases was 498.363 (95%CI: 37.949-6544.714,  $P<0.001$ )<sup>[24]</sup>. However, as the patients in our study were randomized to one of the three eradication regimens, it is difficult to consider that C-resistant FD cases were concentrated in the R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> treatment group.

There is a genetic polymorphism of cytochrome *P450* (*CYP*) *2C19*. It is classified into three groups: without mutation named the homozygous extensive metabolizer (homEM), with one mutation named the heterozygous extensive metabolizer (hetEM), and with two mutations named the poor metabolizer group (PM). According to a meta-analysis, the efficacy of *H. pylori* eradication therapy with O is dependent on the *CYP2C19* genotype, while that of the regimens containing L or R was independent of the aforementioned *CYP2C19*

metabolizer phenotype<sup>[26]</sup>. In Japan, there was no difference in patients with PUD in the eradication rate by the triple therapy with O<sub>40</sub>A<sub>1500</sub>C<sub>400</sub>, L<sub>60</sub>A<sub>1500</sub>C<sub>400</sub> or R<sub>20</sub>A<sub>1500</sub>C<sub>400</sub><sup>[12]</sup>. There was no significant difference in regard to *CYP2C19* among these treatment groups<sup>[12]</sup>. Although we did not investigate *CYP2C19* genetic polymorphism in our present study, it is unrealistic to think that homEM has been concentrated in the R<sub>20</sub>O<sub>1500</sub>C<sub>800</sub> treatment group, and thus the reason for the lower eradication rate cannot be explained.

It is recognized that more virulent *H. pylori* strains causes stronger inflammation<sup>[27]</sup>. The more antibiotics used for the eradication treatment reach the gastric mucosa in patient with a high inflammation score<sup>[16]</sup>, and makes it easy to cure the patient<sup>[28]</sup>. In our data, the mean inflammation score according to triple site gastric biopsy (#1-#3)<sup>[3,4]</sup> of FD was lower than that of PUD (1.69, 1.83, respectively,  $P=0.0066$ ) (data was not shown). This experience may support the difficulty of eradication treatment in FD patients. Therefore, the eradication for FD patients compared with that for PUD patients requires powerful and fast inhibition of acid secretion. Since antibiotics used for eradication treatment do not show enough antibacterial effects in high acid levels, eradication treatment with not only powerful inhibition of acid secretion but also rapid onset of efficacy is required<sup>[29]</sup>. The reason why the eradication rate is low only in the R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> group seems to lie in the insufficient inhibition of acid secretion compared with those of L and O.

There are many reports that have debated the acid reduced effect of PPIs. In a crossover study conducted in *H. pylori*-negative Japanese homEM and hetEM volunteers, R 10 mg od produced a faster rise of intragastric pH and stronger inhibition of gastric acid secretion from day one of administration than L 30 mg od or O 20 mg od<sup>[30]</sup>. However, in the subsequent report, there was no significant difference in the acid secretion-inhibitory effect between O (20 mg od) and R (10 mg od) in the subjects with the homEM group in a crossover study in *H. pylori*-negative Japanese volunteer<sup>[31]</sup>. Moreover, the median intragastric pH and pH at 5, 6 and 8 hours after administration of O on day one in the subjects with the hetEM and PM group were significantly higher than the corresponding results after administration of R, which implies O inhibits acid secretion faster than R<sup>[31]</sup>. Furthermore, in a crossover study conducted in *H. pylori*-negative Japanese volunteers in the subjects with the homEM and hetEM, L 30 mg orally disintegrating (OD) tablet od induced a significantly faster inhibition of gastric acid secretion than R 10mg od on day 1 (after the second hour, fourth hour of the study, respectively)<sup>[30]</sup>. While R included in LANSAP®800 is not an OD tablet but a capsule, OD tablets and capsules are recognized as a bio-equivalent to the respective dose<sup>[32]</sup>. To take these reports into consideration, there is such a large variety of reports on acid secretion inhibitory effect, that it is difficult to generalize which PPI is most powerful. Although overseas (USA, Germany and, South Korea), L 30 mg bid, O 20 mg bid, or R 20 mg bid are used for *H. pylori* eradication treatment<sup>[33-36]</sup>, only in Japan R 10 mg bid is used. The low eradication rate in FD patients treated with R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> may be due to the slow and weak acid suppression. In FD of which the inflammation score is low and thus eradication is made difficult, it seems necessary to change to the same dosage as in overseas, R 20 mg bid; from R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> to R<sub>40</sub>A<sub>1500</sub>C<sub>800</sub> in order to suppress the acid secretion.

In conclusion, the eradication rates yielded by L<sub>60</sub>A<sub>1500</sub>C<sub>800</sub>, O<sub>40</sub>A<sub>1500</sub>C<sub>800</sub> and R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> in patients with PUD were similar. On the other hand, the eradication rate in patients with FD was lower than that in patients with PUD. The lower eradication rate of FD attributed to the R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> treatment group. Excluding R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> group, there was no difference in eradication rate between PUD and

FD. The cause of the low eradication rate yielded by R<sub>20</sub>A<sub>1500</sub>C<sub>800</sub> in subjects with FD with mild inflammation seemed to be due to the insufficient acid secretion inhibitory effect. The number of cases of *H. pylori* infected FD treated with eradication therapy has been increasing. Though R 20 mg bid is not authorized for use by the Japanese National Health Insurance system, to increase the dose of R in the first-line RAC regimen, R<sub>40</sub>A<sub>1500</sub>C<sub>800</sub>, would be desirable in FD patients to reduce the risk of treatment failure.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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