ORIGINAL ARTICLE

Gut and Liver, Vol. 6, No. 4, October 2012, pp. 452-456

Rifaximin Plus Levofloxacin-Based Rescue Regimen for the Eradication of *Helicobacter pylori*

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Background/Aims: This study assessed the efficacy of a rifaximin plus levofloxacin-based rescue regimen in patients that had failed both triple and quadruple standard regimens for the eradication of *Helicobacter pylori*. **Methods:** We treated patients for *H. pylori* between August 2009 and April 2011. The triple regimen consisted of combined treatment with amoxicillin, clarithromycin, and pantoprazole for 1 week. For failed cases, a quadruple regimen of tetracycline, metronidazole, bismuth dicitrate, and lansoprazole for 1 week was administered. The rescue regimen for persistently refractory cases was rifaximin 200 mg t.i.d., levofloxacin 500 mg q.d., and lansoprazole 15 mg b.i.d. for 1 week. **Results:** In total, 482 patients were enrolled in this study. The eradication rates associated with the first and second regimens were 58% and 60%, respectively. Forty-seven out of 58 patients who failed with the second-line regimen received rifaximin plus levofloxacin-based third-line therapy. The eradication rate for the third regimen was 65%. The cumulative eradication rates were 58%, 85%, and 96% for each regimen, respectively. **Conclusions:** A rifaximin plus levofloxacin-based regimen could be an alternative rescue therapy in patients with resistance to both triple and quadruple regimens for the eradication of *H. pylori*. **(Gut Liver 2012;6:452-456)**

Key Words: *Helicobacter pylori*; Eradication; Rifaximin

INTRODUCTION

Chronic *Helicobacter pylori* infection causes distal stomach-predominant atrophic gastritis. It eventually causes many disorders such as peptic ulcer diseases, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.

The survival capability of this organism within the stomach makes it difficult to eradicate and requires multi-drug regimens consisting of two antibiotics and a strong acid suppressant.[1] Several guidelines suggest the use of 7-day triple therapy, comprising a proton pump inhibitor (PPI), clarithromycin and amoxicillin, as the first line therapy, whereas the 7-day quadruple therapy includes bismuth salts, and is indicated for eradication in patients who failed first line therapy.[2-6]

Nowadays, the prevalence of *H. pylori* resistance to antibiotics is increasing, which is the major cause of treatment failure.[7] Standard triple therapy had failed to eradicate *H. pylori* in up to 25% of patients.[2,8] Concomitant and sequential therapy have been attempted to overcome the treatment failure.[9,10]

New antibiotics have also been applied to increase the eradication rate. Rifaximin is a poorly absorbed rifamycin derivative with a broad spectrum of antibacterial activity covering gram-positive and gram-negative organisms, both aerobes and anaerobes, including *H. pylori*.[11-14] Levofloxacin, a synthetic antibiotic of the fluoroquinolone drug class, is also reported to be as effective for *H. pylori* eradication.[15,16]

However, there is no consensus about treatment in patients who have failed to be eradicated of *H. pylori* infection with both first line triple therapy and second line quadruple therapy.

The aim of this study was to assess the efficacy of a rifaximin plus levofloxacin based regimen for the treatment of two consecutive failure cases with first and second eradication regimens.

MATERIALS AND METHODS

1. Patients

We reviewed medical records of patients in need for *H. pylori* eradication because of peptic ulcer disease, early gastric cancer,

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Received on January 4, 2012. Revised on March 5, 2012. Accepted on March 11, 2012.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2012.6.4.452

family history of gastric cancer, and chronic atrophic gastritis with intestinal metaplasia at CHA Bundang Medical Center between August 2009 and April 2011. All patients underwent an esophagogastroduodenoscopy. *H. pylori* infection was confirmed by rapid urease test or histology. Patients who had history of previous eradication therapy were excluded. The Institutional Review Board of CHA Bundang Medical Center permitted this study. A total of 482 patients were finally enrolled.

2. Treatment strategy

First-line *H. pylori* eradication regimen was clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., and pantoprazole 20 mg b.i.d. for 7 days. Second-line regimen for patients who had failed after the first triple regimen was metronidazole 500 mg t.i.d., tripotassium bismuth dicitrate 300 mg (Bi_2O_3 120 mg) b.i.d., tetracycline 500 mg t.i.d., and lansoprazole 15 mg b.i.d. for 7 days. Patients who had failed with second-line quadruple regimen were treated for 7 days with a third-line regimen of rifaximin 200 mg t.i.d., levofloxacin 500 mg q.d., and pantoprazole 20 mg b.i.d. Eradication of *H. pylori* was determined by the urea breath test (UBT) performed 4 weeks after treatment.

3. UBT

The UBT is based on the ability of *H. pylori* to convert urea to ammonia and carbon dioxide. A 100 mg tablet of ^{13}C-urea was ingested and $^{13}CO_2$ was measured in the expiration breath after 20 minutes. A delta ^{13}C-UBT over baseline value higher than 2% was considered positive as active *H. pylori* infection. Patients were asked to avoid acid-lowering medicine or antibiotics for 1 week before UBT.

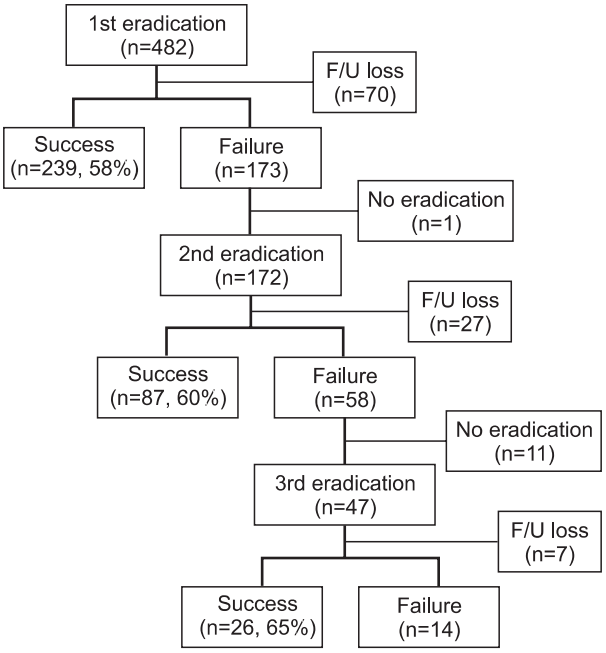

Fig. 1. Enrollment and follow-up (F/U).

4. Adverse effects

During the follow-up visits, presence of drug-related adverse effects such as nausea, vomiting, epigastric discomfort, diarrhea, constipation, bitter taste, and skin rash were recorded.

5. Analysis

Patients who did not perform the urease breath test were grouped as follow-up loss. Any patient who called off further treatment in the group of eradication failure was excluded as dropouts. Per-protocol analysis was used to evaluate the effect of regimens.

RESULTS

1. *H. pylori* eradication rates

A total of 482 patients (mean age, 53±13 years; male:female=2:1) received 7-day triple therapy for *H. pylori* eradication (Fig. 1). Two hundred and thirty-nine (58%) patients succeeded in having *H. pylori* infection eradicated but 173 patients failed. Patients who did not receive UBT after treatments were categorized as follow-up loss groups, and 70 patients did not perform UBT after triple therapy.

One patient did not want second line treatment due to side effects such as nausea and diarrhea. Therefore, 172 patients who failed in triple therapy received the second quadruple therapy. Eighty-seven patients (60%) were eradicated of *H. pylori* but 58 patients failed. Twenty-seven patients were lost in follow-up.

Forty-seven out of the 58 patients received third eradication medicine. Twenty-six (65%) patients achieved success with eradication of *H. pylori* and 14 patients failed to eradicate. Cumulative eradication rates of three consecutive regimens were 58%, 85%, and 96%, respectively (Fig. 2).

2. Adverse effects

Six patients (15%) reported side effects in third-line treat-

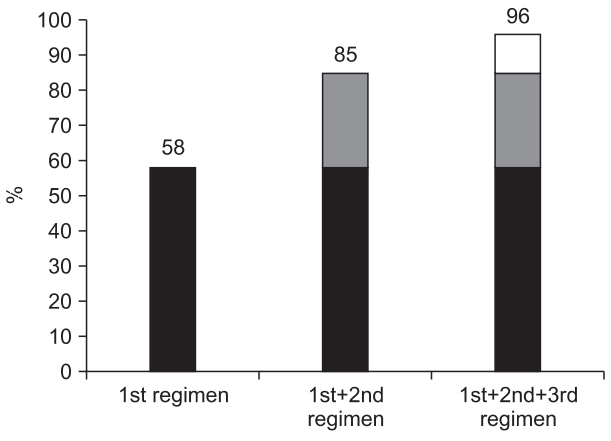

Fig. 2. Cumulative eradication rates of *Helicobacter pylori* (per protocol).

ment: five patients complained of mild epigastric discomfort and one patient reported transient dizziness.

3. Compliance to treatment

Seven of 47 patients who agreed to third line treatment were lost for follow-up UBT, but any drop-out was not reported due to drug intolerance.

DISCUSSION

The prevalence of *H. pylori* infection in Korea is considerably high in adults (59.6%).[17] Patients who need to eradicate *H. pylori* have increased due to the national screening program for early detection of gastric cancer. However, the success rate of eradication is continuously decreasing, which is of great concern.[17] Several factors have been suggested as the reasons behind this failure. Poor compliance and resistance to antibiotics are generally considered to be the main causes.

Resistance of *H. pylori* to metronidazole and clarithromycin is a growing concern. According to a single center study in Korea, the rate of resistance to clarithromycin increased from 16.7% to 38.5% between the year 2007 and 2009 compared with the period between 2003 and 2005.[18] The resistance rate to metronidazole in Korea was 27.1% to 27.5% between 2003 and 2010.[19,20] As resistance to these antibiotics has recently been increasing, the eradication rate has been decreasing even as low as 61% to 76% in primary care settings in Italy[21] and even 47.4% in Turkey.[22] Therefore, more patients are still *H. pylori* positive even after standard triple and quadruple eradication therapy, but we do not have any recommended guideline for third line therapy.

Rifamycin deriatives (like rifampicin, rifabutin, and rifaximin) display antibacterial activity against *H. pylori*.[11,13] Rifabutin is being used increasingly in some rescue therapies after failed first or second eradication therapy. Some studies using rifabutin based regimens reported 60% to 79% eradication rates.[23,24] There are no reported resistant strains of *H. pylori* against rifabutin, which is why it may be effective as a rescue therapy for patients who did not respond to the existing eradication therapy.[12] However, popular use of rifabutin is able to induce serious side effects such as bone marrow suppression and the development of rifampicin-resistant tuberculosis in areas where prevalence of tuberculosis is high.

Rifaximin is one of the new alternative antibiotics. It is a poorly absorbed drug and almost devoid of adverse effects. Bioavailability within the gastrointestinal tract is fairly high and capable of inhibiting the growth of *H. pylori* with intermediate minimum inhibitory concentration (MIC) value, which is between that of amoxicillin and colloidal bismuth subcitrate.[25] MIC value of rifaximin is affected even by lowering the pH from 7.2 to 6, because of its low absorption. A subsequent study showed lack of antagonism towards metronidazole and omeprazole.[26] Eradication rates of *H. pylori* with rifaximin plus clarithromycin and rifaximin plus metronidazole were 73% and 60%, respectively in a single-blind randomized study.[27]

Table 1. Changes in the Eradication Rates of *Helicobacter pylori* with Each Standard Regimen in Korea

	Year		
	1997–2000	2001–2005	2006–2009
Eradication rates with triple regimen[8,30-35]	76.3–95.0	75.0–91.7	75.0–88.9
Eradication rates with quadruple regimen[30,32,34-36]	80.0–91.7	75.0–98.0	75.0–96.0

Data are presented as percentage.

Levofloxacin was recently used to treat *H. pylori* infection both for first- and second-line treatments. Studies using levofloxacin as an alternative to clarithromycin as a triple regimen reported eradication rates of 90% to 92%, which were better than standard quadruple regimens as a second-line option for *H. pylori* eradication.[28-30] However, Korean studies reported much worse eradication results of 69.8% and 53.3% with levofloxacin based first or second line treatment.[31,32] Recent studies showed the possibility of rifaximin plus levofloxacin combination treatment as an alternative regimen of *H. pylori* eradication therapy.[33,34]

The result of first line triple therapy performed in this study was lower than the expected score, being only 58%. This may be due to either higher regional antibiotic resistance rate of *H. pylori* or poor compliance. Based on published eradication rates of *H. pylori* in Korea from 1997 to 2009, the success rates of eradication showed a tendency to decrease (Table 1).[8,35-41] Eradication rates varied according to the places the study was performed, such as city versus country. The eradication rate of quadruple therapy in this study was 60%. It was also lower than that of other studies.[35,37,39-42] The causes of this high failure rate might be due to reduced dose of tetracycline, higher regional rate of antibiotic resistance or short-term treatment period of 1 week.

The Maastricht III Consensus Report recommended rescue treatment should be based on antimicrobial susceptibility.[43] Performing culture has many limitations in practice and we investigated new antibiotics combination as a rescue regimen. In considering multi-drug resistant *H. pylori* shown by consecutive eradication failures, the eradication rate with a rifaximin plus levofloxacin combination regimen of 65% was not so low, and the cumulative cure rate reaching 96% was a worthy result.

As a rescue treatment after failure of standard first and second-line therapy, repeated quadruple therapy for 2 weeks was studied.[44] Eradication rate was 66.7% at intention-to-treatment and 75% at per-protocol analysis. Of the 45 retreated patients, two (4.4%) patients complied poorly with medication. Compared with this study, present study regimen was just 1-week medication and compliance was excellent without severe side effects.

The present study has some limitations besides lack of microbial susceptibility test. We had only one treatment arm without a comparable regimen such as one antibiotic plus PPI regimen and no data with rifaximin plus levofloxacin treatment in *H. pylori* positive naïve patients as a first line regimen.

In summary, results of the present investigation demonstrated an acceptable efficacy and compliance of rifaximin plus levofloxacin based triple eradication regimen in patients who had failed in standard first and second line treatment. Therefore, this combination regimen could be an alternative rescue therapy for the eradication of *H. pylori*.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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