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Efficacy of triple therapy with esomeprazole, amoxicillin, and sitafloxacin as a third-line *Helicobacter pylori* eradication regimen

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SUMMARY

Objective: To examine the efficacy of third-line *Helicobacter pylori* eradication therapy with esomeprazole, amoxicillin, and sitafloxacin for patients with clarithromycin- and metronidazole-based first- and second-line therapy failure.

Methods: Thirty patients with first- and second-line *H. pylori* eradication failure were treated prospectively with esomeprazole 20 mg twice daily, amoxicillin 750 mg twice daily, and sitafloxacin 100 mg twice daily for 7 days. After 8–12 weeks, the outcome of eradication therapy was assessed by ^{13}C-urea breath test or stool antigen test.

Results: All 30 patients completed the study. Eradication was successful in 25 patients and the eradication rate was 83% in the intention-to-treat and per-protocol analyses. No specific or significant adverse events were recorded in the 30 patients. Patient characteristics such as sex, body mass index, and pepsinogen I/II ratio did not differ between patients who were treated successfully and those who were not treated successfully.

Conclusions: Third-line *H. pylori* eradication therapy with esomeprazole, amoxicillin, and sitafloxacin is as safe and effective as previously reported sitafloxacin-based triple therapy.

1. Introduction

Chronic *Helicobacter pylori* infection causes various gastroduodenal diseases, including ulcers and malignancies.[1–4] Eradication of *H. pylori* can prevent or cure these diseases.[5–7] In fact, some studies have shown that *H. pylori* eradication reduces the incidence of gastric cancer, suggesting that eradication therapy could be the primary therapeutic approach for upper gastrointestinal diseases.[8–12]

Many regimens for *H. pylori* eradication have been tested since the discovery of this bacterium. Generally, a proton pump inhibitor (PPI) and antibiotics are included in the eradication regimen to suppress gastric acid and to kill the bacteria. Bacterial resistance to specific antibiotics significantly reduces the efficacy of an eradication regimen containing the corresponding antibiotics, and resistance is associated with the consumption of antibiotics, which is influenced by socio-economic status and geographic area.[2,13,14]

In Japan, first-line therapy consists of a PPI, amoxicillin (AMX), and clarithromycin (CLR) for 7 days, which results in an eradication rate of 60–70% due to widespread CLR-resistant *H. pylori*.[15] Second-line therapy includes a PPI, AMX, and metronidazole (MNZ), which has an acceptable eradication rate of 90%.[3] No standard third-line therapy has been established, although several regimens have been examined prospectively for their efficacy and adverse events.[14] Candidate third-line antibiotics include fluoroquinolones, one of which, sitafloxacin (STX), has shown good ability to kill *H. pylori* in vitro.[16] In prospective studies, STX-based triple therapy has shown a modest eradication rate of 70–80%.[17–19] Studies of primary resistance against STX have shown that more than 90% of *H. pylori* strains are susceptible to this antibiotic.[18–20] However, the in vivo eradication rate of this third-line therapy has not exceeded 90% in most studies, so there is still room to improve the STX-based third-line eradication regimen.[21]

Therefore, a prospective study of the efficacy of a new third-line Helicobacter eradication regimen containing esomeprazole, AMX, and STX was performed. Esomeprazole is a PPI that was approved by the Ministry of Health, Labor and Welfare of Japan in 2011. It has

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excellent gastric acid control compared to former PPIs such as lansoprazole and rabeprazole.[22,23] However, its efficacy in third-line therapy has not been evaluated.

2. Materials and methods

2.1. Subjects

A prospective exploratory study was conducted to evaluate the efficacy of third-line Helicobacter eradication therapy (UMIN Clinical Trials Registry ID No. 000007971). Adult patients with a peptic ulcer or chronic gastritis in whom CLR-based first-line and MNZ-based second-line therapy had failed were invited to join the study. CLR-based first-line therapy consists of a PPI, AMX (750 mg twice daily), and CLR (200 mg or 400 mg twice daily) for 7 days. MNZ-based second-line therapy consists of a PPI, AMX (750 mg twice daily), and MNZ (50 mg twice daily) for 7 days. Patients with major organ dysfunction or a history of allergy to PPIs, AMX, or STX were excluded. Prior use of esomeprazole was not excluded. Prior use of STX for third-line eradication was excluded. Written informed consent was obtained from all patients. The study protocol was approved by the Institutional Review Board of the University of Tokyo Hospital (approval No. P2012006).

2.2. Eradication

Before beginning third-line eradication therapy, height and weight were recorded, and laboratory tests including liver and renal function tests and pepsinogen were performed. Patients were assigned to receive esomeprazole 20 mg twice daily, AMX 750 mg twice daily, and STX 100 mg twice daily for 7 days. A 7-day treatment duration was applied in this study based on previous third-line Helicobacter eradication reports.[17–19] Compliance and adverse events were assessed through interviews. The outcome of eradication therapy was assessed by ^{13}C-urea breath test or stool antigen test at 8–12 weeks after completing the antimicrobial treatment.

2.3. H. pylori *strains and microbiological examination*

In some cases, *H. pylori* isolates were obtained from biopsy specimens at endoscopy and examined for antimicrobial susceptibility. The minimum inhibitory concentrations (MICs) for AMX, CLR, MNZ, and STX of each strain were determined using the agar dilution method. The presence of the *gyrA* mutation was also examined by direct sequencing, as described previously.[18,24]

2.4. Statistical analysis

Statistical analyses were performed using the Chi-square test, Student *t*-test, or Wilcoxon rank sum test, as appropriate. A *p*-value of <0.05 was considered statistically significant.

Table 1
Demographic characteristics of the patients and results of the eradication therapy

Characteristics	Total ($n=30$)
Age, years, mean ± SE	51.8 ± 2.5
Sex, male/female	15/15
Diagnosis, ulcer/gastritis	15/15
Previous eradication therapy, second/more	28/2
Body mass index, kg/m^2, mean ± SE	23.7 ± 0.6
Pepsinogen I/II ratio, mean ± SE	3.4 ± 0.3
Eradication result, success/failure	25/5
Eradication rate, % (95% CI) (ITT)	83% (65–94%)
Eradication rate, % (95% CI) (PP)	83% (65–94%)

SE, standard error; CI, confidence interval; ITT, intention-to-treat analysis; PP, per-protocol analysis.

Table 2
Patient characteristics according to the eradication results

Characteristics	Patients treated successfully ($n=25$)	Patients not treated successfully ($n=5$)	*p*-Value
Age, years, mean ± SE	50.8 ± 0.9	56.8 ± 3.5	0.38
Sex, male/female	14/11	1/4	0.14
Diagnosis, ulcer/gastritis	13/12	2/3	0.51
Previous eradication therapy, second/more	23/2	5/0	0.51
Body mass index, kg/m^2, mean ± SE	23.6 ± 0.6	23.9 ± 2.7	0.84
Pepsinogen I/II ratio, mean ± SE	3.4 ± 0.3	3.4 ± 0.6	0.96

SE, standard error.

3. Results

Thirty patients with a history of second-line eradication failure were enrolled from April 2012 to December 2015. The mean age of the patients was 51.8 ± 2.5 years, and 15 were male (Table 1). All 30 patients took the full course of medication and underwent a ^{13}C-urea breath test or stool antigen test. Successful eradication was achieved in 25 cases, giving an eradication rate of 83% (95% confidence interval 65–94%) for both the intention-to-treat and per-protocol analyses.

Diarrhea was the most common adverse event, and was recorded in five cases (16.7% of the study cohort). One patient (3.3%) suffered moderate diarrhea with seven defecations over 2 days, but did not require treatment for the diarrhea. A moderate skin eruption after therapy (3.3%) was observed in one patient and a moderate asthma attack during therapy (3.3%) was observed in another patient; both required specific medications. Stomatitis (3.3%) and cystitis (3.3%) were recorded in one patient each, but resolved without specific treatment.

In a subgroup analysis, age, sex, gastric diseases, previous third-line therapy, body mass index, and the pepsinogen I/II ratio did not differ between patients with successful eradication and those with eradication failure (Table 2).

Table 3 lists the characteristics of the *H. pylori* strains isolated before and after third-line therapy. In case EAS025, the *H. pylori*

Table 3
Characteristics of *Helicobacter pylori* strains isolated from patients before and after third-line therapy

Case	Before therapy					Result	After therapy				
	MIC (μg/ml)				*gyrA*		MIC (μg/ml)				*gyrA*
	AMX	CLR	MNZ	STX			AMX	CLR	MNZ	STX	
EAS017	N/A	N/A	N/A	N/A	N/A	Failed	≤0.03	8	32	0.12	N87K
EAS020	≤0.03	32	64	≤0.03	Wild	Successful	N/A	N/A	N/A	N/A	N/A
EAS022	N/A	N/A	N/A	N/A	N/A	Failed	≤0.03	16	64	≤0.03	N87K
EAS025	1.0	32	32	0.12	N87K	Successful	N/A	N/A	N/A	N/A	N/A

MIC, minimum inhibitory concentration; AMX, amoxicillin; CLR, clarithromycin; MNZ, metronidazole; STX, sitafloxacin; N/A, not available.