

## Efficacy of omeprazole and amoxicillin with either clarithromycin or metronidazole on eradication of *Helicobacter pylori* in Chinese peptic ulcer patients

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### Abstract

**AIM:** One-week triple therapy with proton pump inhibitors, clarithromycin and amoxicillin has recently been proposed as the first-line treatment for *Helicobacter pylori* (*H pylori*) infection; however, data regarding the effects of this regimen in China are scarce. The aim of this prospective and randomized study was to compare the efficacy of clarithromycin and metronidazole when they were combined with omeprazole and amoxicillin on eradication of *H pylori* and ulcer healing in Chinese peptic ulcer patients.

**METHODS:** A total of 103 subjects with *H pylori*-positive peptic ulcer were randomly divided into two groups, and accepted triple therapy with omeprazole 20 mg, amoxicillin 1 000 mg and either clarithromycin 500 mg (OAC group,  $n = 58$ ) or metronidazole 400 mg (OAM group,  $n = 45$ ). All drugs were given twice daily for 7 d. Patients with active peptic ulcer were treated with omeprazole 20 mg daily for 2-4 wk after anti-*H pylori* therapy. Six to eight weeks after omeprazole therapy, all patients underwent endoscopies and four biopsies (two from the antrum and two others from the corpus of stomach) were taken for rapid urease test and histological analysis (with modified Giemsa staining) to examine *H pylori*. Successful eradication was defined as negative results from both examination methods.

**RESULTS:** One hundred patients completed the entire course of therapy and returned for follow-up. The eradication rate of *H pylori* for the per-protocol analysis was 89.3% (50/56) in OAC group and 84.1% (37/44) in OAM group. Based on the intention-to-treat analysis, the eradication rate of *H pylori* was 86.2% (50/58) in OAC group and 82.2% (37/45) in OAM group. There were no

significant differences in eradication rates between the two groups on either analysis. The active ulcer-healing rate was 96.7% (29/30) in OAC group and 100% (21/21) in OAM group (per-protocol analysis,  $P > 0.05$ ). Six patients in OAC group (10.3%) and five in OAM group (11.1%) reported adverse events ( $P > 0.05$ ).

**CONCLUSION:** One-week triple therapy with omeprazole and amoxicillin in combination with either clarithromycin or metronidazole is effective for the eradication of *H pylori*. The therapeutic regimen comprising metronidazole with low cost, good compliance and mild adverse events may offer a good choice for the treatment of peptic ulcers associated with *H pylori* infection in China.

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**Key words:** Omeprazole; Amoxicillin; *H pylori*

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### INTRODUCTION

*Helicobacter pylori* (*H pylori*) infects the stomachs of more than 50% of people worldwide, and is responsible for most peptic ulcer diseases, gastritis and gastric malignancies<sup>[1-4]</sup>. According to the Maastricht 2-2000 consensus report<sup>[5]</sup>, eradication of *H pylori* infection is strongly recommended in duodenal and gastric ulcers, whether they are active or not. Cure of the infection not only promotes peptic ulcer healing but also reduces ulcer relapse. Recently, 1-wk triple therapy with a proton-pump inhibitor (PPI) and two antimicrobial agents (clarithromycin, amoxicillin, or metronidazole/tinidazole) has been shown to be one of the most effective regimens and is recommended as the first-line treatment of *H pylori* eradication due to its high cure rates and convenience<sup>[6-8]</sup>. However, as in many other infectious diseases, antibiotic resistance is the major cause of treatment failure. Metronidazole-resistant strains of *H pylori* have been reported to be increasing worldwide<sup>[9-11]</sup>.

Although clarithromycin is an excellent drug for treating *H pylori* infection overseas<sup>[12,13]</sup>, this drug has not

been widely used in China due to its high cost. Therefore, we evaluated the efficacy of 1-wk triple therapy with omeprazole, amoxicillin and clarithromycin (OAC) for *H pylori* eradication and active peptic ulcer healing in Chinese population. We also compared the results of OAC regimen with a conventional traditional triple therapy with omeprazole, amoxicillin and metronidazole (OAM).

## MATERIALS AND METHODS

### Patients

Patients with endoscopically-confirmed peptic ulcers (including scar stage), and biopsy-proven *H pylori* infection were enrolled into this prospective, randomized, investigator-blind, single-center study. Patients excluded from the study included patients with liver cirrhosis, renal failure, or other serious concomitant illnesses; alcoholics; patients were treated in the two months preceding study entry with antibiotics, bismuth preparations, proton pump inhibitors or H<sub>2</sub>-receptor antagonists; patients with known allergy to the medications used; patients with a history of previous gastric surgery; pregnant women; and patients who previously underwent eradication therapy. These criteria were ascertained by means of a complete history, physical examination, appropriate hematological and biochemical tests. A total of 103 patients (85 men and 18 women) who were recruited prospectively in the gastroenterology unit at Affiliated Zhongda Hospital of Southeast University, fulfilled the criteria for admission to the study. All patients gave their fully informed written consent before entering the study. The study also received the approval of the Medical Ethics Committee of Southeast University.

### Eradication methods

Patients were randomly divided into two groups, and accepted triple therapy with omeprazole 20 mg, amoxicillin 1 000 mg and either clarithromycin 500 mg (OAC group, *n* = 58) or metronidazole 400 mg (OAM group, *n* = 45). All drugs were given twice daily for 7 d. Patients with active peptic ulcer were treated with omeprazole 20 mg daily for 2-4 wk after anti-*H pylori* therapy. Each patient was asked to return at the end of antibiotic treatment for a structured clinical interview to assess adverse events and compliance.

### Evaluation of eradication therapy

Six to eight weeks after omeprazole therapy, all patients underwent endoscopies and four biopsies (two from the antrum and another two from the corpus of the stomach) were taken for rapid urease test and histological analysis (with modified Giemsa staining) to examine *H pylori*. Successful eradication was defined as negative results from both examination methods. The healing of active ulcer was also evaluated during endoscopic examination.

### Statistical analysis

The results of treatment were evaluated with per-protocol (PP) analysis (which included only patients who completed the study) and intention-to-treat (ITT) analysis (which included also patients who did not complete the study). The demographic and clinical characteristics of the two groups

were compared by  $\chi^2$  test. The results of treatment were compared by  $\chi^2$  test or Fisher's exact test. *P* < 0.05 was considered statistically significant.

## RESULTS

### Demographic and clinical characteristics

The demographic and clinical characteristics of the 103 patients in the two groups are shown in Table 1. No significant differences in demographic and clinical characteristics were found between the two groups.

**Table 1** Baseline characteristics of patients in two groups

	OAC ( <i>n</i> = 58)	OAM ( <i>n</i> = 45)
Age (yr, mean±SD)	52±11	50±12
Sex (M/F)	48/10	37/8
Gastric ulcer, active	10	8
Gastric ulcer, scar	13	11
Duodenal ulcer, active	21	14
Duodenal ulcer, scar	14	12

### Eradication rates of *H pylori*

Of the 103 patients enrolled in this study, 3 (2.9%) withdrew from the study because of drug-related adverse events. Of them, two patients (each from OAC group and OAM group) with skin rash and one from OAC group with diarrhea discontinued the treatment. As a result, 100 patients (97.1%, 56 patients in OAC group and 44 patients in OAM group) completed the entire course of therapy and returned for follow-up. The eradication rates based on PP or ITT analyses are shown in Table 2. There were no significant differences in eradication rates between the two groups.

**Table 2** Eradication rates in two treatment groups

	OAC ( <i>n</i> = 58)	OAM ( <i>n</i> = 45)	$\chi^2$	<i>P</i>
PP analysis (%)	50/56(89.3)	37/44(84.1)	0.59	0.44
ITT analysis (%)	50/58(86.2)	37/45(82.2)	0.31	0.58

Numbers in parentheses indicate percentages.

### Healing rates of active peptic ulcer

The active ulcer-healing rate on PP analysis was 96.7% (29/30) in OAC group and 100% (21/21) in OAM group. There were no significant differences between the two groups ( $\chi^2 = 0.71$ , *P* > 0.05).

### Adverse events and compliance

Completed questionnaires about the adverse events and compliance were obtained from all the 103 patients. Adverse events were noticed (Table 3) in six patients in OAC group, and five patients in OAM group, with no statistically significant differences between the two groups ( $\chi^2 = 0.02$ , *P* = 0.90). The symptoms of adverse events were mild and did not necessitate any additional treatment in both groups. None of the other serious events such as hepatic or renal functional damages were found by means of biochemical

examination in the two groups. All patients, except for two who had acute allergic skin rashes and one who had diarrhea, were able to take the study medication completely for the full study period. Thus, 100 patients (97.1%) had an excellent compliance.

**Table 3** Adverse events during treatment

	OAC (n = 58)	OAM (n = 45)
Skin rash	1	1
Diarrhea	1	1
Headache	2	0
Nausea	1	1
Anorexia	1	0
Metallic taste	0	2
Total (%)	6/58 (10.3)	5/45 (11.1)

## DISCUSSION

Many authors have reported a correlation between *H pylori* infection and peptic ulcers<sup>[1,7,8]</sup>. Incidence of *H pylori* infection was higher in patients with gastroduodenal ulcers than in subjects without gastroduodenal disorders. The eradication of *H pylori* has been strongly recommended in all patients with peptic ulcer, including those with complications<sup>[5]</sup>. Eradication of *H pylori* could assure rapid symptom relief and accelerate ulcer healing<sup>[14]</sup>, prevent ulcer relapse and reduce complications<sup>[7,8,15-18]</sup>. Furthermore, eradication of *H pylori* could also improve the healing of intractable ulcers<sup>[19-21]</sup>. However, the survival capabilities of *H pylori* in the stomach made it difficult to be eradicated, and effective treatment required multi-drug regimens consisting of two antibiotics (usually selected from clarithromycin, metronidazole, amoxicillin, and tetracycline) combined with PPI or bismuth compounds<sup>[5,22,23]</sup>. Although the optimal treatment of *H pylori* infection is still a matter of debate, the effectiveness of PPI based 1-wk triple therapy has now been well established and remains one of the first-line therapies of choice<sup>[6,14,24,25]</sup>.

Clarithromycin is a new generation of macrolide antibiotic that inhibits bacterial protein synthesis. Its antibacterial spectrum is similar to that of erythromycin, but it is more acid-stable, better absorbed, and is thought to be an effective drug for treating *H pylori* infection<sup>[7,12,13]</sup>. Among several eradication regimens, PPI with clarithromycin and amoxicillin is thought to be one of the most effective treatments of *H pylori*. Amoxicillin resistance was rarely reported<sup>[26]</sup> but clarithromycin resistance has increased year after year<sup>[27]</sup>, and eradication rates with clarithromycin-containing regimens decreased significantly<sup>[28]</sup>. The present study showed that the *H pylori* eradication rate in OAC group was 89.3% (50/56, PP analysis). The result is in accordance with previous reports from China and Spain<sup>[29,30]</sup>. However, in a study from Japan by Ogura *et al*<sup>[31]</sup>, eradication was achieved in 39/40 (98%) by PP analysis in clarithromycin-based triple therapy for non-resistant *H pylori* infection. These results indicate that the therapeutic effect of clarithromycin for *H pylori* eradication is not quite consistent. It may be related to different resistance to clarithromycin of infecting *H pylori* strains in various countries and regions. Widespread use of

antimicrobial drugs has resulted in a worldwide increase in the prevalence of antibiotic resistance in *H pylori*, 5-11% of clinical *H pylori* strains isolated in China are resistant to clarithromycin<sup>[32,33]</sup>. Although clarithromycin was not available in China before 1996, the other members of macrolides such as spiramycin, erythromycin and roxithromycin have been widely used over the past years for the treatment of respiratory infection, sexually transmitted diseases and other infectious diseases. Thus, *H pylori* is able to develop resistance to clarithromycin rapidly after contact with it, as cross-resistance exists between macrolides. Some studies have shown that clarithromycin resistance in *H pylori* substantially affected the success rate of eradication regimens containing clarithromycin<sup>[28]</sup>. In the present randomized study, there were no significant differences between OAC and OAM treatment groups in terms of *H pylori* eradication and ulcer healing, confirming that 1-wk triple therapy with omeprazole and amoxicillin in combination with either clarithromycin or metronidazole has the same effectiveness on eradicating the bacterium. Both eradication regimens were well tolerated and patient compliance was excellent. However, clarithromycin is too expensive to be widely used in China.

Antibacterial treatment of *H pylori* is difficult because of the very rapid development of resistance to antimicrobial agents, especially to nitroimidazoles, such as metronidazole and tinidazole, and clarithromycin<sup>[34]</sup>. The resistance of *H pylori* to metronidazole and clarithromycin strongly affected the success of regimens involving these drugs. The prevalence of resistance to these anti-microbial agents varied with gender, ethnic group and country of origin<sup>[34]</sup>. It was reported from Hong Kong (China) that almost 50% of pre-treatment strains of *H pylori* were resistant to metronidazole and over 10% to clarithromycin<sup>[33]</sup>. Metronidazole resistance has been shown to reduce *H pylori* eradication rates in the regimens containing amoxicillin and metronidazole<sup>[35,36]</sup>. Several studies have shown a significantly higher rate of metronidazole resistant *H pylori* among women<sup>[37-39]</sup>, indicating that this drug can be widely used for pelvic inflammatory diseases in females<sup>[37]</sup>. In the current study, the number of men was absolutely more than that of women either in OAC or in OAM group. Whether the sex bias of patients was related to the better eradication in OAM group remains unknown. We did not test *in vitro* sensitivity to metronidazole and clarithromycin. Although Epsilometer (E) test has been recommended as the best and simplest method for routine testing of antibiotic sensitivity to *H pylori*, the technique is not yet widely available in China. On the other hand, the exact mechanism responsible for the development of *H pylori* resistance to metronidazole still remains obscure, antimicrobial effectiveness *in vivo* was poorly predicted by sensitivity *in vitro*<sup>[37]</sup>. This is largely because the current breakpoints, which are the *in vitro* concentrations defining the cut off between sensitive and resistant strains, do not correlate with levels required for eradication of infection from the gastric mucosa.

In the past, prevention of peptic ulcer recurrence was based on long term use of H<sub>2</sub>-receptor antagonists or PPIs. Since *H pylori* was recognized, it has been well understood that eradicating the bacterium could significantly reduce the recurrence of peptic ulcer diseases<sup>[8,16-18]</sup>. In our study, the

ulcer relapse rate during the 12-mo follow-up was 66.7% (4/6) in *H pylori*-positive patients and none of the 24 *H pylori*-negative patients relapsed (data not shown). In conclusion, 1-wk triple therapy with omeprazole and amoxicillin in combination with either clarithromycin or metronidazole is equally effective for eradication of *H pylori* and ulcer healing. Clarithromycin is the most expensive antimicrobial drug used to treat *H pylori* infection. Metronidazole with lower cost, good compliance and mild adverse events may offer a good choice for the treatment of peptic ulcers associated with *H pylori* infection in China.

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