Levofloxacin-containing Second-line Anti-*Helicobacter pylori* Eradication in Taiwanese Real-world Practice

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Background: Quinolone-containing triple therapy is recommended as an option for non-bismuth containing second-line *Helicobacter pylori* eradication. Current available Taiwanese reports in the literature used 7-day quinolone-containing triple therapy. As a result, some physicians still prescribe 7-day regimens in real-world practice in Taiwan. This study aimed to further assess the appropriateness of 7-day levofloxacin-containing triple therapy as second-line therapy.

Methods: We enrolled 61 patients who failed *H. pylori* eradication using the standard triple therapy for 7 days and were prescribed levofloxacin-containing second-line triple therapy (levofloxacin 500 mg once daily, amoxicillin 1 g twice daily, and esomeprazole 40 mg twice daily). Routine follow-up with either endoscopy or urea breath test was done 8 weeks later to assess treatment response.

Results: The eradication rates were 78.7% in the intention-to-treat analysis and 81% in the per-protocol analysis. The incidence of adverse events was 6.6%. Drug compliance was 95.1%. Antibiotic resistance showed the following results: Amoxicillin (0%), levofloxacin (23.5%), clarythromycin (35.3%), metronidazole (17.6%), and tetracycline (0%).

Conclusion: The 7-day levofloxacin-containing triple therapy provides an unacceptable per-protocol report card as the second-line treatment for anti-*H. pylori* eradication in Taiwan and should be modified by either extending the duration to 10-14 days or seeking other regimens.
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Key words: 7-day levofloxacin-containing triple therapy, fluoroquinolone, second-line anti-*Helicobacter pylori* therapy

At a Glance Commentary

Scientific background of the subject

Current available Taiwanese reports in the literature used 7-day quinolone-containing triple therapy as an option for non-bismuth containing second-line *Helicobacter pylori* eradication. As a result, some physicians still prescribe 7-day regimens in real-world practice in Taiwan.

What this study adds to the field

This study provides an important message that the 7-day levofloxacin-containing triple therapy cannot attain an acceptable per-protocol report card as the second-line treatment for anti-*H. pylori* eradication in Taiwan and should be modified by either extending the duration to 10-14 days or seeking other regimens.

The most widely used second-line therapy for *Helicobacter pylori* eradication is quadruple therapy, consisting of a proton pump inhibitor (PPI), a bismuth salt, metronidazole, and tetracycline, as recommended by the Maastricht 3-2005 and second Asian Pacific Consensus Report.[1,2] However, bismuth salts are not available worldwide anymore. Alternative second-line therapies with a good treatment report card are still in demand. Antibiotic resistance is one of the important factors in patients' non-responsiveness to initial treatment.[3] Usually, it is not suggested to repeat the same regimens when considering a second-line treatment for *H. pylori*.[4]

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Fluoroquinolone-containing second-line therapy has emerged to be an encouraging strategy for eradication failures owing to the remarkable *in vitro* activity against *H. pylori*.[5-9] Besides, levofloxacin-containing triple therapy has the advantage of being good orally absorptive and well tolerated antimicrobial drugs. Moreover, the synergistic effect of quinolone and PPIs on the strains of *H. pylori* enhanced this effect.[6,10] Unfortunately, the existing Taiwanese reports on fluoroquinolone-containing second-line therapy have mentioned unacceptable eradication rates of less than 80%.[11-13] The main drawback in these reports could be the short treatment duration with only a 7-day course.[11-15] Many physicians, especially local medical doctors, still prescribe 7-day regimens. We, therefore, conducted this retrospective study to determine the appropriateness of 7-day levofloxacin/amoxicillin/PPI regimen as second-line therapy.

METHODS

Patients and study design

Sixty-one consecutive *H. pylori*-infected outpatients of at least 18 years of age with endoscopically proven peptic ulcer diseases or gastritis and who failed first-line eradication therapies with standard triple regimens (PPI twice daily, 500 mg of clarithromycin twice daily, and 1 g of amoxicillin twice daily) were enrolled. Criteria for exclusion included (a) ingestion of antibiotics, bismuth, or PPIs within 4 weeks before; (b) use of nonsteroidal anti-inflammatory drugs within 4 weeks before; (c) patients with allergic history to the medications used; (d) patients with previous gastric surgery; (e) coexistence of serious concomitant illness (e.g., decompensated liver cirrhosis, uremia); (f) pregnant women; and (g) incomplete chart recordings.

Treatment allocation

These *H. pylori*-infected outpatients who failed first-line eradication therapies were treated with levofloxacin-containing triple therapy (40 mg esomeprazole twice daily, 1 g of amoxicillin twice daily, and 500 mg of levofloxacin once daily) for 7 days. In all these patients who received anti-*H. pylori* eradication treatment, the patients were asked to return in the 2nd week to assess drug compliance and adverse events, as per our policy. Patients with peptic ulcers in initial endoscopy received an additional 3 weeks of esomeprazole 40 mg orally once daily, while patients with gastritis only took 3 weeks of antacid following eradication therapy. To assess eradication efficacy, repeated endoscopy with rapid urease test and histological examination was performed at 8 weeks after the completion of anti-*H. pylori* therapy. For patients who refused to undergo follow-up endoscopy, urea breath test was used to confirm the *H. pylori* status. The absence of *H. pylori* after a previous eradication therapy was defined as (1) negative results of both rapid urease test and histology or (2) a negative result of urea breath test at 8 weeks. A double-check of urea breath test at 16 weeks was performed for all the participants whose infection were eradicated to avoid possible bias. The technicians who performed the *H. pylori* tests (rapid urease test and urea breath test) or filled in the questionnaires, as well as the pathologists were blinded to the eradication regimens that the patients received. This study was approved by both the Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital (IRB101-3169B).

Follow-up for adverse events and compliance

Since only those patients who were registered as receiving anti-*H. pylori* treatments were enrolled, a complete medical history and demographic data of each patient was available, including age, sex, and medical history, history of smoking, alcohol, and coffee or tea consumption. Smoking was defined as using one pack or more of cigarettes per week. Adverse events such as abdominal pain, diarrhea, constipation, dizziness, taste perversion, headache, anorexia, nausea, vomiting, and skin rash that interfered with patient's quality of life were recorded. Poor compliance was defined as taking less than 80% of the total medication.[16]

Outcomes

The primary endpoint of our study was successful eradication of *H. pylori*. Additional analyses were conducted on the adverse events during therapies.

Diagnosis of *H. pylori* infection

Rapid urease test

One gastric antrum specimen and one corpus biopsy specimen each were collected during endoscopy for testing by using a commercial rapid urease test (Pronto Dry; Medical Instrument Corp., Solothurn, Switzerland).[17] The results of the rapid urease test were interpreted as positive if the color of the gel turned pink or red 1 h after examination at room temperature.

Urea breath test

The urea breath test was performed at 8 weeks in accordance with our previous studies.[18] The cut-off value was set at 4.8% of δ13CO2. Staffs who performed the tests were blinded to the *H. pylori* status.

Culture and antimicrobial resistance

Two antral gastric and corpus biopsy specimens each were obtained for isolation of *H. pylori*. *H. pylori* culture was obtained by rubbing the specimens on the surface of

a Campy-BAP agar plate [Brucella agar (Difco, Sparks, MD, USA) + IsoVitalex (Gibco, Grand Island, NY, USA) +10% whole sheep blood]. Then, they were incubated at 37 C under microaerobic conditions (5% O_2, 10% CO_2, and 85% N_2) for 4-5 days. The results were considered positive if one or more colonies of gram-negative bacilli with positive oxidase, catalase, and urease tests were found. The *H. pylori* strains were tested for tetracycline, metronidazole, and clarithromycin susceptibility using the E-test (AB Biodisk, Solna, Sweden). *H. pylori* strains with a minimal inhibitory concentration (MIC) values >4 μg/ml, 8 μg/ml, and >1 μg/ml were considered to be resistant to tetracycline, metronidazole, and clarithromycin, respectively.

Statistical analysis

Chi-square test with or without Yates correction for continuity and Fisher's exact test were used when appropriate to compare the treatment outcome and host factors using SPSS program (version 10.1, Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study groups

A total of 61 *H. pylori*-infected patients who failed first-line therapy were enrolled in our study. The subjects were all included in the intention-to-treat (ITT) analysis for *H. pylori* eradication. The clinical characteristics of patients at entry are summarized in Table 1. Among the 61 subjects, three patients discontinued medication because of poor compliance to adverse events, and eventually, 58 patients were excluded from per-protocol (PP) analysis for *H. pylori* eradication and they finished all the medications. The eradication rates were 78.7% in the ITT analysis and 81% in the PP analysis [Table 2].

Adverse events, complications, and antibiotic resistance

Interviews regarding the adverse events were carried out in all patients. The incidence of adverse events was 6.6% and the drug compliance was 95.1%. Dizziness and headache were the most common adverse events [Table 3].

H. pylori strains were isolated from 17 (73.9%) of the 23 enrolled patients who had undergone endoscopy and bacterial culture in order to check *H. pylori* status on enrollment. Antibiotic resistance results were amoxicillin (0%), levofloxacin (23.5%), clarythromycin (35.3%), metronidazole (17.6%), and tetracycline (0%).

Univariate analysis showed that none of the clinical factors influenced the efficacy of *H. pylori* eradication. Only 33% (1/3) of patients with poor compliance showed eradication, while 81% (47/58) with good compliance showed successful eradication [Table 4].

Table 1: Demographic data and endoscopic appearance of the patients (*N*=61)

Characteristics	7-day treatment courses
Age (years) (mean±SD)	58.6±14.3
Gender (male/female)	24/37
Smoking	5 (8.2%)
Alcohol consumption	3 (4.9%)
Previous history of peptic ulcer	44 (72.1%)
Endoscopic findings	
Gastric ulcer	17 (27.9%)
Duodenal ulcer	16 (26.2%)
Gastric and duodenal ulcer	11 (18.0%)
Unspecified (including peptic ulcer)	17 (27.9%)
Antibiotic sensitivity (susceptible/resistant)	
Amoxicillin	17/0 (0%)
Levofloxacin	13/4 (23.5%)
Clarythromycin	11/6 (35.3%)
Metronidazole	14/3 (17.6%)
Tetracycline	17/0 (0%)

Table 2: The major outcomes of *H. pylori* eradication among the patients

Eradication rate (*N*=61)	
Intention-to-treat	78.7% (48/61)
Per-protocol	81.0% (47/58)
Adverse events	6.6% (4/61)
Compliance	95.1% (58/61)

Table 3: Adverse events among the patients (*N*=61)

Adverse events	Case number and percentage (*n*/%)
Abdominal pain	1 (1.64)
Diarrhea	0 (0)
Constipation	0 (0)
Dizziness/headache	3 (4.91)
Taste pervasion	0 (0)
Nausea/vomiting	1 (1.64)
Skin rash	0 (0)

DISCUSSION

The American College of Gastroenterology Guidelines on the Management of *H. pylori* Infection[19] recommend that rescue therapy should consist of a PPI, quinolone, and amoxicillin as one of the options for second-line *H. pylori* eradication which has not been previously used. There are a handful of studies in the literature on levofloxacin in second-line treatment, comparing a levofloxacin-containing regimen with the guideline-recommended second-line quadruple therapy.[7-9,20,21] Eradication rates of a levofloxa-

Table 4: Univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication

Principal parameter	Case no.	Eradication rate (%)	*P* value
Age			
<60 years	33	84.8 (28)	0.202
60 years	28	71.4 (20)	
Sex			
Female	37	78.4 (29)	0.941
Male	24	79.2 (19)	
Smoking			
(−)	56	78.6 (44)	1.000
(+)	5	80.0 (4)	
Alcohol consumption			
(−)	58	79.3 (46)	0.519
(+)	3	66.7 (2)	
Previous history of peptic ulcer			
(−)	17	64.7 (11)	0.160
(+)	44	84.1 (37)	
Compliance			
Good	58	81.0 (47)	0.112
Poor	3	33.3 (1)	
Amoxicillin resistance			
Susceptible	17	64.7 (11)	-
Resistant	-	-	
Levofloxacin resistance			
Susceptible	13	69.2 (9)	0.584
Resistant	4	50.0 (2)	

cin-containing regimen with treatment duration of 10 days were higher than those of a 7-day treatment course.[22-24] However, currently available Taiwanese reports in the literature used 7-day quinolone-containing triple therapy. As a result, some physicians still prescribe 7-day regimens in actual clinical practice in Taiwan. The results of current study further emphasized the low ITT and PP results with 7-day quinolone-containing triple therapy.

Levofloxacin is a levorotatory isomer of ofloxacin with known activity against many gram-negative and gram-positive bacteria. The mode of action of levofloxacin is based on the inhibition of bacterial DNA topoisomerase II.[25] The advantages of levofloxacin-containing triple therapy are that there is an *in vivo* synergistic effect of quinolone antimicrobial agents and PPIs on the strains of *H. pylori*,[10] and is simple and well tolerated with a high compliance (95.1%) as shown in the present study. The relatively low incidence of adverse events of levofloxacin-containing triple therapy was the key factor to the good compliance.

Poor compliance could be caused by the side effects of medicines and poor understanding of the relations between bad compliance and the risk of developing resistant strains. One of the reasons for the high compliance of 95.1% observed could be the good patient–health care communication status for these registered patients. By doing so, most of these patients, except three, finished all the medications in the present study. However, there was still 66.7% of patients with poor compliance who failed to eradicate *H. pylori* in the present study.

Antibiotic resistance is one of the important factors for the success of *H. pylori* eradication. Primary resistance to fluoroquinolones is increasing in many parts of the world.[7] The resistance to levofloxacin in a previous Taiwanese report was 21.2%.[11] The increasing use of quinolones in different countries could be the reason for the increase in resistance to these antibiotics. In the present study, the resistance of levofloxacin was still 23.5%. It is important to realize this issue and the use of levofloxacin should be confined to "rescue" therapy to evade increasing *H. pylori* resistance toward such an antibiotic.[7-9] The other important reason for failure in previously mentioned studies could be that the duration of fluoroquinolone-containing therapies was too short. Together, these should explain why the eradication rates of the 7-day levofloxacin-containing triple therapy in Taiwan had dropped below 80%, including the present study, even with an increased dose of 750 mg daily in one study.[15]

Cytochrome P450 2C19 (CYP2C19) polymorphism of PPIs could play a role in affecting the eradication of *H. pylori.* Studies with CYP2C19 slow metabolizers have shown that the combination of a PPI plus amoxicillin (dual therapy) can reliably cure more than 90% of *H. pylori* infections, especially in Asian populations.[26-29]

Generally, clinicians should prescribe therapeutic regimens that have 90% or greater (grade B level) and probably 95% or greater (grade A level) PP eradication rate to meet the existing practice in the field of other common bacterial infectious diseases.[30] It is therefore concluded that 7-day levofloxacin-containing triple therapy provides an unacceptable PP report card as the second-line *H. pylori* eradication treatment in Taiwan and should be modified by either extending the duration to 10-14 days or seeking other regimens.

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