Original Article

Duration of the Metronidazole-Containing Regimen for Eradication of Helicobacter pylori Infection in Northern Japan

Shinsaku Fukuda, Tadashi Shimoyama*, Muneko Tanaka, Fumika Nakasato, Michio Fukushi and Akihiro Munakata

First Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki 036-8562, Japan

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SUMMARY: Metronidazole is often used to eradicate clarithromycin-resistant Helicobacter pylori. The aim of this study was to determine the appropriate duration of metronidazole-containing treatment for the eradication of H. pylori infection in northern Japan. We enrolled 83 H. pylori-positive patients in whom first-line triple therapy consisting of a proton pump inhibitor, amoxicillin and clarithromycin had failed. Prior to the second-line therapy, patients underwent endoscopy to obtain H. pylori strains to test the susceptibility to antibiotics. Patients were administered lansoprazole (30 mg b.d.), amoxicillin (750 mg b.d.) and metronidazole (250 mg b.d.) for 5 or 7 days, and the treatment results were tested by 13C-UBT. None of the isolated H. pylori strains was amoxicillin- or metronidazole-resistant. All the patients completed the regimen without major adverse effects. The eradication rate was 95.1% (39/41; 95% confidence interval [CI], 83.5 - 99.4%) in the 41 patients who were treated for 5 days and 95.2% (40/42; 95% CI, 83.8 - 99.4%) in the 42 patients treated for 7 days. The results suggest that 5 days could be a sufficient duration for triple therapy of lansoprazole, amoxicillin and metronidazole as a second-line H. pylori eradication therapy in areas where metronidazole-resistant strains are rare.

INTRODUCTION

Eradication of Helicobacter pylori infection is usually performed in patients with peptic ulcer diseases. At present, in Japan, only one regimen (first-line therapy) is approved by the Japanese system of health insurance; 1-week of triple therapy with a proton pump inhibitor (PPI) (either lansoprazole [LPZ] or omeprazole [OPZ]), amoxicillin (AMOX) and clarithromycin (CLA) (1). However, failure of H. pylori eradication by this regimen has been increasing. The most common cause for the failure of first-line therapy in Japan is bacterial resistance to CLA (2). On the other hand, resistance to AMOX is very rare, and acquisition of resistance to AMOX also rarely occurs even after the failure of first-line therapy (3). Japanese are different from other Asian populations for the prevalence of the metronidazole (MNZ)-resistant strain (4,5). This is especially true in northern Japan, where the prevalence of MNZ-resistant strains in the general population is less than 5% (6).

Recent Japanese studies have demonstrated that triple therapies consisting of PPI, AMOX and MNZ achieved eradication rates of 88 - 96% (7-9). Thus, triple therapy with PPI, AMOX and MNZ appears to be an effective regimen to eradicate H. pylori infection in Japan. However, in these studies, the duration of the treatment was 1 week or 10 days. In other countries, the duration of the eradication regimens containing MNZ is often 10 - 14 days. Therefore, it is necessary to elucidate that 1 week is a sufficient duration for the triple therapy consisting of PPI, AMOX and MNZ in Japan. If a similar eradication rate is achieved by both 5 and 7 days of treatment, the duration of the regimen could not be necessary longer than 7 days. In this study, therefore, we compared the efficacy of 5 and 7 days of triple therapy consisting of LPZ, AMOX and MNZ.

MATERIALS AND METHODS

Patients and protocols: A total of 83 consecutive patients provided their consent to receive the present treatments and were enrolled in this study between June 2003 and December 2004. All the patients were diagnosed as having peptic ulcer diseases, and had been unsuccessfully treated with first-line triple therapy consisting of a PPI (OPZ or LPZ), AMOX and CLA. Infection of H. pylori was confirmed by 13C-urea breath test (UBT). Prior to the second-line therapy, patients underwent endoscopy, and gastric biopsies were obtained to isolate H. pylori strains in order to test the susceptibility to antibiotics. Forty-one patients received LPZ (30 mg b.d.), AMOX (750 mg b.d.) and MNZ (250 mg b.d.) for 5 days and 42 patients were treated for 7 days. Patients who were receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or other antibiotics or who were older than 70 years old were excluded. The details of each group are shown in Table 1. There were no significant differences in mean age, gender and proportion of smokers between groups. After finishing the treatment, patients were allowed to take an H2-receptor antagonist once daily to relieve dyspeptic symptoms. PPIs and other anti-ulcer agents that might affect the viability of H. pylori or urease activity were not used after finishing the treatment. 13C-UBT was performed at least 5 weeks after finishing the treatment to determine the treatment results. All subjects provided written informed consent before their treatment.

Table 1. Patient characteristics and the treatment results

<table>
<thead>
<tr>
<th>Duration</th>
<th>n (M/F)</th>
<th>Mean age (SD)</th>
<th>Smoking (%)</th>
<th>Eradication rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>24/17</td>
<td>48.1 (12.2)</td>
<td>57.1</td>
<td>95.1 (83.5 - 99.4)</td>
</tr>
<tr>
<td>7 days</td>
<td>23/19</td>
<td>49.0 (11.0)</td>
<td>61.9</td>
<td>95.2 (83.8 - 99.4)</td>
</tr>
</tbody>
</table>
endoscopy and this study was approved by the ethics committee of Hirosaki University.

**H. pylori culture and determination of the minimum inhibitory concentration (MIC):** Biopsy specimens were inoculated onto Skirrow blood agar and cultured for 3-5 days at 37°C at high humidity under strict aerobic conditions (N2 80%, CO2 15%, O2 5%). The bacteria were identified as *H. pylori* by colonial morphology, positive oxidase, catalase and urease reactions. The MIC of isolated *H. pylori* strains to AMOX and MNZ were determined by an agar dilution method. When the MIC of AMOX, CLA and MNZ were 0.5 μg/mL, 1.0 μg/mL and 16.0 μg/mL or higher, the strain was assessed as resistant.

**Statistical analysis:** The significance of differences in the patient characteristics was tested by chi-square or two-tailed t test, while the eradication rates were compared using Fisher’s exact probability test. A P value of less than 0.05 was considered significant.

**RESULTS**

All the 83 patients completed the 5 or 7 day regimen, and there were no major adverse effects requiring the cessation of treatment. The eradication rate was estimated as 95.1% (39/41; 95% confidence interval [CI], 83.5-99.4%) in patients who were treated for 5 days and 95.2% (40/42; 95% CI, 83.8-99.4%) in patients treated for 7 days using both intention-to-treat analysis and per protocol analysis. The eradication rate was not significantly different between the groups.

No strain was resistant to both AMOX and MNZ, while infection by the CLA-resistant strain was seen in 33 of the 41 patients (80.5%) who were treated for 5 days and 35 of the 42 patients (83.3%) treated for 7 days. Failure of eradication was seen in 3 patients infected with the CLA-resistant strain and 1 patient infected with the CLA-susceptible strain. Resistance to CLA was not associated with treatment failure of this second-line therapy in this series of patients.

**DISCUSSION**

Antibiotic-resistance is the most common cause of the failure of eradication of *H. pylori* in many countries (10,11). Consumption of antimicrobial agents before eradication therapy increases antibiotic-resistant *H. pylori* strains, and the failure of eradication therapy is also associated with acquisition of antibiotic-resistance (12). In particular, resistance to CLA is easily acquired by *H. pylori* (13), and the prevalence of CLA-resistance has been increasing remarkably. However, in Japan, only AMOX and CLA are approved for the treatment of *H. pylori* infection, and therefore, eradication therapy which does not contain CLA is required for patients who fail first-line therapy.

To date, regimens containing MNZ were recognized to have a high eradication rate in patients who fail first-line therapy (7-9). In Japanese *H. pylori* strains, MNZ-resistant strain is less frequent comparing with other Asian countries (4,5), and this may be associated with higher eradication rate. In other countries, where MNZ-resistant strains are frequently seen, the duration of the regimes containing MNZ is often 10-14 days (14,15). However, our present study demonstrated that eradication of *H. pylori* was successful in most patients even when triple therapy of PPI, AMOX and MNZ was administered for only 5 days. Generally, since a shorter treatment period is associated with better compliance and fewer side effects, the treatment period should be 5 days rather than 7 days in areas where MNZ-resistance is rare. Additionally, our results might also indicate that 7 days of therapy with PPI, AMOX and MNZ would eradicate *H. pylori* even in patients who failed to take their medicine several times during the regimen.

Although a high eradication ratio was achieved, it is possible that viable bacterial cells had decreased after the first-line therapy. Susceptibility to CLA and duration after finishing the first-line therapy could affect the number of bacteria. If a decrease of bacteria by CLA played a role in the successful eradication, failure of second-line therapy should be seen in patients infected with a CLA-resistant strain. However, in our results, treatment failure was not associated with the presence of a CLA-resistant strain. In the present study, most patients received the second-line therapy within 3 months after the failure of first-line therapy. We can not preclude the possibility that a decrease in bacterial cells by the first-line therapy affected the results of the second-line therapy. Therefore, a lower eradication rate would be seen in patients who receive second-line therapy after long duration since their failed first-line therapy.

A shorter duration of treatment is also favorable for the MNZ-containing regimen from another point of view. Since the administration of MNZ has been associated with malignancies such as lung cancer (16), the Japanese system of health insurance has limited the use of MNZ to only cases of trichomoniasis. Considering the risk of malignancies, shorter duration is better for the regimens containing MNZ. The duration and the total amount of MNZ for the treatment of *H. pylori* infection are smaller than those approved for trichomoniasis even if the duration of the regimen is 7 days. There has been no report which shows malignancies associated with administration of MNZ for trichomoniasis. Therefore, patients can eradicate *H. pylori* safely if the treatment is performed for 5 days.

In conclusion, in patients who failed first-line therapy for *H. pylori* eradication, triple therapy of LPZ, AMOX and MNZ achieved high eradication rates even when the duration was 5 days. The frequency of MNZ-resistance is much lower in northern Japan than in western and southern Japan. The necessary duration of MNZ-containing regimens should be studied in these different regions in Japan, since the treatment results will be affected by the prevalence of MNZ-resistant strains.

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**REFERENCES**


