Comparative Study of Clarithromycin- versus Metronidazole-Based Triple Therapy as First-Line Eradication for *Helicobacter pylori*

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Keywords

Helicobacter pylori · Clarithromycin · Metronidazole

Abstract

Introduction: Clarithromycin (CAM)-based triple therapy comprising proton pump inhibitors and amoxicillin is administered as first-line eradication treatment against *Helicobacter pylori* infection. However, the eradication rate achieved with CAM-based triple therapy has decreased to <80% owing to the emergence of CAM-resistant strains. This prospective randomized study aimed to compare the efficacy of CAM-based and metronidazole (MNZ)-based triple therapy in terms of *H. pylori* eradication. **Methods:** *H. pylori*-positive patients were treated with CAM-based triple therapy comprising esomeprazole and amoxicillin (EAC group) or with MNZ-based triple therapy comprising esomeprazole and amoxicillin (EAM group). **Results:** *H. pylori* eradication rates achieved in the intention-to-treat (ITT) and per protocol (PP) analyses were 70.6 and 72.7%, respectively, in the EAC group. Eradication rates obtained via ITT and PP analyses were 91.7 and 94.3%, respectively, in the EAM group. In the EAC group, eradication rates were significantly lower in

patients harboring CAM-resistant strains than in those harboring CAM-sensitive strains. In contrast, eradication rates were comparable between patients harboring CAM-resistant strains and those harboring CAM-sensitive strains in the EAM group. **Conclusion:** MNZ-based triple therapy consisting of esomeprazole and amoxicillin is superior to CAM-based triple therapy containing esomeprazole and amoxicillin as first-line eradication treatment against *H. pylori*.

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Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide [1]. Geographically, gastric cancer is very common in East Asia, where the prevalence rate of *Helicobacter pylori* infection is high [2]. *H. pylori* is a gram-negative bacterium that colonizes human gastric mucosa and then causes a wide variety of gastric disorders [3]. Chronic gastric infection due to *H. pylori* initially causes chronic active gastritis, which can then lead to the development of peptic ulcers, atrophic gastritis, gastric cancer, and mucosa-associated lymphoid tissue

lymphoma [3]. *H. pylori* infection is now a widely accepted primary cause of gastric cancer [4]. This claim is adequately supported by a large body of epidemiological and clinical evidence. First, around 90% of patients with gastric cancer demonstrate *H. pylori* seropositivity [4, 5]. Second, a prospective and long-term study showed that gastric cancer has been observed more frequently in Japanese patients with *H. pylori* infection than in those without an infection [6]. Third, eradication of *H. pylori* substantially reduced the incidence of gastric cancer in high-risk patients who underwent endoscopic resection [7]. Fourth and finally, a protective effect against gastric cancer has been reported to persist for more than 10 years after *H. pylori* eradication [8]. Therefore, *H. pylori* can be considered one of the most important causes of gastric cancer [9].

H. pylori-associated gastric cancer is one of the best examples of inflammation-related cancer [10, 11]. Genetic and epigenetic alterations accumulate within gastric epithelial cells infected with *H. pylori* in response to the progression of chronic inflammation [10, 11]. In fact, advanced stages of *H. pylori*-associated chronic gastritis bearing severe gastric atrophy and intestinal metaplasia are considered precancerous conditions, because gastric cancer tends to originate from gastric mucosa demonstrating these signs [6]. However, it should be noted that eradication of *H. pylori* reduces the risk for gastric cancer even in the presence of severe gastric atrophy and intestinal metaplasia [7]. Thus, *H. pylori* eradication is the most effective strategy for prevention of gastric cancer.

Proton pump inhibitor (PPI)-containing triple therapy with amoxicillin (AMPC) and clarithromycin (CAM) is widely used as a first-line eradication therapy for *H. pylori* in Japan [12]. Patients who demonstrate first-line eradication treatment failure are usually treated with PPI-containing triple therapy comprising AMPC and metronidazole (MNZ) [13, 14]. Although a multicenter study conducted in 2001 reported that the eradication rate using first-line therapy was around 90%, the rate decreased to 70–80% in 2014 [13, 15]. A possible explanation for the decreased eradication rate is the prevalence of CAM-resistant *H. pylori* in Japan [16, 17]. Okamura et al. [16] reported that the rate of CAM resistance is above 30 and 50% in old and young patients, respectively. Therefore, we hypothesized that MNZ-based triple therapy containing PPI and AMPC is superior to CAM-based triple therapy as a first-line eradication option. The aim of this study was to compare the efficacy of MNZ-based triple therapy and CAM-based triple therapy as *H. pylori* eradication treatments.

Fig. 1. Flow diagram of patient enrollment in this study. EAC, clarithromycin-based triple therapy comprising esomeprazole and amoxicillin; EAM, metronidazole-based triple therapy comprising esomeprazole and amoxicillin.

Patients

This prospective randomized controlled study was designed to determine whether MNZ-based triple therapy was superior to CAM-based triple therapy as a first-line eradication treatment for *H. pylori*. Patients who underwent esophagogastroduodenoscopy for further examination and follow-up of upper gastrointestinal symptoms and *H. pylori*-associated diseases including peptic ulcers and chronic gastritis at Kindai University Hospital from June 2013 to August 2015 were enrolled. Patients who underwent esophagogastroduodenoscopy for follow-up of postendoscopic submucosal dissection for early gastric cancer were also enrolled. Exclusion criteria were as follows: age <19 years; history of *H. pylori* eradication therapy; allergy to PPI, AMPC, CAM, or MNZ; severe liver dysfunction; severe kidney dysfunction; severe heart disease; pregnancy; alcohol abuse; drug addiction. Written informed consent was obtained from each patient before administering the treatment, and the study protocol was approved by the Kindai University Ethics Committee. In addition, this trial is registered with the University Hospital Medical Information Network (000011203).

Study Design

A total of 140 patients who met the inclusion criteria and agreed to receive *H. pylori* eradication therapy were enrolled in this study. Assessment of *H. pylori* infection was performed via rapid urease tests, culture methods, serum *H. pylori* antibody tests, and stool *H. pylori* antigen tests. Patients were regarded as *H. pylori*-positive when at least one of these tests yielded positive results. Either CAM-based triple therapy containing esomeprazole and AMPC (EAC) or MNZ-based triple therapy containing esomeprazole and AMPC (EAM) was administered as first-line eradication therapy against *H. pylori*. Patients were randomly divided into two groups: EAC group and EAM group. Patients in the EAC group were administered esomeprazole 20 mg, CAM 400 mg, and AMPC 750 mg twice a day for 7 days, and those in the

Fig. 2. *H. pylori* eradication rates. Patients were treated with clarithromycin (CAM)-based triple therapy comprising esomeprazole and amoxicillin (EAC) or metronidazole-based triple therapy comprising esomeprazole and amoxicillin (EAM). Eradication rates were calculated via intention-to-treat (ITT) and per protocol (PP) analyses (a). Eradication rates in the EAC and EAM groups were calculated in patients harboring CAM-susceptible and CAM-resistant strains (b). ** $p < 0.01$, as compared with EAM group (a) or with CAM-susceptible group (b).

EAM group were administered esomeprazole 20 mg, MNZ 500 mg, and AMPC 750 mg twice a day for 7 days. Eradication of *H. pylori* was confirmed via a urea breath test at 4 weeks after treatment completion. Susceptibility to CAM and MNZ was tested using gastric biopsy specimens obtained during endoscopy as previously described [18, 19].

Statistical Analysis

Intention-to-treat (ITT) and per protocol (PP) analyses were used to evaluate the eradication rate. χ^2 analysis was used for the statistical analysis, and a p value < 0.05 indicated statistical significance.

Results

Patients

A total of 140 patients were enrolled in this study, and 136 patients completed the first-line eradication therapy. As shown in Figure 1, 68 and 72 patients were treated with EAC and EAM protocols, respectively. Two patients in each group dropped out owing to loss to follow-up or poor treatment compliance. None of the patients who completed the first-line eradication therapy showed serious adverse effects that required discontinuation of eradication therapy. As shown in Table 1, no significant differences were observed in terms of baseline characteristics such as age, sex, and diseases between the EAC and EAM groups. In addition, the rate of CAM-resistant *H. pylori* isolated from gastric mucosa samples was comparable between the EAC and EAM groups.

Table 1. Clinical characteristics of the patients

	EAC (n = 68)	EAM (n = 72)	p
Mean age $\pm$ SD, years	65.1 $\pm$ 10.0	62.7 $\pm$ 11.1	0.71
Sex (male/female)	32/36	36/36	0.93
Diseases			
Gastritis	45	44	0.78
Gastric ulcer	6	9	0.59
Duodenal ulcer	4	5	0.81
Follow-up of post-endoscopic therapy for early gastric cancer	13	14	0.96
Clarithromycin resistance (%)	27/60 (45)	23/67 (34.3)	0.5

EAC, clarithromycin-based triple therapy comprising esomeprazole and amoxicillin; EAM, metronidazole-based triple therapy comprising esomeprazole and amoxicillin.

Eradication Efficacy

Eradication of *H. pylori* was confirmed via a urea breath test at 4 weeks after the completion of the first-line therapy. As shown in Figure 2a and Table 2, *H. pylori* eradication rates per the ITT and PP analyses were 70.6% (48/68) and 72.7% (48/66), respectively, in the EAC group. Eradication rates obtained in the ITT and PP analyses were 91.7% (66/72) and 94.3% (66/70), respectively, in the EAM group. Thus, the eradication rates in the EAM group were significantly higher than those observed in the EAC group.

We then addressed the effects of CAM resistance on the eradication rates. As shown in Figure 2b and Table 2, the eradication rates were 87.9% (29/33) and 51.9%

Table 2. *H. pylori* eradication rates

	EAC (n = 68)	EAM (n = 72)	<i>p</i> (χ^2 test)
Eradication rate (ITT)	48/68 (72.7)	66/72 (94.3)	0.00135
Eradication rate (PP)	48/66 (70.6)	66/70 (91.7)	0.000644
Clarithromycin susceptible	29/33 (87.9)	40/44 (90.9)	
Clarithromycin resistant	14/27 (51.9)	22/23 (95.7)	
<i>p</i>	0.00345	0.653	

Data are presented as number/total number (%). EAC, clarithromycin-based triple therapy comprising esomeprazole and amoxicillin; EAM, metronidazole-based triple therapy comprising esomeprazole and amoxicillin; ITT, intention to treat; PP, per protocol.

(14/27) in EAC-treated patients harboring CAM-susceptible and CAM-resistant *H. pylori* strains, respectively. In contrast, the eradication rates were 90.9% (40/44) and 95.7% (22/23) in EAM-treated patients bearing CAM-susceptible and CAM-resistant *H. pylori* strains, respectively. Thus, lower eradication rates in the EAC group were associated with a lower rate of eradication in patients harboring CAM-resistant *H. pylori* strains.

Discussion

CAM-based triple therapy containing PPI and AMPC is frequently used as first-line eradication therapy against *H. pylori* infection in Japan [13, 15]. Although the eradication rate achieved using this first-line regimen was reported to be around 90% in 2001, the rate decreased to less than 80% by 2014 [13, 15]. The progressive increase in the incidence of CAM-resistant *H. pylori* strains is considered to be responsible for the decline in the eradication rate [16, 17]. In this prospective randomized study, we compared the efficacy of EAM with that of EAC. We found that the eradication rate achieved with EAM was much higher than that achieved using EAC in the ITT and PP analyses. This finding was independent of the CAM susceptibility of the strain in the EAM group. On the other hand, the eradication rate achieved using EAC was much lower in patients harboring CAM-resistant strains than in those harboring CAM-susceptible strains. We found that the eradication rates achieved via EAC and EAM were comparable in patients harboring CAM-sensitive *H. pylori* strains (87.9 vs. 90.9%). In contrast, the eradication rate achieved via EAM was much higher than that achieved via EAC against CAM-susceptible *H. pylori*

strains (51.9 vs. 95.7%). The percentage of CAM resistance was 39.3%, whereas that of MNZ resistance was 3.67%. In addition, no major adverse effects requiring discontinuation of eradication treatment were seen in both the EAC and EAM groups. Taken together, our results suggest that MNZ-based triple therapy containing PPI and AMPC is superior to CAM-based triple therapy as a first-line *H. pylori* eradication treatment owing to the high prevalence of CAM resistance and relatively lower prevalence of MNZ resistance. In line with our results, Nishizawa et al. [13] also claimed that MNZ-based therapy was superior to CAM-based therapy.

Vonoprazan (VPZ), a novel potassium-competitive acid blocker, has been recently used as first-line eradication of *H. pylori* [20–22]. Murakami et al. [21] report that the eradication rate achieved with first-line VPZ-based triple therapy containing CAM and AMPC was 92.6% and that achieved with second-line VPZ-based triple therapy containing MNZ and AMPC was 98.0%, even in the presence of CAM-resistant strains. Although the molecular mechanisms accounting for the high VPZ-mediated eradication rates remain unknown, one possible explanation may be enhanced antimicrobial activity of CAM and AMPC in the presence of VPZ [21]. VPZ, which demonstrates a potent ability to inhibit gastric acid production, is considered to create an environment where antimicrobials exert their optimal activity. Thus, CAM-based triple therapy containing VPZ and AMPC could be an effective first-line treatment. It should be noted, however, that the eradication rates achieved with CAM-based triple therapy containing VPZ and AMPC have been reported to be relatively low (86.3, 87.9%) in two studies [20, 22]. Further clinical studies addressing the efficacy of CAM-based triple therapy containing VPZ and AMPC are required to determine the efficacy of this regimen, especially in the setting of CAM-resistant strains.

H. pylori eradication is the most effective approach for the prevention of gastric cancer. Eradication of this organism prevents metachronous development of gastric cancer in patients who have undergone endoscopic treatment for early gastric cancer and demonstrate severe gastric atrophy and/or intestinal metaplasia [7]. Thus, eradication of *H. pylori* is also effective for the prevention of gastric carcinogenesis even at advanced stages of chronic gastritis with precancerous mucosal abnormalities such as severe gastric atrophy and/or intestinal metaplasia. Currently, several eradication regimens against *H. pylori* are available. Imprudent selection of eradication regimens might cause the emergence and expansion of antibiotic-resistant strains without the prevention of gastric

cancer. Future studies directly comparing the efficacy and safety of *H. pylori* eradication regimens are necessary to establish an appropriate regimen as a first-line treatment.

In conclusion, MNZ-based triple therapy containing esomeprazole and AMPC is superior to CAM-based triple therapy containing esomeprazole and AMPC as first-line eradication treatment against *H. pylori*.

Disclosure Statement

The authors have no conflicts of interest to declare.

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