GASTROENTEROLOGY

Low-dose rabeprazole, amoxicillin and metronidazole triple therapy for the treatment of Helicobacter pylori infection in Chinese patients

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Abstract

Background: Rabeprazole in combination with amoxicillin and metronidazole (RAM) has been shown to be an effective second-line treatment of Helicobacter pylori infection. The effects were compared of 7-day low-dose and high dose rabeprazole in RAM for the primary treatment of H. pylori infection in Chinese patients.

Methods: Helicobacter pylori-positive dyspeptic patients were randomized to receive either (i) rabeprazole 10 mg, amoxicillin 1000 mg and metronidazole 400 mg (RAM-10) or (ii) high-dose rabeprazole 20 mg, amoxicillin 1000 mg and metronidazole 400 mg (RAM-20), each given twice daily for 7 days. Helicobacter pylori eradication was confirmed by 13C-urea breath test 5 weeks after stopping medications. Side-effects of treatments were documented.

Results: A total of 120 patients were eligible for analysis. By intention-to-treat and per-protocol analysis, the eradication rates were 83% and 86% in the RAM-10 group and 75% and 76% in the RAM-20 group, respectively (P = 0.26 and P = 0.17). Both regimens were well-tolerated and compliance was >98% in both groups.

Conclusions: Low-dose rabeprazole in combination with amoxicillin and metronidazole is an effective, economical and well-tolerated therapy for the treatment of H. pylori infection in Chinese population.

Key words: amoxicillin, eradication, Helicobacter pylori, metronidazole, rabeprazole.

INTRODUCTION

It is accepted that Helicobacter pylori is one of the major causes of dyspepsia, peptic ulcer and gastric cancer.1,2 Eradication of H. pylori significantly reduces the relapse of peptic ulcers and may possibly reduce the incidence of gastric cancer.3-5 In the Asia Pacific Consensus conference on the management of H. pylori infection, the recommended regimens include the use of proton pump inhibitor (PPI)/ranitidine bismuth citrate in standard dose plus two antibiotics consisting of clarithromycin plus either amoxicillin or metronidazole, each given twice daily for 7 days.1

Bacterial resistance to metronidazole or clarithromycin is an important factor leading to treatment failure.6 Primary resistance to metronidazole and clarithromycin is common in Hong Kong and significantly affects the effectiveness of the standard triple therapies recommended by the Asia Pacific consensus conference.1,7,8 The problem is compounded by the cost of these eradication regimens because clarithromycin is an expensive antibiotic. Non-clarithromycin-based triple therapies using a PPI plus amoxicillin and metronidazole have been shown to be an effective and economical treatment for H. pylori infection in Asian countries.9,10 Rabeprazole is a benzimidazole PPI with a rapid onset of action.11-13 In vitro studies have demonstrated that rabeprazole has a more potent antibacterial activity against H. pylori when compared with either omeprazole or lansoprazole.14-17 Reports from Japan have demonstrated that rabeprazole in combination with amoxicillin and metronidazole is an effective second-line treatment of H. pylori infection after failure of PPI, amoxicillin and clarithromycin regimen.18,19 However,
rabeprazole in combination with amoxicillin and metronidazole as a primary treatment of *Helicobacter pylori* infection has been inadequately studied. A systematic review of the efficacy of rabeprazole-based therapies in *H. pylori* eradication has demonstrated that low-dose rabeprazole (20 mg/day) in combination with amoxicillin and clarithromycin was equally effective as the high-dose rabeprazole regimens for *H. pylori* eradication.  

Thus the aims of the present study were to perform a head-to-head comparison of 1-week low-dose (20 mg/day) rabeprazole, amoxicillin and metronidazole triple therapy versus 1-week high-dose (40 mg/day) rabeprazole, amoxicillin and metronidazole triple therapy for the treatment of *H. pylori* infection in Chinese patients; and (ii) to determine the clinical response and safety profile of the two regimens.

**METHODS**

**Patient characteristics**

Patients with newly diagnosed *H. pylori* infection with either active duodenal ulcer (DU) >5 mm in size, or non-ulcer dyspepsia (NUD) were recruited from the endoscopic unit of the Department of Medicine, Queen Mary Hospital, Hong Kong. Dyspepsia was defined as persistent or recurrent upper abdominal pain or discomfort over the preceding 3-month period in accordance with the Rome criteria for dyspepsia. Patients were excluded if (i) they were under 18 or over 80 years of age; (ii) gastric ulcer was found on endoscopy; (iii) H₂-receptor antagonists, PPI, bismuth compounds and/or antibiotics and/or regular intake of NSAIDs were used within the 4 weeks prior to study entry; (iv) had active ulcer bleeding, previous gastric or duodenal surgery; (v) had history of allergy to the study medications; or (vi) had significant concomitant medical diseases. The study was approved by the local Institutional Review Board (IRB) and written informed consent was obtained from all patients before the beginning of the study. We followed the recommendation of the Consolidated Standards of Reporting Trials (CONSORT) trial guidelines for reporting the results.

During endoscopy, two antral biopsies and one corpus biopsy were taken. One antral biopsy was used for rapid urease test (RUT) and the rest were sent for histological examination of *H. pylori* status by hematoxylin and eosin stains and Giemsa stain. Specimens were read by experienced pathologists who were blinded to all clinical information, including the RUT results. The *H. pylori* infection was defined as positivity of both tests. Equivocal cases were excluded from the study. This approach has been validated at Queen Mary Hospital before with an accuracy of 100%.

**Treatment regimens**

Patients were then randomized into either 1-week of rabeprazole 10 mg, amoxicillin 1000 mg and metronidazole 400 mg (RAM-10), each given twice daily for 7 days; or 1 week of rabeprazole 20 mg, amoxicillin 1000 mg and metronidazole 400 mg (RAM-20), each given twice daily for 7 days; or 1 week of rabeprazole 20 mg, amoxicillin 1000 mg and metronidazole 400 mg (RAM-20), each given twice daily for 7 days. Randomization was performed by drawing a sequentially numbered sealed envelope that contained a preassigned computer-generated randomized treatment. Patients were given antibiotics whenever necessary. The patients were given a diary in which they recorded any side-effects and symptoms during treatment period. Side-effects were also documented by a direct questioning approach during scheduled visits at day 14 in addition to self-reporting. Eradication was determined by a validated 13C-urea breath test (13C-UBT) 5 weeks after the end of treatment. This protocol has been validated at Queen Mary Hospital with a sensitivity and specificity of 96.5% and 97.7%, respectively. Briefly, patients were fasted 4 h before the test. No test meal was given and a pre-dose breath sample was obtained. The patients were asked to drink 75 mg 13C-urea powder dissolved in 50 mL of water. The second breath sample was collected at 30 min after the administration of the 13C-urea drink. The cut-off value used for determining the test result was 5%. All patients were kept in a sitting position over the whole testing period. The collected samples were analyzed by the purpose-built isotope ratio mass spectrometer.

**Clinical response**

Symptoms such as daytime epigastric pain, nocturnal abdominal pain, bloating or post-prandial fullness, belching, acid reflux and heartburn were assessed by the investigators. All symptoms were rated as absent, mild (transient and easily tolerated), moderate (discomfort and affecting normal activities) and severe (incapacitating symptoms with inability to perform daily activities). The clinical response of each subject was assessed at the follow-up visit by a gastroenterologist who was blinded to the *H. pylori* status of the patient. Symptom response was defined as complete resolution of pretreatment symptoms. Symptom improvement was defined as shifting from severe to moderate or from mild to moderate to mild following the treatment. If all symptoms were resolved, the patient was classified as ‘cure’. Symptom improvement was assigned when some pretreatment symptoms were improved, while a failure was assigned when there was no improvement. If a patient was asymptomatic before treatment or if the patients were not assessed, an indeterminate status was assigned.

**Statistical analysis**

The intention-to-treat analysis principle was applied, which included all patients who had taken at least one tablet of the study drugs. In the per-protocol analysis, patients with poor drug compliance (<75% intake of study drugs) and defaulters were excluded from the analysis. The χ² and student’s t-tests were used for statistical analyses. All analyzes were performed using SPSS...
version 11.0 (SPSS, Chicago, IL, USA). In view of the high prevalence of metronidazole-resistant *H. pylori* strains in Hong Kong, an expected efficacy of 60% successful eradication was adopted. To detect a 25% difference in efficacy of the tested regimens with a power of 80% and \( \alpha \) at 5%, at least 57 patients in each arm were required.

**RESULTS**

A total of 120 patients were recruited from June 2003 to November 2003. Sixty patients were randomized to receive RAM-10 and 60 patients to receive RAM-20 (Fig. 1). Three patients were excluded from the per-protocol analysis (two patients were non-compliant to the protocol and one patient refused follow up). The baseline characteristics of the patients and their respective diagnosis are listed in Table 1. The mean age of these patients was 49 years (range 18–80 years). There were 53 men (mean age 54 years) and 67 women (mean age 45 years). Overall the distribution of endoscopic diagnoses was similar between the two groups, although more patients with DU were in the RAM-20 group (20% vs 7%, \( P = 0.06 \)).

**Helicobacter pylori eradication**

The results of *H. pylori* eradication are listed in Table 2. By intention-to-treat analysis, the eradication rates in RAM-10 and RAM-20 groups were 83% (50/60) and 75% (45/60), respectively (\( P = 0.26 \)). By per-protocol analysis, the eradication rate in the RAM-10 group was 86% (50/58) and in the RAM-20 group was 76% (45/59) (\( P = 0.17 \)). There was no statistical difference in *H. pylori* eradication rates between the two groups in both analyses. The combined eradication rate in patients with DU, gastroduodenal erosions and NUD were 69%, 90% and 80%, respectively (\( P = 0.41 \)).

**Clinical response**

The three most common symptoms reported by the patients at the baseline visit were belching (74%), bloating or post-prandial fullness (57%) and epigastric pain (57%). In terms of symptom response, there was no difference in the proportion of patients with cure, improvement, or failure between the two treatment groups (Table 2).

**Side-effects**

Drug compliance was excellent. Ninety-eight percent (59/60) of the patients in the RAM-10 group and 97% (58/60) of the patients in the RAM-20 group completed the study medications. There was no hospitalization or mortality during the study period. The most common side-effects were increase in stool frequency/loose stool, dizziness, malaise and nausea. The total proportion of

***Table 1*** Study patients

<table>
<thead>
<tr>
<th></th>
<th>RAM-10</th>
<th>RAM-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (intention-to-treat)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td>51 (18–80)</td>
<td>47 (18–77)</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/35</td>
<td>28/32</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Gastroduodenal erosions</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>NUD</td>
<td>49</td>
<td>45</td>
</tr>
</tbody>
</table>

DU, duodenal ulcer; NUD, non-ulcer dyspepsia; RAM-10, rabeprazole 10 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d. for 7 days, RAM-20, rabeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d. for 7 days.

***Table 2*** Helicobacter pylori eradication rates

<table>
<thead>
<tr>
<th></th>
<th>RAM-10</th>
<th>RAM-20</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eradication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>50/60 (83)</td>
<td>45/60 (75)</td>
<td>0.261</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td>50/58 (86)</td>
<td>45/59 (76)</td>
<td>0.169</td>
</tr>
<tr>
<td><strong>Clinical response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>13 (22)</td>
<td>21 (35)</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>30 (50)</td>
<td>27 (45)</td>
<td>0.394</td>
</tr>
<tr>
<td>Failure</td>
<td>16 (27)</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1 (2)</td>
<td>5 (8)</td>
<td></td>
</tr>
</tbody>
</table>

RAM-10, rabeprazole 10 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d. for 7 days, RAM-20, rabeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d. for 7 days.
amoxicillin (750 mg b.i.d.) and metronidazole (250 mg b.i.d.) in 123 patients who failed first-line *H. pylori* treatment. Antibiotics resistance pattern and cytochrome p450 (CYP)2C19 genotype were studied. The intention-to-treat eradication of the rabeprazole–amoxicillin combination was 59%, while the eradication for the rabeprazole–amoxicillin–metronidazole combination was 82% (*P* < 0.01). The CYP2C19 genotypes and metronidazole resistance did not influence the treatment outcome. They concluded that low-dose rabeprazole, amoxicillin, metronidazole regimen is an effective second-line treatment of *H. pylori* infection in Japan. The reasons for the efficacy of the low-dose regimen are believed to be due to a faster onset of anti-secretory action. Furthermore, the metabolism of rabeprazole is less dependent on the CYP2C19 system and therefore allows higher drug concentration, which may contribute to a higher eradication rate even in subjects with extensive metabolizer genotype.

It has been shown by the MACH2 study that in vitro metronidazole resistance could be partially overcome by the use of PPI; in that study *H. pylori* eradication with metronidazole–clarithromycin combination treatment was 43%, but increased to 76% when omeprazole was added. This may explain the satisfactory *H. pylori* eradication rate despite the presence of metronidazole resistance in the two Japanese studies. Clarithromycin is an expensive antibiotic. In view of the current health and economic environment, the establishment of a cheap, well-tolerated and effective therapy is more sensible for developing countries, where a high prevalence of *H. pylori* infection usually exists. Unfortunately, antibiotics sensitivity was not performed in the current study. However, it is reasonable to assume that the metronidazole resistance rate should not differ greatly from our previous cohorts. Further comparative studies with antibiotic sensitivity data are warranted in this aspect.

The intention-to-treat eradication rates of RAM-10 and RAM-20 obtained in the present study were comparable to those achieved with rabeprazole–amoxicillin–clarithromycin reported in a recent meta-analysis of rabeprazole-based therapies for *H. pylori* eradication. In that meta-analysis, 7-day rabeprazole–amoxicillin–clarithromycin had a mean eradication rate of 78%. Interestingly, when low-dose rabeprazole (20 mg/day) and high-dose rabeprazole (40 mg/day) regimens were analyzed separately, the low-dose rabeprazole regimen had a mean eradication rate of 81%, while the high-dose rabeprazole regimen had a mean eradication rate of 75%, suggesting that the low-dose regimen is at least as effective as the high-dose regimen. However, a direct head-to-head comparative study will be needed to confirm the aforementioned observation. A recent Asian study using low-dose rabeprazole–amoxicillin–clarithromycin combination also reported a satisfactory intention-to-treat eradication rate of 82%. Furthermore, the low-dose rabeprazole regimen has a satisfactory ulcer healing rate and side-effects profile.

Both regimens were well tolerated and side-effects were present in 25% of the RAM-10 group and 33% of the RAM-20 group. The most common side-effects were increase in stool frequency/loose stool, dizziness

### DISCUSSION

We reported a randomized study with head-to-head comparison of 7-day low-dose rabeprazole (20 mg/day), amoxicillin and metronidazole (RAM-10) triple therapy versus 7-day high-dose rabeprazole (40 mg/day), amoxicillin and metronidazole (RAM-20) triple therapy for the eradication of *H. pylori* infection, which has a *H. pylori* metronidazole resistance rate of 38–49%. The *H. pylori* eradication rates were similar between the two treatment groups (RAM-10 and RAM-20) by intention-to-treat (83% vs 75%) or per-protocol (86% vs 76%) analysis, respectively.

To the best of our knowledge, this is the first prospective randomized study to compare the efficacy of low-dose rabeprazole–amoxicillin–metronidazole with high- dose rabeprazole–amoxicillin–metronidazole for treating *H. pylori* infection. The only report of rabeprazole–amoxicillin–metronidazole regimen as a primary treatment of *H. pylori* infection was a 4-arm study with 19 patients in the RAM group and the dosage of rabeprazole used was 40 mg/day. In that study, the intention-to-treat eradication rate was 89% in the RAM-20 group. However, RAM is commonly used as a second-line treatment regimen for patients with treatment failures. Murakami et al. reported an open-label study of 1-week high-dose rabeprazole (20 mg b.i.d.), amoxicillin (750 mg b.i.d.) and metronidazole (250 mg b.i.d.) for the treatment of 92 patients who failed first-line *H. pylori* treatment consisting of a PPI, amoxicillin and clarithromycin. The intention-to-treat eradication rate was 88% overall and the eradication rate for metronidazole-resistant strains was 82%. In another study, Isomoto et al. performed a head-to-head comparison of 2-week rabeprazole (20 mg b.i.d.) and amoxicillin (1000 mg b.i.d.) and 1-week rabeprazole (10 mg b.i.d.),
and malaise. In general, both regimens were well tolerated by the patients and compliance was 98% in both groups. Thus, the low-dose rabeprazole–amoxicillin–metronidazole regimen appears to be an economical treatment according to the results of the present study.

In conclusion, this head-to-head comparison study showed similar H. pylori eradication rates between low-dose rabeprazole–amoxicillin–metronidazole regimen and the high-dose rabeprazole–amoxicillin–metronidazole regimen. Both regimens were well tolerated. Low-dose rabeprazole–amoxicillin–metronidazole based triple therapy is an effective and economical treatment of H. pylori infection in Chinese population.

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REFERENCES

23 Altman DG, Schulz KE, Moher D et al. The revised CONSORT statement for reporting randomized trials:


