

# Proton pump inhibitor-amoxicillin-clarithromycin versus proton pump inhibitor-amoxicillin-metronidazole as first-line *Helicobacter pylori* eradication therapy

Toshihiro Nishizawa,<sup>1,2</sup> Hidekazu Suzuki,<sup>2,\*</sup> Masayuki Suzuki,<sup>1</sup> Masahiko Takahashi<sup>1</sup> and Toshifumi Hibi<sup>2</sup>

<sup>1</sup>Division of Gastroenterology, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan

<sup>2</sup>Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

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The aim of this study was to compare the efficacy and tolerability of the first-line *Helicobacter pylori* (*H. pylori*) eradication regimen composed of proton pump inhibitor, clarithromycin, and amoxicillin, with those of a regimen composed of proton pump inhibitor, metronidazole, and amoxicillin. Data of patients, who were administered the first-line *H. pylori* eradication regimen at Tokyo Medical Center between 2008 and 2011, were reviewed. All patients had *H. pylori* gastritis without peptic ulcer disease. The 7-day triple regimen composed of lansoprazole, clarithromycin, and amoxicillin was administered to 55 patients, and that composed of omeprazole, metronidazole, and amoxicillin was administered to 55 patients. Intention-to-treat and per-protocol eradication rates were 74.5 and 80.4%, respectively, for the regimen of lansoprazole, clarithromycin, and amoxicillin, whereas the corresponding rates were 96.4 and 100%, respectively, for the regimen of omeprazole, metronidazole, and amoxicillin. In conclusion, first-line *H. pylori* eradication therapy composed of omeprazole, metronidazole, and amoxicillin was significantly more effective than that composed of lansoprazole, clarithromycin, and amoxicillin, without differences in tolerability.

**Key Words:** *Helicobacter pylori*, eradication, antibiotics

Eradication of *Helicobacter pylori* (*H. pylori*) infection has been reported as an effective strategy in the treatment of peptic ulcers and gastric mucosa-associated lymphoid tissue lymphoma, in addition to the prevention of recurrence of gastric cancer after endoscopic resection.<sup>(1–6)</sup> The first-line regimen for the treatment of *H. pylori* infection in Japan is triple therapy with a proton pump inhibitor (PPI), amoxicillin (AMX), and clarithromycin (CLR), administered for 7 days. Failure of this first-line therapy against *H. pylori* infection has been reported in approximately 20% of infected patients.<sup>(7,8)</sup> At the 2008 meeting of the Japanese Society for Helicobacter Research, the mean national CLR resistance rates from 2002 to 2006 were reported to be 18.9, 21.2, 27.7, 29.0, and 27.2%. The mean nationwide CLR resistance rate determined by the Japanese Society of Chemotherapy was 7.0% (21/302) in 2000, indicating an increase of resistance by approximately 20% over several years.<sup>(9)</sup> Furthermore, it appears that the prevalence of CLR-resistant *H. pylori* is increasing rapidly, and therefore, a resultant decrease in eradication achieved by the therapy, currently available under the national health insurance scheme, is a concern.

Failure of therapy with PPI-AMX-metronidazole (MNZ), administered for 1 week as a second-line regimen after failure of

the first-line regimen, has been reported in approximately 10% of infected patients. Although the prevalence of *H. pylori* resistant to MNZ has been reported to be 8–80% in different countries, that in Japan has been reported to be 5–12%.<sup>(10,11)</sup>

These findings suggest that the first-line therapy with PPI-AMX-MNZ may be recommended in Japan. The aim of our retrospective study was to compare the efficacy and tolerability of the 7-day first-line *H. pylori* eradication regimen composed of PPI, CLR, and AMX, with those of a regimen composed of PPI, MNZ, and AMX.

## Patients and Methods

Data of patients, who were administered first-line *H. pylori* eradication therapy at the Tokyo Medical Center between April 2008 and November 2011, were reviewed. Patients who had received a previous eradication therapy and had known peptic ulcer diseases and had used nonsteroidal anti-inflammatory drug, aspirin or clopidogrel were excluded from the study. Endoscopic examinations were conducted before treatment for all the patients, and *H. pylori* positivity was confirmed by the results of the <sup>13</sup>C-urea breath test or the presence of *H. pylori*-specific IgG antibodies in the serum.

The 7-day triple regimen composed of lansoprazole (30 mg, b.d.), CLR (400 mg, b.d.), and AMX (750 mg, b.d.) was administered to 55 patients, and that composed of omeprazole (20 mg, b.d.), MNZ (250 mg, b.d.), and AMX (750 mg, b.d.) was administered to 55 patients. The choice of regimen for *H. pylori*-associated gastritis was random. If the day of the week of patient's first visit was Tuesday, Wednesday, or Thursday, the regimen composed of lansoprazole, CLR, and AMX was chosen. If the day of the week of patient's first visit was Monday or Friday, the regimen composed of omeprazole, MNZ, and AMX was chosen. Eradication was confirmed by the results of the <sup>13</sup>C-urea breath test at 12 weeks after completion of the therapy. The <sup>13</sup>C-urea used was 100 mg <sup>13</sup>C-labelled urea produced by Otsuka Pharmaceutical Co. Ltd., Japan. The procedure was modified from the European standard protocol for detection of *H. pylori*. The study was approved by the Ethics Committee of National Hospital Organization Tokyo Medical Center, and informed consent was given by all the patients prior to the treatments.

**Statistical analysis.** Statistical analyses were performed

\*To whom correspondence should be addressed.  
E-mail: hsuzuki@a6.keio.jp

**Table 1.** Comparison of first-line *H. pylori* eradication regimen composed of lansoprazole, amoxicillin, and clarithromycin (LAC) with that composed of omeprazole, amoxicillin, and metronidazole (OAM)

Characteristics	LAC (n = 55)	OAM (n = 55)	p value
Age (mean ± SD)	57.9 ± 14.9	60.1 ± 12.2	0.396
Sex (male/female)	28/27	28/27	0.849
Adverse effects	13.7% (7/51)	11.3% (6/53)	0.711
Eradication rate (ITT)	74.5% (41/55)	96.4% (53/55)	0.001
Eradication rate (PP)	80.4% (41/51)	100% (53/53)	0.001

using the chi-square, Fisher's exact, and Student's *t* tests, as appropriate. *p* values of less than 0.05 were considered to indicate statistical significance.

## Results

One hundred ten patients were enrolled; of these 6 patients dropped out of the study. Table 1 shows the demographic data for these patients. The baseline characteristics were not statistically different between the 2 groups. The combination of lansoprazole, CLR, and AMX resulted in eradication rates of 74.5% (intention-to-treat; ITT) and 80.4% (per protocol; PP). The combination of omeprazole, MNZ, and AMX resulted in eradication rates of 96.4% (ITT) and 100% (PP). The regimen composed of omeprazole, MNZ, and AMX was significantly more effective than that composed of lansoprazole, CLR, and AMX (*p*<0.05 for ITT, *p*<0.01 for PP, Table 1).

The compliance of the patients with the prescribed treatment was excellent. Adverse events were observed in 7 of 51 patients (13.7%) in the PPI + CLR + AMX group and 6 of 53 patients (11.3%) in the PPI + MNZ + AMX group. In all the cases, the side effects were mild and mainly included mild diarrhea, taste disturbance, or stomatitis.

## Discussion

One week of triple therapy using a PPI combined with AMX and CLR is recommended as the first-line treatment choice for the eradication of *H. pylori* in Japan. The resistance to CLR is easily acquired and widespread prescription of CLR over the years lead to the spread of resistance of *H. pylori* to CLR. Sasaki *et al.*<sup>(12)</sup> reported the eradication rates of first-line eradication therapy with CLR from 1995 to 2008 (divided into four terms; 1997–2000, 2001–2003, 2004–2006, 2007–2008), and the eradication rate decreased significantly from 90.6 to 80.2%, 76.0, and 74.8%. The study demonstrated the evident decline in eradication rates for the triple therapy using a PPI, AMX, and CLR in Japan.

The present study showed an excellent eradication rate of 96.4% (ITT) and 100% (PP) with a 7-day regimen of MNZ, AMX, and PPI as the first-line treatment. This regimen composed of PPI, MNZ, and AMX was significantly more effective than that composed of PPI, CLR, and AMX, without differences in tolerability. The first-line regimen with CLR should be changed into

another regimen such as the regimen with MNZ in order to improve the eradication rate, because recent prevalence of CLR resistance is estimated as more than 30% in Japan.

We previously reported the resistant rates of *H. pylori* to AMX after unsuccessful eradication. The resistance rates to AMX (MIC≥0.06 µg/ml) in groups with no history of eradication treatment, a history of 1 treatment failure, and a history of 2 treatment failures were 13.6, 26.5, and 49.5%, respectively. The MIC<sub>90</sub> of AMX increased by 2-fold after every eradication failure, and accumulation of *PBP1* mutations were associated with a gradual increase in the resistance to AMX.<sup>(13)</sup> These results suggest that the first-line therapy with less chances of failure should be recommended to prevent further spread of AMX-resistant *H. pylori* strains.

Although lansoprazole does not have a significant advantage over omeprazole in *H. pylori* eradication,<sup>(14)</sup> drug costs of lansoprazole are more expensive than those of omeprazole. Niv also reported that there was no statistically significant difference between omeprazole and lansoprazole as part of a PPI-based triple therapy for eradication of *H. pylori*.<sup>(15)</sup> The costs of CLR for 7 days are five times more expensive than those of MNZ for 7 days. Drug costs of omeprazole, MNZ, and AMX for 7 days are \$ 46, and those of lansoprazole, CLR, and AMX for 7 days are \$ 76. The 7-day regimen of omeprazole, MNZ, and AMX would save \$ 30 per a patient treated. The present study demonstrated that the high eradication rate could be achieved despite of its low cost.

In conclusion, the triple therapy with PPI, MNZ, and AMX appeared to serve as an encouraging first-line strategy in Japan. Given the recent surge of CLR resistance compared to MNX resistance, new strategies for first-line regimens against *H. pylori* infection should be considered.

## Conflict of Interest

No potential conflicts of interest were disclosed.

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