Helicobacter pylori Infection
A Randomized, Controlled Study Comparing 2 Rescue Therapies
After Failure of Standard Triple Therapies

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Abstract: Antibiotic resistance to amoxicillin in second-line eradication therapy for Helicobacter pylori infection is much less frequent than resistance to metronidazole. We conducted a randomized, controlled study to compare the efficacies of standard quadruple rescue therapy and a new therapy with amoxicillin replacing metronidazole for patients failing first-line eradication treatment. We randomly assigned 120 patients who failed H. pylori eradication using a proton pump inhibitor plus clarithromycin and amoxicillin to undergo a 1-week rescue therapy with esomeprazole, bismuth subcitrate, and tetracycline plus either metronidazole (EBTM group, n = 62) or amoxicillin (EBTA group, n = 58). We used follow-up endoscopy 8 weeks after the end of treatment to assess the treatment response. We also examined and analyzed antibiotic resistances and CYP2C19 genotypes.

Intention-to-treat analysis demonstrated that the EBTA group had a significantly lower eradication rate than the EBTM group (62% vs. 81%, respectively, p = 0.02). Per-protocol analysis showed similar results (64% vs. 83%, p = 0.01). However, the EBTA group had less frequency of adverse events than the EBTM group (19% vs. 44%, p < 0.01). Both groups had good drug compliance (both 97%). Antibiotic susceptibility tests showed that the frequency of amoxicillin-resistant strains was much less than that of metronidazole-resistant strains (0% vs. 54%, respectively), and there were no significant differences between H. pylori eradication rates and antibiotic resistances.

In conclusion, EBTA quadruple therapy demonstrated a lower eradication rate than standard EBTM therapy in second-line rescue treatment. The discrepancy between in vitro antibiotic susceptibility and in vivo eradication response is probably due to drug interactions between combined antibiotics or some unknown causes, and should not be neglected in H. pylori therapy.

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Abbreviations: b.d. = twice a day, CI = confidence interval, EBTA = esomeprazole, bismuth subcitrate, tetracycline plus amoxicillin, EBTM = esomeprazole, bismuth subcitrate, tetracycline plus metronidazole, hetEM = heterogeneous extensive metabolizer, homEM = homogeneous extensive metabolizer, ITT = intention-to-treat, PM = poor metabolizer, PP = per-protocol, PPI = proton pump inhibitor, q.d.s. = 4 times a day.

INTRODUCTION

Helicobacter pylori (H. pylori) infection plays an important role in the development of chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.2,13,23 Failure rates of standard first-line, proton pump inhibitor (PPI)-based triple therapies range from 5% to 35%.7,9,25 The main reasons for eradication failure are resistant bacteria, poor patient compliance, rapid metabolism of PPI, and a high bacterial load.7,11

When administering a second-line treatment for H. pylori infection, it is important to choose adequate antibiotics that do not face resistance problems.17 The Maastricht III Consensus Report16 recommended a 1-week quadruple regimen comprising PPI, bismuth, metronidazole, and tetracycline as second-line therapy. However, accumulating data show that this rescue regimen fails in 5%–63% of patients.1,3,24 Therefore, a considerable proportion of patients with potentially curable diseases remain at risk of developing complications of peptic ulcers, gastric adenocarcinomas, and lymphomas after both first- and second-line treatments.

Our 2009 study15 revealed the following rates of antibiotic resistance in H. pylori strains with failure of first-line therapy: metronidazole (57%), clarithromycin (59%), amoxicillin (6%), tetracycline (0%), and levofloxacin (21%). This finding suggests that tetracycline, amoxicillin, and levofloxacin are better candidates for antibiotic use than metronidazole in the second-line treatment of H. pylori infection. It is worth noting that tetracycline and amoxicillin have lower drug resistance rates than levofloxacin in rescue therapy, and both are much cheaper than levofloxacin. However, second-line rescue therapy using the combination of tetracycline and amoxicillin has rarely been reported.

We therefore conducted the current multicenter, randomized, controlled study to compare the efficacies of standard quadruple rescue therapy and a new quadruple therapy consisting of tetracycline and amoxicillin in salvage treatment for H. pylori infection. Additionally, we investigated the impact of antibiotic resistance and polymorphism of CYP2C19 on second-line therapy.

PATIENTS AND METHODS

Patients

One hundred twenty consecutive H. pylori-infected adult patients (aged ≥18 years) with persistent H. pylori infection...
following standard first-line triple therapy (PPI b.d., clarithromycin 500 mg b.d., amoxicillin 1 g b.d.) were recruited for this study and gave informed consent. The presence of *H. pylori* after a previous eradication therapy was defined as 1) positive results of both rapid urease test and histology, 2) a positive culture result, or 3) a positive result of $^{13}$C urea breath test. Criteria for exclusion were a) ingestion of antibiotics, bismuth, or *H. pylori* within 2 weeks before our investigation, b) an allergic history to the medications used, c) previous gastric surgery, d) the coexistence of serious concomitant illness (for example, decompensated liver cirrhosis and uremia), and e) pregnancy.

**Methods**

Using a computer-generated number sequence, the eligible patients were randomized to either EBTA (esomeprazole 40 mg b.d., bismuth subcitrate 120 mg q.d.s., tetracycline 500 mg q.d.s., and amoxicillin 500 mg q.d.s.) or EBTM (esomeprazole 40 mg b.d., bismuth subcitrate 120 mg q.d.s., tetracycline 500 mg q.d.s., metronidazole 250 mg q.d.s.) therapy. All drugs were taken 1 hour before meals or night sleep, and administered for 7 days. Patients were asked to return at the second week to assess drug compliance and adverse events. Patients with peptic ulcers in initial endoscopy received an additional 4 weeks of monotherapy with esomeprazole 40 mg orally once daily, while patients with gastritis had only 3 weeks of antacids following eradication therapy. To assess eradication efficacy, repeated endoscopy with rapid urease test, histologic examination, and culture were performed at 8 weeks after the end of anti-*H. pylori* therapy. If patients refused a follow-up endoscopy, $^{13}$C urea breath tests were conducted to assess *H. pylori* status. Eradication was defined as 1) negative results of all the rapid urease test, histology, and culture, or 2) a negative result of urea breath test. The study was approved by the Medical Committee of the Kaohsiung Medical University Hospital.

**Questionnaire**

We obtained a complete medical history and demographic data from each patient, including age; sex; medical history; history of smoking; and alcohol, coffee, and tea consumption. Adverse events were prospectively evaluated. We assessed adverse events according to a 4-point scale system: none; mild (discomfort annoying but not interfering with daily life); moderate (discomfort sufficient to interfere with daily life); and severe (discomfort resulting in discontinuation of eradication therapy). Skin rash was evaluated using toxicity criteria: none; mild (transient flushing or macular rash); moderate (urticaria or fever ≥38°C); and severe (exfoliative or ulcerative dermatitis). Compliance was checked by counting unused medication at the completion of treatment. Poor compliance was defined as taking <70% of the total medication.

**Rapid Urease Test**

The rapid urease test was performed according to our previous studies. A biopsy specimen taken from the antrum was placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8) to which 2 drops of 1% phenol red solution were added, and was incubated at 37°C for up to 24 hours. If the yellowish color around the area of inserted specimen changed to bright pink within the 24-hour limit, the urease test was considered positive. In our laboratory, the sensitivity and specificity of rapid urease test are 96% and 91%, respectively.

**Histologic Examination**

Two biopsy specimens were taken from the lesser curvature sites of the antrum and the corpus, respectively. They were fixed in 10% buffered formalin, embedded in paraffin, and sectioned.

The sections, 4-μm thick, were stained with a hematoxylin and eosin stain and a modified Giemsa stain to observe the presence of curved rod shape bacteria on the mucosal surface. *H. pylori* specimens were assessed by a histopathologist (HH Tseng), who was blinded to patient status and the results of other laboratory tests.

**Urea Breath Test**

The urea breath test was performed according to our previous studies. The cutoff value was set at 4.8% of $^{13}$CO$_2$. Staff members blind to the *H. pylori* status performed the tests.

**Culture and Antimicrobial Resistance**

One antral gastric biopsy specimen was obtained for isolation of *H. pylori*, using previously described culture methods. All stock cultures were maintained at −80°C in Brucella broth (Difco, Detroit, MI) supplemented with 20% glycerol (Sigma Chemical Co., St. Louis, MO). The organisms were identified as *H. pylori* by Gram staining; colony morphology; and positive oxidase, catalase, and urease reactions. As previously described in more detail, the antibiotic susceptibility was tested by E test (AB Biodisk, Solna, Sweden). *H. pylori* strains with a minimum inhibitory concentration (MIC) value ≥8 μg/mL, ≥4 μg/mL, and >0.5 μg/mL were considered to be resistant to metronidazole, tetracycline, and amoxicillin, respectively.

**Genotyping of CYP2C19**

Blood sampling for genotyping of CYP2C19 was carried out before endoscopy for those subjects who gave informed consent for genetic study. The CYP2C19 genotype was determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotypes were classified into 3 groups: homogeneous extensive metabolizer (homEM; CYP2C19*1/CYP2C19*1); heterogeneous extensive metabolizer (hetEM; CYP2C19*1/CYP2C19*2 and CYP2C19*1/CYP2C19*3); and poor metabolizer (PM; CYP2C19*2/CYP2C19*2, CYP2C19*2/CYP2C19*3, and CYP2C19*3/CYP2C19*3).

**Statistical Analysis**

The primary outcome variables were the rates of eradication, adverse events, and compliance. Chi-square test with or without Yates correction for continuity and the Fisher exact test were used when appropriate to compare the major outcomes between groups using the SPSS program (v. 10.1, Chicago, IL). A p value less than 0.05 was considered statistically significant. The sample size was 61 subjects per group, with a power of 0.80 and a significance level of 0.05 (alpha = 0.05, 2-sided). The sample size was estimated in order to detect a difference of 10% in the eradication rate between the EBTA and the EBTM therapy (assumed eradication rate of 77%).

Eradication rates were evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis includes all randomized patients who had taken at least 1 dose of study medication. Patients who were noncompliant or lost to follow-up were included for ITT analysis. Patients who had unknown final *H. pylori* status due to loss of follow-up were considered treatment failures in ITT analysis. The PP analysis excluded the patients with unknown *H. pylori* status following therapy and those with poor compliance.

To determine the independent factors affecting the treatment response, we analyzed 14 host and bacterial parameters by univariate analysis. These variables include the following: age (<60 or ≥60 yr), sex, history of current smoking (<1 pack/week or ≥1 pack/week), history of current alcohol consumption (<80 g/d or ≥80 g/d), ingestion of coffee (<1 cup/d
or \( \geq 1 \) cup/d), ingestion of tea (<1 cup/d or \( \geq 1 \) cup/d), coexistence of a systemic disease (yes or no), previous history of peptic ulcer disease (yes or no), endoscopic appearance (ulcer or gastritis), CYP2C19 genotype (homEM, hetEM, or PM), drug compliance (good or poor), and antibiotic susceptibility. Those variables found to be significant by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify independent factors for eradication outcome.

**RESULTS**

Characteristics of the Study Groups

A total of 120 *H. pylori*-infected patients were randomly assigned to either EBTA (n = 58) or EBTM (n = 62) therapies. The subjects were all included in the ITT analysis for *H. pylori* eradication. Data regarding the clinical characteristics of patients upon entry are summarized in Table 1. The 2 groups had comparable age; sex; history of smoking; alcohol, coffee, and tea consumption; and endoscopic findings. Additionally, there were no differences between the EBTA and EBTM groups, respectively, in antibiotic resistance for tetracycline (4% vs. 0%), amoxicillin (0% vs. 0%), and metronidazole (56% vs. 50%). Figure 1 summarizes the patient disposition. Among the subjects, 4 with poor compliance and 2 lost to follow-up were excluded from PP analysis for *H. pylori* eradication.

Eradication of *H. pylori*

Table 2 lists the eradication rates of the EBTA and EBTM groups. The ITT analysis demonstrated a significantly lower eradication rate for the EBTA group (62%; 95% confidence interval [CI], 50%–75%) than for the EBTM group (81%; 95% CI, 71%–91%) (difference, 19%; 95% CI, 3%–32%; \( p = 0.02 \)). According to the PP analysis, *H. pylori* infection was eradicated in 64% (35/55) of the EBTA group (95% CI, 52%–76%) and 83% (49/59) of the EBTM group (95% CI, 74%–92%). By PP analysis, the eradication rate in the EBTA group was also lower than in the EBTM group (difference, 19%; 95% CI, 4%–35%; \( p = 0.01 \)).

Adverse Events and Compliances

All patients were included in the ITT analysis for adverse events and compliances. In total, 19% of the EBTA group and 44% of the EBTM group reported at least 1 adverse event during

| TABLE 1. Demographic Data and Antibiotic Resistance of 2 Patient Groups |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Characteristic              | EBTA Group (n = 58) | EBTM Group (n = 62) | \( p \) |
| Age, yr (mean \( \pm SD \)) | 54.3:11.0 | 53.6:11.7 | 0.75 |
| Sex (M/F)                   | 30/28 | 30/32 | 0.72 |
| Smoking                     | 9 (16%) | 8 (13%) | 0.68 |
| Alcohol consumption         | 3 (5%) | 5 (8%) | 0.72 |
| Ingestion of coffee         | 15 (26%) | 9 (15%) | 0.12 |
| Ingestion of tea            | 21 (36%) | 20 (32%) | 0.65 |
| NSAID user                  | 7 (12%) | 5 (8%) | 0.47 |
| Underlying diseases         | 19 (33%) | 19 (31%) | 0.80 |
| Endoscopic findings         | 0.16 |
| Gastritis                   | 34 (63%) | 27 (47%) | 0.98 |
| Gastric ulcer               | 8 (15%) | 9 (15%) | 1.00 |
| Duodenal ulcer              | 12 (22%) | 22 (38%) | 0.18 |
| CYP2C19 genotype            | 0.43 |
| HomEM                       | 24 (50%) | 18 (42%) | 0.32 |
| HetEM                       | 21 (44%) | 19 (44%) | 0.98 |
| PM                          | 3 (6%) | 6 (14%) | 0.66 |
| Antibiotic sensitivity*     | 0.83 |
| Tetracycline                | 24/1 | 30/0 | 0.46 |
| Amoxicillin                 | 25/0 | 30/0 | 0.46 |
| Metronidazole               | 11/14 | 15/15 | 0.66 |

*Abbreviations: NSAID = nonsteroidal antiinflammatory drug, SD = standard deviation.

*Fifty-two *H. pylori* stains were available.

| TABLE 2. Major Outcomes of EBTA and EBTM Quadruple Rescue Therapy |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Outcome                     | EBTA Group (n = 58) | EBTM Group (n = 62) | \( p \) |
| Intention-to-treat analysis  | 62% (36/58) | 81% (50/62) | 0.02 |
| Per-protocol analysis       | 64% (35/55) | 83% (49/59) | 0.01 |
| Adverse events              | 19% (11/58) | 44% (27/62) | <0.01 |
| Compliance                  | 97% (56/58) | 97% (60/62) | 1.00 |

\( ^{*} \) Fifty-two *H. pylori* stains were available.
eradication therapy (Table 2). The EBTA group had less frequency of adverse events than the EBTM group (p = 0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5% vs. 16%, respectively; Table 3). Two patients in the EBTA group stopped the anti- H. pylori medication because of abdominal cramping pain (n = 1) and nausea (n = 1). In the EBTM group, no patients discontinued treatment because of adverse effects.

All patients but 4 (2 in the EBTA group and 2 in the EBTM group) took more than 70% of the assigned tablets. Both groups displayed similar compliance rates (both 97%).

**Antibiotic Resistance**

H. pylori strains were isolated from 55 (81%) of the 68 enrolled patients who underwent endoscopy with bacterial culture to check H. pylori status on enrollment. Tetracycline- and metronidazole-resistant strains were found in 2% (1/55) and 53% (29/55) of the patients, respectively. No strains developed resistance to amoxicillin.

In the EBTA group, the H. pylori eradication rate for the tetracycline-susceptible strains was 67% by ITT analysis and 68% by PP analysis. The only 1 strain with tetracycline resistance was not eradicated by EBTA therapy (Table 4). All the strains in the subgroup were susceptible to amoxicillin.

**TABLE 3. Adverse Events of EBTA and EBTM Quadruple Rescue Therapy**

| Adverse Event       | EBTA Group* (n = 58) | EBTM Group* (n = 62) | P   |
|---------------------|----------------------|----------------------|-----|
| Abdominal pain      | 2 (1/0/1)            | 4 (3/1/0)            | 0.41|
| Constipation        | 1 (1/0/0)            | 0 (0/0/0)            | 0.30|
| Diarrhea            | 0 (0/0/0)            | 2 (1/1/0)            | 0.39|
| Dizziness           | 3 (1/2/0)            | 8 (5/3/0)            | 0.29|
| Taste perversian    | 3 (2/1/0)            | 3 (3/0/0)            | 0.55|
| Headache            | 1 (1/0/0)            | 7 (3/4/0)            | 0.09|
| Anorexia            | 0 (0/0/0)            | 5 (4/1/0)            | 0.09|
| Nausea              | 3 (2/0/1)            | 10 (5/5/0)           | 0.06|
| Vomiting            | 1 (1/0/0)            | 6 (3/3/0)            | 0.14|
| Skin rash           | 0 (0/0/0)            | 0 (0/0/0)            | —   |
| Fatigue             | 3 (1/2/0)            | 3 (2/1/0)            | 0.72|
| Other               | 2 (0/2/0)            | 2 (2/0/0)            | 0.26|

*Total number of patients (number of patients who suffered mild/moderate/severe adverse event).

**TABLE 4. Antibiotic Resistance and H. pylori Eradication Rate**

| Eradication Rate | ITT Analysis | PP Analysis |
|------------------|--------------|-------------|
|                  | No. (%) P    | No. (%) P   |
| EBTA group       |              |             |
| Tetracycline-resistant | 0.36 | 0.35 |
| (−)              | 16/24 (67)   | 15/22 (68)  | 0.39 |
| (+)              | 0/1 (0)      | 0/1 (0)     | —   |
| Amoxicillin-resistant | —     | —           | —   |
| (−)              | 16/25 (64)   | 15/23 (65)  | —   |
| (+)              | —            | —           | —   |
| EBTM group       |              |             |
| Tetracycline-resistant | —     | —           | —   |
| (−)              | 24/30 (80)   | 24/29 (83)  | —   |
| (+)              | —*           | —*          | —*  |
| Metronidazole-resistant | 0.65 | 0.56 |
| (−)              | 11/15 (73)   | 11/14 (79)  | —   |
| (+)              | 13/15 (87)   | 13/15 (87)  | —   |

*No strain developed resistance to tetracycline.

**TABLE 5. Univariate Analysis for Possible Confounders Influencing the Efficacy of H. pylori Eradication Therapy**

| Parameter                  | No. of Patients | Eradication Rate (%) | P   |
|---------------------------|-----------------|----------------------|-----|
| Age, yr                   |                 |                      | 0.56|
| <60                       | 91 (70)         | (75)                 |     |
| ≥60                       | 29 (75)         | (75)                 |     |
| Sex                       |                 |                      | 1.00|
| Female                    | 60 (72)         | (72)                 |     |
| Male                      | 60 (72)         | (72)                 |     |
| Smoking                   |                 |                      | 0.92|
| (−)                       | 103 (72)        | (72)                 |     |
| (+)                       | 8 (75)          | (75)                 |     |
| Alcohol consumption       |                 |                      | 1.00|
| (−)                       | 112 (71)        | (71)                 |     |
| (+)                       | 8 (75)          | (75)                 |     |
| Ingestion of coffee       |                 |                      | 0.92|
| (−)                       | 96 (72)         | (72)                 |     |
| (+)                       | 24 (71)         | (71)                 |     |
| Ingestion of tea          |                 |                      | 0.56|
| (−)                       | 79 (73)         | (73)                 |     |
| (+)                       | 41 (68)         | (68)                 |     |
| NSAID user                |                 |                      | 0.28|
| (−)                       | 108 (73)        | (73)                 |     |
| (+)                       | 12 (58)         | (58)                 |     |
| Underlying diseases       |                 |                      | 0.44|
| (−)                       | 82 (70)         | (70)                 |     |
| (+)                       | 38 (76)         | (76)                 |     |
| Presence of ulcer         |                 |                      | 0.27|
| (−)                       | 61 (64)         | (64)                 |     |
| (+)                       | 51 (60)         | (60)                 |     |
| CYP2C19 genotype          |                 |                      | 0.76|
| HomEM                     | 42 (67)         | (67)                 |     |
| HetEM                     | 40 (65)         | (65)                 |     |
| PM                        | 9 (78)          | (78)                 |     |
| Compliance                |                 |                      | 0.32|
| Good                      | 116 (72)        | (72)                 |     |
| Poor                      | 4 (50)          | (50)                 |     |
| Tetracycline resistance   |                 |                      | 0.27|
| Susceptible               | 54 (74)         | (74)                 |     |
| Resistant                 | 1 (0)           | (0)                  |     |
| Metronidazole resistance  |                 |                      | 0.96|
| Susceptible               | 26 (73)         | (73)                 |     |
| Resistant                 | 29 (72)         | (72)                 |     |
| Amoxicillin resistance    |                 |                      |     |
| Susceptible               | 55 (73)         | (73)                 |     |
| Resistant                 | —               | —                    | —   |
In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80% and 83% by ITT and PP analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either ITT or PP analyses (Table 4).

Confounders Influencing Efficacy of Anti-\(H.\) pylori Therapy

Table 5 lists the relationships between the 14 possible confounding factors and the efficacy of eradication therapy. None of the factors, including age, sex, smoking, coffee or tea consumption, coexistence of an underlying disease, previous history of ulcer, CYP2C19 genotype, and antibiotic resistance to tetracycline or metronidazole, significantly influenced the eradication efficacy.

DISCUSSION

In the current study, we conducted a head-to-head, randomized, controlled trial to assess the efficacies of EBTA and EBTM therapies for \(H.\) pylori infection after the failure of standard triple therapies. The data clearly demonstrated that the eradication rate of EBTM therapy was markedly higher than that of EBTA therapy, whether using ITT (81% vs. 62%) or PP analysis (83% vs. 64%).

The rate of antibiotic resistance to metronidazole in the \(H.\) pylori strains isolated from patients failing first-line therapy in the current study was 53%. There were no amoxicillin-resistant strains. Most guidelines recommend that rescue therapy should be based on antimicrobial susceptibility, especially in third-line rescue therapy. Theoretically, amoxicillin is a better choice of antibiotic than metronidazole, according to the data of drug sensitivity tests in this study. However, our data indicated that EBTA therapy had a lower eradication rate than EBTM therapy. The finding was comparable with results of a previous study, in which the substitution of amoxicillin for metronidazole in the bismuth/tetracycline/metronidazole triple therapy markedly reduced cure rate in first-line therapy.

The rationale for the discrepancies between in vitro antibiotic resistance and in vivo eradication rate is unclear. Nonetheless, synergy between tetracycline and metronidazole as well as its hydroxymetabolites for \(H.\) pylori eradication has been observed in vitro. On the other hand, Sorice et al have proposed that bacteriostatic drugs like tetracycline may interfere with the bactericidal action of penicillin. The bactericidal action of penicillin is to inhibit cell wall formation and depends on how fast the bacteria are multiplying. Bacteriostatic antibiotics, such as tetracycline, may reduce the effect of penicillin by inhibiting cellular protein synthesis required for cell division. Therefore, the poor eradication efficacy of the EBTA group may result from the drug interaction between tetracycline and amoxicillin. Aforementioned findings suggest that drug interactions between combined antibiotics in rescue therapies should not be overlooked in \(H.\) pylori eradication therapy, although antimicrobial susceptibility is crucial for the choice of antibiotics.

In the current study, up to 44% of those treated with EBTM reported at least 1 adverse event during eradication therapy. However, none discontinued treatment owing to adverse effects. The rate of adverse events in the EBTA group was significantly lower than that in the EBTM group; only 19% of the EBTA group experienced adverse events. It is worth noting that the EBTM group had a higher frequency of nausea than the EBTA group (16% vs. 5%). Nonetheless, EBTA and EBTM rescue regimens exhibited comparable compliance (both 97%).

PPIs have 2 potential mechanisms of action in the treatment of \(H.\) pylori. They possess anti-\(H.\) pylori activity, and, by reducing gastric acid secretion, they also increase the bioavailability and activity of some antibiotics. Most PPIs are, to a large extent, metabolized in the liver by cytochrome P450 isozyme CYP2C19. A polymorphism of the corresponding gene allows patients to be classified as homEMs, hetEMs, and PMs. Rapid metabolism of PPI may have a negative effect on \(H.\) pylori eradication in homEMs. However, there were no significant differences in eradication rates among the 3 groups of metabolizers in the current study. In this study, multivariate analysis disclosed that the type of regimen was the only independent factor predictive of treatment outcome. The other factors including age, sex, the presence of peptic ulcer, and lifestyles did not affect the eradication efficacy.

In conclusion, in the current study we found that patients with EBTA therapy exhibited fewer adverse effects than those with EBTM therapy in second-line rescue treatment. However, EBTM therapy had a lower eradication rate than EBTM therapy. The drug interactions between combined antibiotics may account for the discrepancies between in vitro antibiotic resistance and in vivo eradication rate, and should not be neglected in \(H.\) pylori rescue therapy.

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