Triple Therapy with Ecabet Sodium, Amoxicillin and Lansoprazole for 2 Weeks as the Rescue Regimen for *H. pylori* Infection

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Abstract

Background/Aim Ecabet sodium has an anti-*H. pylori* effect. We assessed the efficacy of ecabet sodium in the rescue therapy for the eradication of *H. pylori*.

Methods A total of 74 patients with failed eradication of *H. pylori* after triple therapy with lansoprazole 30 mg bid, amoxicillin 750 mg bid and clarithromycin 200 mg bid were enrolled. They were randomly assigned to the three treatment groups as follows: LAC, lansoprazole 30 mg + amoxicillin 750 mg + clarithromycin 200 mg bid for 1 week; LAC2E, lansoprazole 30 mg bid + amoxicillin 750 mg bid + clarithromycin 200 mg bid + ecabet sodium 2 g bid for 1 week; and LA2E, lansoprazole 30 mg bid + amoxicillin 750 mg bid + ecabet sodium 2 g bid for 2 weeks. Eradication of *H. pylori* was assessed by the 13C-urea breath test after treatment.

Results Eradication rates in intention-to-treat and per-protocol analyses were 20.0% (95% CI: 6.8-40.7) and 20.0% (6.8-40.7) with LAC, respectively, and 16.0% (4.5-36.1) and 17.4% (5.0-38.8) with LAC2E. In contrast, respective rates with LA2E were 75% (53.3-90.2) and 85.7% (63.7-97.0), which were significantly higher than those with LAC ($p < 0.001$ for both ITT and PP) and LAC2E ($p < 0.001$ for both ITT and PP).

Conclusion Triple therapy with ecabet sodium, lansoprazole and amoxicillin for 2 weeks was effective as the rescue therapy after failure of the standard clarithromycin-based regimen.

Key words: Ecabet sodium, *H. pylori*, eradication, resistance, clarithromycin, metronidazole

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Introduction

Eradication of *Helicobacter pylori* (*H. pylori*) infection is now conducted for a variety of upper gastrointestinal tract disorders, including peptic ulcer and gastric mucosa-

associated lymphoid tissue lymphoma (MALToma), and after endoscopic resection of gastric cancer in the early stage (1-5). The current standard first-line regimen for the eradication of *H. pylori* in Japan is the triple regimen with a proton pump inhibitor (PPI), amoxicillin and clarithromycin (6), while the standard second-line therapy consists of a

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Table 1. Demographic Clinical Characteristics of Patients Enrolled to the Study

	LAC	LAC2E	LA2E	p value
Number	25	25	24	
Age, y $\pm$ SE	52.7 $\pm$ 2.4	52.8 $\pm$ 2.4	54.0 $\pm$ 2.4	> 0.2 ¹⁾
Gender (male/female)	14/11	15/10	15/9	> 0.2 ²⁾
Smoking/non-smoking	10/15	10/15	9/15	> 0.2 ²⁾
GU/DU/GDU/gastritis	14/9/1/1	10/9/4/2	15/7/2/0	> 0.2 ²⁾
CAM-S/CAM-R/unknown	6/15/4	1/16/8	2/8/14	> 0.2 ²⁾
MNZ-S/MNZ-R/unknown	11/5/9	9/3/13	10/4/10	> 0.2 ²⁾

1) one-way ANOVA

2) Fisher's exact test

Abbreviations: GU = gastric ulcer, DU = duodenal ulcer, GDU = gastroduodenal ulcer, LAC = lansoprazole, amoxicillin and clarithromycin for 1 week, LAC2E = lansoprazole, amoxicillin, clarithromycin and ecabet sodium for 1 week

LA2E = lansoprazole, amoxicillin and ecabet sodium for 2 weeks

CAM-S=clarithromycin-sensitive strain of *H. pylori*; CAM-R = clarithromycin-resistant strain of *H. pylori*; MNZ-S = metronidazole-sensitive strain of *H. pylori*; MNZ-R = metronidazole-resistant strain of *H. pylori*.

PPI, amoxicillin and metronidazole (7).

An increase in the incidence of clarithromycin-resistant strains of *H. pylori* (8), which currently stands at approximately 30% or higher in Japan (9), has resulted in a decrease in the eradication rate of first-line treatment with a PPI, amoxicillin and clarithromycin in Japan to around 70% (9). Further, while the metronidazole-based second line therapy achieves eradication rates of approximately 90% (7) (10), the incidence of metronidazole resistant-strains is also increasing (11). Development of alternative rescue regimens with efficacy against strains resistant to clarithromycin and metronidazole is of clinical importance.

Ecabet sodium, developed as a gastric mucosal defensive agent for the treatment of peptic ulcer, has an anti-pepsin effect and induces prostaglandins in gastric mucosa (12-14). Ecabet sodium inhibits the urease activity of *H. pylori* and the growth of *H. pylori* in acidic conditions (15) (16). This anti-bacterial effect of ecabet sodium is observed even in strains resistant to clarithromycin and metronidazole (16).

Here, we investigated the usefulness of ecabet sodium in eradication therapy for *H. pylori* in patients in whom the initial therapy with lansoprazole, amoxicillin and clarithromycin failed.

Materials and Methods

This multi-center randomized controlled study at 11 hospitals in Japan was performed from 2005 to 2008. The protocol was approved in advance by the institutional review board (IRB) of each hospital.

Patients

Patients with peptic ulcer or gastritis for whom eradication of *H. pylori* failed on initial therapy with a triple regimen consisting of lansoprazole 30 mg bid, amoxicillin 750 mg bid and clarithromycin 200 mg bid for 1 week, the standard first-line therapy in Japan, were invited to participate in

the study. Eradication failure was diagnosed based on a positive result in at least one of the following tests: rapid urease test, ¹³C-urea breath test, culture, or histology after eradication therapy.

Written informed consent was obtained from each patient before enrollment to the study. Exclusion criteria were age <20 or >80 years; use of antimicrobial agents within 3 months of the study; use of a PPI within 2 months of the study; two or more previous eradication failures; use of steroid or NSAIDs; severe general condition, such as renal insufficiency or liver dysfunction; unhealed ulcer; history of gastrectomy; inability to undergo repeated eradication therapy; allergy to agents used in this study; and serious complications considered to prevent completion of the study. Demographic characteristics of the subjects are summarized in Table 1. Subjects with compliance of less than 100% were considered to have dropped out.

Eradication regimens and determination of success or failure of eradication

A total of 74 eligible subjects were randomly assigned to the three treatment groups as follows: LAC, lansoprazole 30 mg bid + amoxicillin 750 mg bid + clarithromycin 200 mg bid for 1 week; LAC2E, lansoprazole 30 mg bid + amoxicillin 750 mg bid + clarithromycin 200 mg bid + ecabet sodium 2 g bid for 1 week; and LA2E, lansoprazole 30 mg bid + amoxicillin 750 mg bid + ecabet sodium 2 g bid for 2 weeks. Eradication of *H. pylori* was assessed by ¹³C-urea breath testing at 4 weeks after treatment.

Susceptibility to clarithromycin was assessed by either or both culture and measurement of A to G or C mutations at positions 2142 and 2143 of the 23S rRNA gene of *H. pylori* (17). Strains were considered resistant when the mean inhibitory concentration (MIC) for clarithromycin was ≥ 1 μ g/mL or mutation of 23S rRNA was determined (18). Susceptibility to metronidazole was assessed by culture testing, and considered positive when MIC was $16 \geq \mu$ g/mL.

Statistics

Eradication rates were calculated based on intention-to-treat (ITT) and per-protocol (PP) analyses and demonstrated with 95% confidential intervals. Comparison of eradication rates among regimen groups was assessed by Fisher's exact test. P-values less than 5% were considered statistically significant.

Figure 1. Flow of patients enrolled to the study.

Results

Of 74 patients, 25 were assigned to the LAC, 25 to the LAC2E, and 24 to the LA2E groups (Fig. 1). There were no statistically significant differences between groups in mean age, male/female ratios, smoker/non-smoker ratios, or types of ulcer or gastritis (Table 1). Two patients who did not come to the hospital in the LAC2E and three whose compliance was less than 100% in the LA2E group were excluded from analysis.

Eradication rates by ITT analysis were 20.0% (95% CI: 6.8%-40.7%) in the LAC, 16.0% (95% CI: 4.5%-36.1%) in the LAC2E, and 75% (95% CI: 53.3%-90.2%) in the LA2E groups. Respective rates by PP analysis were 20.0% (95% CI: 6.8%-40.7%), 17.4% (95% CI: 5.0%-38.8%), and 85.7% (95% CI: 63.7%-97.0%). Eradication rate in the LA2E group was significantly higher than those in the LAC and LAC2E groups ($p < 0.001$ for both of LAC and LAC2E) (Table 2).

Susceptibility to clarithromycin was assessed in 59 of the 74 patients. Of these 59, 49 (83%) were infected with clarithromycin-resistant strains of *H. pylori*. Eradication rates with these clarithromycin-resistant strains by the ITT analysis were 6.7% (95% CI: 0.2%-31.9%) in the LAC, 12.5% (95% CI: 1.6%-38.3%) in the LAC2E and 83.3% (95% CI: 58.6%-96.4%) in the LA2E groups (Table 3). Re-

Table 2. Eradication Rates of *H. pylori* in the Three Groups

		Eradication rate (%), (n/n)	95% CI
ITT	LAC	20.0% (5/25)	6.8% – 40.7%
	LAC2E	16.0% (4/25)	4.5% – 36.1%
	LA2E	75.0% (18/24) ^{a,b}	53.3% – 90.2%
PP	LAC	20.0% (5/25)	6.8% – 40.7%
	LAC2E	17.4% (4/23)	5.0% – 38.8%
	LA2E	85.7% (18/21) ^{a,b}	63.7% – 97.0%

a: Significantly higher than LAC ($p < 0.001$), b: significantly higher than LA2CE ($p < 0.001$)

LAC, lansoprazole, amoxicillin and clarithromycin, 1 week

LAC2E, lansoprazole, amoxicillin, clarithromycin and ecabet sodium, 1 week

LA2E, lansoprazole, amoxicillin and ecabet sodium, 2 weeks

ITT, Intention to treat; PP, per protocol.

Table 3. Eradication Rates in Patients Infected with Clarithromycin-resistant Strains of *H. pylori*

ITT or PP	Regimen	Eradication rate (%) (n/n)	95% CI
ITT	LAC	6.7% (1/15)	0.2% – 31.9%
	LAC2E	12.5% (2/16)	1.6% – 38.3%
	LA2E	83.3% (15/18) ^{a,b}	58.6% – 96.4%
PP	LAC	6.7% (1/15)	0.2% – 31.9%
	LAC2E	12.5% (2/16)	1.6% – 38.3%
	LA2E	88.2% (15/17) ^{a,b}	63.6% – 98.5%

a: $p < 0.001$ when compared with LAC, b: $p < 0.001$ when compared with LAC2E

LAC, lansoprazole, amoxicillin and clarithromycin, 1 week

LAC2E, lansoprazole, amoxicillin, clarithromycin and ecabet sodium, 1 week

LA2E, lansoprazole, amoxicillin and ecabet sodium, 2 weeks

ITT, Intention to treat; PP, per protocol.

spective rates by PP analysis were 6.7% (95% CI: 0.2-31.9), 12.5% (95% CI: 1.6-38.3), and 88.2% (95% CI: 63.6-98.5). The eradication rate in the LA2E group was significantly higher than those in the LAC and LAC2E groups on both ITT and PP analyses.

Susceptibility to metronidazole was assessed in 40 of the 74 patients. Of these 40, 12 (30%) were infected with metronidazole-resistant strains of *H. pylori* (Table 4), all of which were resistant to clarithromycin. In patients infected with metronidazole-sensitive strains, eradication was achieved in 3 of 11 in the LAC group and 1 of 9 in the LAC2E group. However, these regimens were unable to eradicate infection in patients with metronidazole-resistant strains. In contrast, the LA2E regimen was able to eradicate infection in 8 of 8 patients (100%) infected with metronidazole-sensitive strains and 4 of 4 (100%) infected with metronidazole-resistant strains of *H. pylori*.

No adverse events were observed in the LAC group. In the LAC2E group, dysgeusia and hot flashes were observed in one patient each. In the LA2E group, loose stool was observed in two patients and diarrhea in two (Table 5). Of 2 diarrhea cases, one patient discontinued the treatment.

Discussion

In the present study, we compared the eradication rates obtained with three anti-*H. pylori* regimens, LAC, LAC2E and LA2E, in patients in whom eradication by the triple regimen with a PPI, clarithromycin and amoxicillin had failed. Results showed that the LA2E regimen may represent a candidate rescue regimen after the failure of eradication with the triple PPI/clarithromycin/amoxicillin therapy.

One of the major causes of eradication failure with triple PPI/clarithromycin/amoxicillin therapy is bacterial resistance

to clarithromycin (6). The incidence of clarithromycin-resistant strains in the present patients, all of whom had failed eradication by this therapy, was 83% (49/59). This finding indicates that rescue therapy should not be based around clarithromycin-containing regimens. Unfortunately, at the time the present study was started, metronidazole had yet to be permitted for use in Japan, and the same regimen as in initial therapy was repeated. This explains why our study regimens included LAC, which was also used as the first-line regimen. Recently, triple therapy consisting of a PPI, amoxicillin and metronidazole was approved as a second-line regimen for the eradication of *H. pylori* in Japan. As demonstrated in this study, however, the incidence of metronidazole-resistant strains of *H. pylori* is relatively high in patients who fail in the initial therapy, and several adverse events related to metronidazole have been reported (19) (20). These findings highlight the need for a variety of rescue strategies for patients with eradication failure. Recently, eradication with new regimens which include levofloxacin and rifabutin have been performed (21). However, adverse events related to these new regimens and drugs have not been fully elucidated.

Several reports have demonstrated that ecabet sodium used with any of several regimens increases the eradication rate of *H. pylori* infection: Ohkusa et al (22) reported that ecabet sodium increased the eradication rates of dual therapy with lansoprazole and amoxicillin from 58% to 78%; Kagaya et al (23) reported that this agent increased the eradication rate by dual lansoprazole/amoxicillin therapy from 43% to 79%; and Kim et al (24) reported that it increased the eradication rate with triple PPI/amoxicillin/clarithromycin therapy from 78.8% to 88.6%. In the present study, therefore, we examined the eradication rates of ecabet sodium-based regimens, such as LAC2E for 1 week and LA2E for 2 weeks, in comparison with LAC for 1 week in patients in whom eradication of *H. pylori* with the triple PPI/amoxicillin/clarithromycin therapy had failed. Results showed no statistically significant differences in eradication rate between the LAC2E and LAC groups, whereas LA2E for 2 weeks yielded a markedly higher eradication rate than those with LAC2E and LAC.

In their study, Kim et al enrolled patients who had never undergone eradication therapy, while the present study patients had all failed eradication. This difference might, at least to some extent, explain the difference in results be-

Table 4. Eradication Rates in Patients Infected with Metronidazole-sensitive and Resistant Strains of *H. pylori*

Regimens	Metronidazole-sensitive	Metronidazole-resistant
LAC	20.0 (1/5)	27.3 (3/11)
LAC2E	0.0 (0/3)	11.1 (1/9)
LA2E	100.0 (4/4)	100.0 (8/8)

LAC: lansoprazole, amoxicillin and clarithromycin, 1 week

LAC2E: lansoprazole, amoxicillin, clarithromycin and ecabet sodium, 1 week

LA2E: lansoprazole, amoxicillin and ecabet sodium, 2 weeks

Table 5. Adverse Events Observed in the Study Regimens (%)

	LAC (n = 25)	LAC2E (n = 25)	LA2E (n = 24)
Loose stool	0 (0.0)	1 (4.0)	2 (8.0)
Diarrhea	0 (0.0)	0 (0.0)	2 (8.0)
Dysgeusia	0 (0.0)	1 (4.0)	0 (0.0)
Hot flashes	0 (0.0)	1 (4.0)	0 (0.0)

LAC, lansoprazole, amoxicillin and clarithromycin, 1 week

LAC2E, lansoprazole, amoxicillin, clarithromycin and ecabet sodium, 1 week

LA2E, lansoprazole, amoxicillin and ecabet sodium, 2 weeks

tween the two studies, (24). However, our present eradication rate by triple therapy with lansoprazole, amoxicillin and ecabet sodium for 2 weeks was 85%, and 88.2% in those infected with clarithromycin-sensitive and -resistant strains of *H. pylori*, respectively. This regimen also attained eradication in patients infected with either metronidazole-resistant or metronidazole-sensitive strains. We therefore consider that ecabet sodium is effective against *H. pylori* strains irrespective of susceptibility to other antimicrobial agents, such as clarithromycin and metronidazole, when used with a PPI and amoxicillin for 2 weeks.

Although the bactericidal effect of ecabet sodium is not as strong as that of antibiotics, it potently inhibits the growth and urease activity of *H. pylori*. Interestingly, its bactericidal effect is enhanced in acidic conditions. We therefore consider that the effect of ecabet sodium is complementary to that of antibiotics, because the bioavailability of antibiotics is decreased in acidic conditions, whereas the anti-*H. pylori* effect of ecabet sodium is in contrast enhanced. One reason for eradication failure with a regimen consisting of a PPI and antibiotics is insufficient acid inhibition with a PPI. However, the bactericidal effect of ecabet sodium is increased when acid inhibition is insufficient. The addition of ecabet sodium to *H. pylori* eradication regimens theoretically increases eradication rates, particularly in those patients in whom the acid inhibition attained with a PPI is insufficient.

We assume that a second reason for the higher eradication with the LA2E regimen is related to the duration of the treatment period. Duration of most dual PPI/amoxicillin therapies that provided eradication rates higher than 80% were 2 weeks or longer (25) (26). Because amoxicillin is a time-dependent antibiotic (27) (28), further increases in eradication rates with amoxicillin-based therapy may require longer treatment periods.

Several limitations of our study warrant mention. First, the sample size was relatively small. However, the eradication rate with LA2E for 2 weeks was significantly higher than that with LAC and LAC2E for 1 week. Second, we did not measure the bactericidal effect of ecabet sodium in individual strains by culture testing. Thirdly, we did not test the eradication rate by LA for 2 weeks. Therefore, our study results could not demonstrate whether ecabet sodium really had an additional effect on the dual PPI/amoxicillin therapy. Together, the present results should thus be considered as providing preliminary guidance for future studies under a more appropriate design. Allowing for these limitations, the present results indicate that the triple therapy with lansoprazole, amoxicillin and ecabet sodium for 2 weeks is effective as a rescue regimen after the failure of eradication by the standard regimen.

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

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Abbreviations: LAC: lansoprazole, amoxicillin and clarithromycin for 1 week, LAC2E: lansoprazole, amoxicillin, clarithromycin and ecabet sodium for 1 week, LA2E: lansoprazole, amoxicillin and ecabet sodium for 2 weeks

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