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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.

strain had a relatively high MIC for AMX of 1.0 μg/ml and for STX of 0.12 μg/ml with the N87K *gyrA* mutation before therapy, but this case was treated successfully with the third-line regimen used. Conversely, the *H. pylori* strain with the lowest MICs for AMX and STX was recovered from case EAS022 after the third-line therapy failed.

4. Discussion

Sitafloxacin-based *H. pylori* eradication therapy is often used in Japan.[14] As third-line therapy, eradication rates of 70–78% were reported in three previous prospective studies.[17–19] Furuta et al. conducted a randomized study with four arms, which showed 84–91% eradication.[25] These third-line therapy regimens with STX used rabeprazole or lansoprazole as the PPI. In this study, the efficacy of esomeprazole was examined; this is the latest conventional PPI approved in Japan, and was used for third-line *H. pylori* eradication in combination with AMX and STX. An eradication rate of 83% was obtained and the adverse events were not specific or severe. This efficacy is in line with prior STX-based third-line regimens with rabeprazole or lansoprazole. Contrary to expectations, the substitution of esomeprazole for rabeprazole or lansoprazole did not improve the eradication rate.

Several studies have compared the efficacy of eradication with different PPIs with the aim of improving the eradication regimen. McNicholl et al. performed a meta-analysis of randomized control trials of Helicobacter eradication using esomeprazole, and reported the superiority of esomeprazole over first-generation PPIs.[26] The varying acid-inhibiting potential of PPIs may affect the eradication efficacy. In other cases, different usage of cytochrome P450 (CYP), which metabolizes PPIs, as well as its single nucleotide polymorphism, may affect the results . However, it is not clear whether differences in the PPI affect third-line eradication therapy.

In a previous study, enhanced bactericidal activity of STX at near-neutral pH was found.[18] In addition, a low pepsinogen I/II ratio, which indicates advanced atrophy and hypochlorhydria clinically, was associated with a high eradication efficacy using STX.[18] Therefore, it was hypothesized that STX-based therapy would be beneficial with sufficient acid suppression. However, this was not the case with the esomeprazole-based third-line therapy evaluated in the present study. In this study, the eradication rate did not reach 90%, and the pepsinogen I/II ratio did not affect the eradication results. The replacement of esomeprazole with vonoprazan, a novel potassium-competing acid blocker that has superior gastric acid control over conventional PPIs,[27] may improve the efficacy of STX-based third-line therapy. It is also possible that factors other than acid suppression, such as bacterial resistance, are critical to the eradication outcome.[13,14]

A breakpoint for STX has not been established, and studies have used different breakpoints of 0.12 and 1.0 μg/ml.[19,20,28] As shown in Table 3, a strain with 0.12 μg/ml MIC of STX was eradicated successfully, but eradication was unsuccessful for a strain with a MIC of less than 0.03 μg/ml. In a previous study on the use of rabeprazole, STX, and AMX, a strain with a STX MIC of 0.12 μg/ml was not eradicated, while a strain with a MIC of 0.24 μg/ml was treated successfully.[18] These results indicate the difficulty in interpreting in vitro MIC testing in terms of the results of current third-line eradication therapy. In this study, *H. pylori* strains were isolated from only two patients among the five with unsuccessful treatment, because culture was negative in two of the patients and an endoscopy was not performed in the other patient. In the two patients with negative culture results, the ^{13}C-urea breath test, histology, and rapid urease test were all positive, indicating that the culture test was false-negative. More cases are required to determine the breakpoint of STX, particularly in third-line therapy.

At the time when this study was performed, no other study using esomeprazole as third-line therapy with STX had been reported. Recently, Mori et al. published a randomized study that compared AMX with MNZ as third-line therapy in combination with STX.[28] In that study, esomeprazole was used as the PPI, and eradication rates of 81% and 72%, respectively, were obtained with a 10-day third-line regimen. Although the study contained an extremely high percentage of STX-resistant *H. pylori* (57% with a MIC >1.0 μg/ml) compared to other third-line studies, the eradication rate in the intention-to-treat analysis was comparable to that of the 7-day protocol used in the present study. Previously, Furuta et al. examined the efficacy of 1- and 2-week regimens of STX-based third-line therapy and found no statistically significant difference between the different treatment durations.[25] In contrast, recent consensus statements developed by the Canadian Association of Gastroenterology and the Canadian Helicobacter Study Group strongly recommend a duration of 14 days for all *H. pylori* treatments.[29] Therefore, the appropriate duration of third-line eradication regimens, as well as of first- and second-line therapy, may require re-evaluation in Japan.

In conclusion, third-line *H. pylori* eradication therapy with esomeprazole gave an eradication rate of 83%, which is comparable to previous STX-based third-line therapy. This suggests that the substitution of esomeprazole for reported PPIs could be another option for third-line *H. pylori* eradication therapy.

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References

1. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;**345**:784–9.
2. Graham DY. *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology* 2015;**148**. 719-731.e3.
3. Asaka M, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter* 2010;**15**:1–20.
4. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. *Gut* 2012;**61**:646–64.
5. Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackbourn SJ, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* 1988;**2**:1437–42.
6. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet* 1993;**342**:575–7.
7. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*. *Lancet* 1998;**352**:878.
8. You WC, Brown LM, Zhang L, Li JY, Jin ML, Chang YS, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 2006;**98**:974–83.
9. Ogura K, Hirata Y, Yanai A, Shibata W, Ohmae T, Mitsuno Y, et al. The effect of *Helicobacter pylori* eradication on reducing the incidence of gastric cancer. *J Clin Gastroenterol* 2008;**42**:279–83.
10. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;**372**:392–7.
11. Mabe K, Takahashi M, Oizumi H, Tsukuma H, Shibata A, Fukase K, et al. Does *Helicobacter pylori* eradication therapy for peptic ulcer prevent gastric cancer? *World J Gastroenterol* 2009;**15**:4290–7.

12. Shichijo S, Hirata Y, Sakitani K, Yamamoto S, Serizawa T, Niikura R, et al. Distribution of intestinal metaplasia as a predictor of gastric cancer development. *J Gastroenterol Hepatol* 2015;**30**:1260–4.
13. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016;**43**:514–33.
14. Song M, Ang TL. Second and third line treatment options for *Helicobacter pylori* eradication. *World J Gastroenterol* 2014;**20**:1517–28.
15. Kawai T, Takahashi S, Suzuki H, Sasaki H, Nagahara A, Asaoka D, et al. Changes in the first line *Helicobacter pylori* eradication rates using the triple therapy—a multicenter study in the Tokyo metropolitan area (Tokyo *Helicobacter pylori* study group). *J Gastroenterol Hepatol* 2014;**29**(Suppl 4):29–32.
16. Sanchez JE, Saenz NG, Rincon MR, Martin IT, Sanchez EG, Martinez MJ. Susceptibility of *Helicobacter pylori* to mupirocin, oxazolidinones, quinupristin/dalfopristin and new quinolones. *J Antimicrob Chemother* 2000;**46**:283–5.
17. Matsuzaki J, Suzuki H, Nishizawa T, Hirata K, Tsugawa H, Saito Y, et al. Efficacy of sitafloxacin-based rescue therapy for *Helicobacter pylori* after failures of first- and second-line therapies. *Antimicrob Agents Chemother* 2012;**56**:1643–5.
18. Hirata Y, Ohmae T, Yanai A, Sakitani K, Hayakawa Y, Yoshida S, et al. Sitafloxacin resistance in *Helicobacter pylori* isolates and sitafloxacin-based triple therapy as a third-line regimen in Japan. *Int J Antimicrob Agents* 2012;**39**:352–5.
19. Murakami K, Furuta T, Ando T, Nakajima T, Inui Y, Oshima T, et al. Multi-center randomized controlled study to establish the standard third-line regimen for *Helicobacter pylori* eradication in Japan. *J Gastroenterol* 2013;**48**:1128–35.
20. Sugimoto M, Sahara S, Ichikawa H, Kagami T, Uotani T, Furuta T. High *Helicobacter pylori* cure rate with sitafloxacin-based triple therapy. *Aliment Pharmacol Ther* 2015;**42**:477–83.
21. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 1998;**13**:1–12.
22. Miner Jr P, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol* 2003;**98**:2616–20.
23. Rohss K, Wilder-Smith C, Naucler E, Jansson L. Esomeprazole 20 mg provides more effective intragastric acid control than maintenance-dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers. *Clin Drug Investig* 2004;**24**:1–7.
24. Tankovic J, Lascols C, Sculo Q, Petit JC, Soussy CJ. Single and double mutations in *gyrA* but not in *gyrB* are associated with low- and high-level fluoroquinolone resistance in *Helicobacter pylori*. *Antimicrob Agents Chemother* 2003;**47**:3942–4.
25. Furuta T, Sugimoto M, Kodaira C, Nishino M, Yamade M, Uotani T, et al. Sitafloxacin-based third-line rescue regimens for *Helicobacter pylori* infection in Japan. *J Gastroenterol Hepatol* 2014;**29**:487–93.
26. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012;**36**:414–25.
27. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. *Aliment Pharmacol Ther* 2015;**42**:719–30.
28. Mori H, Suzuki H, Matsuzaki J, Tsugawa H, Fukuhara S, Miyoshi S, et al. Efficacy of 10-day sitafloxacin-containing third-line rescue therapies for *Helicobacter pylori* strains containing the *gyrA* mutation. *Helicobacter* 2016;**21**:286–94.
29. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016;**151**. 51-69.e14.