Dual therapy for third-line *Helicobacter pylori* eradication and urea breath test prediction

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Abstract

We evaluated the efficacy and tolerability of a dual therapy with rabeprazole and amoxicillin (AMX) as an empirical third-line rescue therapy. In patients with failure of first-line treatment with a proton pump inhibitor (PPI)-AMX-clarithromycin regimen and second-line treatment with the PPI-AMX-metronidazole regimen, a third-line eradication regimen with rabeprazole (10 mg q.i.d.) and AMX (500 mg q.i.d.) was prescribed for 2 wk. Eradication was confirmed by the results of the 13C urea breath test (UBT) at 12 wk after the therapy. A total of 46 patients were included; however, two were lost to follow-up. The eradication rates as determined by per-protocol and intention-to-treat analyses were 65.9% and 63.0%,
respectively. The pretreatment UBT results in the subjects showing eradication failure; those patients showing successful eradication comprised 32.9 ± 28.8 permil and 14.8 ± 12.8 permil, respectively. The pretreatment UBT results in the subjects with eradication failure were significantly higher than those in the patients with successful eradication (P = 0.019). A low pretreatment UBT result (< 28.5 permil) predicted the success of the eradication therapy with a positive predictive value of 81.3% and a sensitivity of 89.7%. Adverse effects were reported in 18.2% of the patients, mainly diarrhea and stomatitis. Dual therapy with rabeprazole and AMX appears to serve as a potential empirical third-line strategy for patients with low values on pretreatment UBT.

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Key words: Helicobacter pylori; Amoxicillin; Dual therapy; Eradication; Urea breath test

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TO THE EDITOR

Eradication of Helicobacter pylori (H. pylori) has been reported as an effective strategy in the treatment of peptic ulcers and gastric mucosa-associated lymphoid tissue lymphomas and also prevents the recurrence of gastric cancer after endoscopic resection[8,9]. 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 d. Failure of this first-line therapy against H. pylori infection has been reported in approximately 20% of infected patients.[8,9]. With the increase in the frequency of CLR-resistant H. pylori, there is rising concern about the potential decline in the eradication rate of this infection[10]. Although therapy with PPI-AMX-metronidazole (MNZ) administered for 1 wk has been found to be effective as a second-line regimen in patients failing the first-line regimen, approximately 10% of patients fail to respond to even second-line treatment, necessitating the establishment of an alternative third-line strategy for the effective eradication of H. pylori[11].

Although H. pylori bacteria easily develop resistance to CLR and MNZ, H. pylori has been considered to seldom become resistant to AMX. AMX is the preferred antibiotic because it is bactericidal and resistance is rare; therefore, it can be used again after treatment failure[12]. A number of studies have suggested that good success rates for H. pylori eradication could be obtained with AMX and PPI dual therapy if the effective PPI dose and frequency of administration were increased[13]. The majority of patients who experience two eradication failures have the rapid metabolizer genotype of CYPI2C19. Because omeprazole and lansoprazole are extensively metabolized by CYP2C19 in this genotype, their plasma concentrations will not attain sufficient levels to inhibit acid secretion, and therefore, antibiotics such as AMX will be less stable in the stomach, resulting in a lower eradication rate[13]. The PPI rabeprazole is a substitute of benzimidazole. CYP2C19 is less involved in the metabolism of rabeprazole than that of omeprazole and lansoprazole[14]. Moreover, rabeprazole has a greater and more rapid acid-inhibitory effect than does omeprazole. Several reports on the pharmacokinetics and pharmacodynamic characteristics of PPIs have indicated that a sufficient plasma concentration of PPIs can be achieved in patients with the rapid metabolizer genotype of CYP2C19 by frequent PPI dosing[14,15]. Furuta et al[16] recently reported an excellent eradication rate of 87.8% following dual therapy with rabeprazole 4 times/day and AMX as a third-line rescue. However, their study was completed at only one or two centers. Our study was designed as a prospective, multicenter trial with the participation of 16 Japanese hospitals affiliated with the National Hospital Organization to investigate the efficacy of dual therapy with 4 times daily dosing of rabeprazole and AMX as empiric third-line rescue therapy.

A total of 46 patients (26 males, 20 females; age 60.7 ± 12.9 years, mean ± SD) referred to us between January 2009 and January 2012 were enrolled. Endoscopic examinations were conducted before treatment in all patients, and H. pylori positivity was confirmed by histology, stool antigen test, H. pylori-specific IgG antibodies or the 13C-urea breath test. All patients had a history of two treatment failures (first-line treatment used: triple therapy with PPI-AMX-CLR for 7 d; second-line treatment used: triple therapy with PPI-AMX-MNZ for 7 d). The exclusion criteria in this study were (1) age < 18 years; (2) presence of clinically significant underlying disease (hepatic or renal disease, diabetes mellitus); (3) history of gastric surgery; and (4) allergy to any of the drugs used in the study. H. pylori eradication failure was defined as a positive 13C-urea breath test (UBT) at the end of 12 wk after completion of treatment. The 13C-urea used was 100 mg 13C-labelled urea, produced by Otsuka pharmaceutical Co., LTD, Japan. The procedure was modified from the European standard protocol for the detection of H. pylori[17].
chose 2.5 permil for cut-off level of the rise in the delta value of $^{13}$CO$_2$ at 15 min after the ingestion of $^{13}$C-urea.

The treatment regimen was rabeprazole 10 mg q.i.d. and AMX 500 mg q.i.d. administered for 2 wk. Participants were requested to return at the conclusion of the therapy for an interview regarding any adverse events. Successful H. pylori eradication was defined as a negative UBT at the end of 12 wk after completion of treatment. Statistical analyses were performed using the chi-square, Fisher’s exact and Student’s $t$ tests, as appropriate. $P$ values of less than 0.05 were accepted as representing statistical significance. The study was conducted with the approval of the Ethics Committee of the National Hospital Organization Tokyo Medical Center, and informed consent was obtained from all patients prior to the examinations. The clinical trial registration number of the University Hospital Medical Information Network was R000003204.

Of the 46 patients enrolled, 2 dropped out of the study, leaving 44 patients in the per protocol (PP) set. H. pylori eradication was confirmed in 29 patients, representing an eradication rate of 63.0% [95% confidence intervals (CI): 47.6%-76.8%] by intention-to-treat (ITT) analysis and 65.9% [95% CI: 50.1%-79.5%] by PP analysis (Table 1). Patient compliance with the prescribed treatment was excellent. Adverse events were recorded in 8 patients (18.2%; 95% CI: 8.2%-32.7%). Six patients had mild diarrhea or soft stools but went on to complete the study. Two patients developed stomatitis.

Because the numerical results of the UBT are a function of the total urease activity within the stomach, they represent a quantitative index of the density of gastric H. pylori colonization[10]. As a low pretreatment UBT value could be one of the predictive factors for eradication success, the pretreatment UBT value was analyzed. The pretreatment UBT results in the subjects with eradication failure and in those with successful eradication were 32.9 ± 28.8 and 14.8 ± 12.8 (permil, mean ± SD), respectively. The results of the statistical analysis showed that the pretreatment UBT results in the subjects with eradication failure were significantly higher than in the patients with successful eradication ($P = 0.019$, effect size 0.81). We plotted original receiver operator characteristic (ROC) curves for the pretreatment UBT results to establish the appropriate cutoff value. According to the ROC curves, the optimal cutoff value in our population was 28.5.

When patients were assigned to two groups (UBT results ≤ 28.5 permil and > 28.5 permil), the eradication rates were 81.3% (26/32) and 25.0% (3/12), respectively ($P = 0.001$). A low pre-treatment UBT value (≤ 28.5 permil) predicted the success of the eradication therapy with a sensitivity of 89.7%, specificity of 60.0%, positive predictive value of 81.3%, negative predictive value of 75.0% and accuracy of 79.5%.

Currently, a standard third-line therapy still remains to be established. H. pylori isolates after two eradication failures are often resistant to both MNZ and CLR. The alternative candidates for third-line therapy are fluoroquinolones-AMX-PPI, rifabutin-AMX-PPI, and high-dose PPI/AMX therapy[19-21]. Gisbert et al[21] conducted a prospective multicenter study to evaluate the outcomes of treatment with a third-line levofloxacin-based regimen. The patients were treated for 10 d with a regimen consisting of omeprazole, levofloxacin and AMX. The eradication rates as determined by PP and ITT analyses were 66% and 60%, respectively. However, resistance to fluoroquinolones has been shown to be easily acquired, and in countries with a high rate of use of these drugs, the resistance rates are relatively high. González Carro et al[21] evaluated the efficacy of a third-line rifabutin-based triple therapy. The patients were treated with PPI, rifabutin and AMX for 10 d. The eradication rates as determined by PP and ITT analyses were 62.2% and 60.8%, respectively. However, it has been suggested that the use of rifabutin be reserved for the treatment of multidrug-resistant Mycobacterium tuberculosis strains[25].

Our results for the dual therapy with 4 times daily dosing of rabeprazole and AMX for 14 d, which yielded eradication rates in the PP and ITT analyses of 65.9% and 63.0%, were as successful as other empirical third-line therapy regimens. In particular, a low pretreatment UBT result (≤ 28.5 permil) predicted the success of the eradication therapy with a positive predictive value of 81.3%, sensitivity of 89.7% and specificity of 60.0%, so the dual therapy appeared to serve as a promising option for empiric third-line rescue therapy in patients with a low pretreatment UBT value.

We recently reported the resistant rates of H. pylori to AMX. The resistance rates to AMX (MIC ≥ 0.06 µg/mL) in the groups with no history of eradication treatment, a history of one treatment failure, and a history of two treatment failures were 13.6%, 26.5% and 49.5%, respectively. The MICs of AMX increased by 2-fold after each eradication failure[23]. Resistance to AMX in H. pylori was gradually induced after unsuccessful eradication. Because the AMX resistance rate after two treatment failures was relatively high, the eradication rate of the present study was lower than that of previous report by Furuta et al[24]. Therefore, antimicrobial susceptibility testing of H. pylori is desirable before the selection of a suitable third-line therapy, although the culture-based antibiotic susceptibil-

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**Table 1. Demographic characteristics of the patients and the results of eradication therapy**

| Characteristics | Total (n = 46) | Eradication success (n = 29) | Eradication failure (n = 15) | P value |
|----------------|--------------|----------------------------|-----------------------------|---------|
| Age (mean ± SD, yr) | 60.7 ± 12.9 | 59.8 ± 13.4 | 60.8 ± 12.1 | 0.813   |
| Sex (male/female) | 26/20       | 15/14            | 10/5                        | 0.530   |
| Diagnosis (GU/DU/CG) | 23/15/8     | 15/10/4          | 8/3/4                       | 0.450   |
| Pretreatment UBT | 20.4 ± 21.1 | 14.8 ± 12.8 | 32.9 ± 28.8 | 0.019   |
| Eradication rate (ITT) % | 63.0 |                           |                             |         |
| Eradication rate (PP) % | 65.9 |                           |                             |         |

GU: Gastric ulcer; DU: Duodenal ulcer; CG: Chronic gastritis; UBT: Urea breath test; ITT: Intention-to-treat; PP: Per protocol.
ity testing for H. pylori is expensive, time-consuming, and not always available on a routine basis. There are several limitations to our study. First, our eradication study was single armed using the dual therapy, and different doses or superiority over quinolone-based therapy was not evaluated. Second, we did not examine the in vitro susceptibility in patients treated with the dual therapy. Thus, in vitro resistance to AMX was not elucidated. These issues should be re-evaluated in future studies.

Finally, although we did not achieve excellent eradication success, the dual therapy appeared to serve as a promising option for empiric third-line rescue therapy in patients with low pretreatment UBT values. The antimicrobial susceptibility testing of H. pylori is desirable before the selection of a suitable third-line therapy in patients with high pretreatment UBT values.

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