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Rifabutin-based High-dose Proton-pump Inhibitor and Amoxicillin Triple Regimen as the Rescue treatment for *Helicobacter pylori*

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Abstract

Background: Rifabutin has been known to be effective in multidrug-resistant *Helicobacter pylori*-harboring patients undergoing treatment failure for *H. pylori* infection.

Aim: To evaluate the efficacy of 7-day treatment regimen consisting rifabutin daily but increasing the dose of amoxicillin and lansoprazole in patients who have failed first and second eradication and to assess the side effect profiles in South Korea.

Methods: From December 2007 to May 2013, 59 *H. pylori*-infected patients with two previous eradication failures were enrolled for this study prospectively. The eligible patients were randomly assigned to either group A or B. Group A received lansoprazole 30 mg bid, amoxicillin 1.0 g tid and rifabutin 150 mg bid during 7 days, whereas group B received lansoprazole 60 mg bid, amoxicillin 1.0 g tid and rifabutin 150 mg bid during 7 days.

Results: In group A, *H. pylori* eradication was achieved in 25 (78.1%) of the 32 patients in the ITT analysis and in 25 (80.6%) of the 31 patients in the PP analysis. In group B, *H. pylori* eradication was achieved in 26 (96.3%) of the 27 patients in the ITT analysis and in 27 (100%) of the 26 patients in the PP analysis. There was statistically significant difference between the two groups in terms of the eradication rates in PP analysis (p = .047), whereas a marginally statistical significance was found in terms of the eradication rates in ITT analysis (p = .051). Reported side effects were mild, and treatment was well tolerated. No major changes in physical examination or in standard laboratory parameters were observed after treatment.

Conclusions: Rifabutin-based high-dose proton-pump inhibitor (PPI)-combined therapy as empirical rescue treatment is more effective than standard dose PPI-combined rifabutin-based therapy, safe and best tolerable in third-line therapy in the Korean population. The key to successful rescue therapy with rifabutin–amoxicillin–PPI regimen may be to increase doses of PPI.

Helicobacter pylori (*H. pylori*) infection is one of the most prevalent infectious diseases worldwide, which exists in almost 50% of the world's population. *H. pylori* infection plays an important role in gastric adenocarcinoma and the development of chronic gastritis, gastric ulcer, duodenal ulcer, an gastric mucosa-associated lymphoid tissue lymphoma [1,2]. Maastricht III Consensus Report has recommended that proton-pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole treatment for 7–14 days is the first choice for *H. pylori* infection [3]. Although some studies have revealed that the eradication rates of standard triple therapies are around 80% (by per-protocol analysis), most studies have demonstrated the success rate of recommended triple therapies is falling [4–8]. According to recent studies, such eradication rates have plummeted to even 25–60% [9–12].

The main reasons for eradication failure are poor patient compliance, resistant bacteria, low gastric pH,

drug-related side effects, and high bacterial load [4]. In patients who failed initial treatment, a high proportion of *H. pylori* strains developed resistance to metronidazole or clarithromycin. Several salvage therapies of a second-line therapy have been recommended including a quadruple combination of PPI, bismuth, tetracycline, and metronidazole, but they still fail to eradicate the bacterium in 5–43% of the cases with average eradication rate of 76% on the basis of a pooled analysis. Infection harbors antibiotic-resistant strains that are ineradicable after several courses of treatments [13].

Recently, a standard third-line therapy will remain to be established, and European guidelines recommend culture before selection of a third-line treatment based on the microbial sensitivity to the antibiotics. The alternative candidates for third-line therapy are quinolone, tetracycline, rifabutin, and furazolidone; high-dose PPI/amoxicillin therapy is also promising [13,14]. Rifabutin is a spiropiperidyl derivative of rifampin-S, an antitubercular compound and has been shown to exhibit high in vitro activity against *H. pylori,* and no resistant strains have been isolated from patients treated or untreated for *H. pylori* infection [15,16]. Furthermore, rifabutin is chemically stable over a wide pH range, and its antibacterial activity is not affected by the acidic environment of the stomach [17]. Previous clinical trials have suggested that rifabutin may be a promising rescue treatment of *H. pylori* infection, with an eradication rate of around 70% [18,19]. On the other hand, Qasim et al. [20] have achieved only a 38% eradication rate. *H. pylori* eradication rate of rifabutin regimens as third-line treatment was 66%, results being heterogeneous [21].

To improve efficacy, modification in the dosing and duration of regimen were tried. In rescue therapy, high-dose PPI and amoxicillin therapy had advantages. For the rescue therapy, using high-dose PPI and amoxicillin therapy is advantageous, given the fact that this regimen can resolve the problems of clarithromycin and metronidazole resistance and homozygous extensive metabolizers of CYP2C19 gene polymorphisms, which are main reasons for the eradication failure. [21]. The aim of this study was to evaluate the efficacy of 7-day treatment regimen consisting rifabutin 300 mg daily but increasing the dose of amoxicillin to 1 g tid and lansoprazole 30 mg bid or 60 mg bid in patients who have failed second eradication and to assess the side effect profiles.

Methods

Patients and Eradication Therapy

From December 2007 to May 2013, 59 *H. pylori*-infected patients with two previous eradication failures were enrolled for this study prospectively. The study design was based on a single-centered, randomized, open-label, and controlled clinical trial. The study protocol was approved by the Institutional Review Board at Yongin Severance Hospital and confirmed to the ethical guidelines of the Declaration of Helsinki, 1964, as revised in 2004. The requirement for informed consent was waived, and all subjects signed written informed consent. The intended sample of 55 recruited subjects (32 patients for group A and 27 patients for group B) provided a power of approximately 90%, assuming a significance level <.01. The dropout rate was expected to be <10%, based on the documented good tolerability of drugs. All patients received first-line eradication therapies (lansoprazole 30 mg bid, clarithromycin 500 mg bid, amoxicillin 1 g bid) for 7 days and received second-line eradication therapy (lansoprazole 30 mg bid, tripotassium-dicitrato-bismuthate 600 mg bid, metronidazole 500 mg tid, tetracycline 500 mg qid) for 7 days. The eligible patients were randomly assigned to either group A who received lansoprazole 30 mg bid, amoxicillin 1.0 g tid, and rifabutin 150 mg bid for 1 week or group B who received lansoprazole 60 mg bid, amoxicillin 1.0 g tid, and rifabutin 150 mg bid for 7 days. After an overnight fast, endoscopy was performed and endoscopic findings recorded. *H. pylori* infection was defined a positivity according to at least one of the following two tests: a positive rapid urease test (CLO test Delta West, Bently, Australia) using a specimen from antrum or histologic evidence of *H. pylori* in any of two specimen taken from corpus by hematoxylin and eosin stain. The eradication of *H. pylori* was assessed with ^{14}C-urea breath test 4 weeks after the therapy.

Exclusion criteria included the patients with the coexistence of serious concomitant illness 8 (e.g., liver cirrhosis with decompensation, and uremia), pregnant women, allergic history to the medications used and patients with previous gastric surgery antibiotics, bismuth and PPI within the previous 2 weeks and nonsteroidal anti-inflammatory drugs within the previous 4 weeks. Compliance with therapy was defined as intake of 80% more of the prescribed study medication. Intake of study medication and adverse events were interviewed after the end of treatment. In addition, the patients were instructed to contact the study site immediately in case of any severe adverse event.

^{14}C-urea Breath Test

Patients who had not taken antibiotics or antisecretary drugs were fasted for 6 hours before performing the UB t-test (HeliprobeTM; Noster system AB, Stockholm, Sweden). The gelatin capsule containing ^{14}C-urea was

swallowed with water by the patient to avoid contamination with oral bacteria. Breath samples were taken 10–30 minutes after ingestion. Patients were instructed to exhale into the BreathCard™, which was inserted into the Heliprobe™ (Noster system AB, Stockholm, Sweden) instrument. The result was considered $\Delta > 50$ positive is based on clinical trials using the 1μ Curie 14C-UBT.

Statistical Analysis

The analysis was conducted using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, U.S.A). The eradication rates and their 95% confidence intervals (CI) at both intention-to-treat (ITT) and per-protocol (PP) analyses were calculated for each treatment regimen. For all other variables, Fisher's exact test and *t*-test were used as appropriate, and p values $<.05$ were considered significant. The difference between the proportions eradicated was estimated. Before pooling these estimates, a Fisher's exact test was applied to investigate heterogeneity between the differences. This study was approved by Ethics Committee of our Institution (Yongin Severance Hospital, Yonsei University, Republic of Korea).

Results

Baseline Demographic and Clinical Data

From December 2007 to May 2013, a total of 59 patients were enrolled in the study (mean age, 55.3 years, range, 34–74 years). All patients had been previously treated with two courses of eradication therapy. They took as first-line therapy with PPI, clarithromycin, and amoxicillin and as second-line therapy with quadruple therapy consisting of a PPI, a bismuth salt, metronidazole, and tetracycline. Group A had 32 patients with lansoprazole 30 mg bid including rifabutin 150 mg bid daily and amoxicillin 1 g tid for 7 days. Group B had 27 patients with lansoprazole 60 mg bid including rifabutin 150 mg bid (daily) and amoxicillin 1 g tid for 7 days (Fig. 1).

There were 25 males (mean age 58.8 years) and 34 females (mean age 52.9 years). Indications for eradication therapy mainly included peptic ulcer disease (32/58) and nonulcer disease (27/58). A history of smoking and alcohol use was present in 9 (15.5%) and 12 (20.7%) patients, respectively. Demographic and clinical data are summarized in Table 1. There were no statistically significant differences between the two groups in terms of demographic characteristics, history of smoking and alcohol, and indication for eradication therapy. One patient in group A was not enrolled for PP analysis due to adverse events such as abdominal pain and red-colored urine and one patient in group B due to loss of follow-up; 56 patients were fully compliant with the treatment taking more than 80% of the prescribed tablets. In group A, *H. pylori* eradication was achieved in 25 (78.1%) of the 32 patients in the ITT analysis and in 25 (80.6%) of the 31 patients in the PP analysis. In group B, *H. pylori* eradication was achieved in 26 (96.3%) of the 27 patients in the ITT analysis and

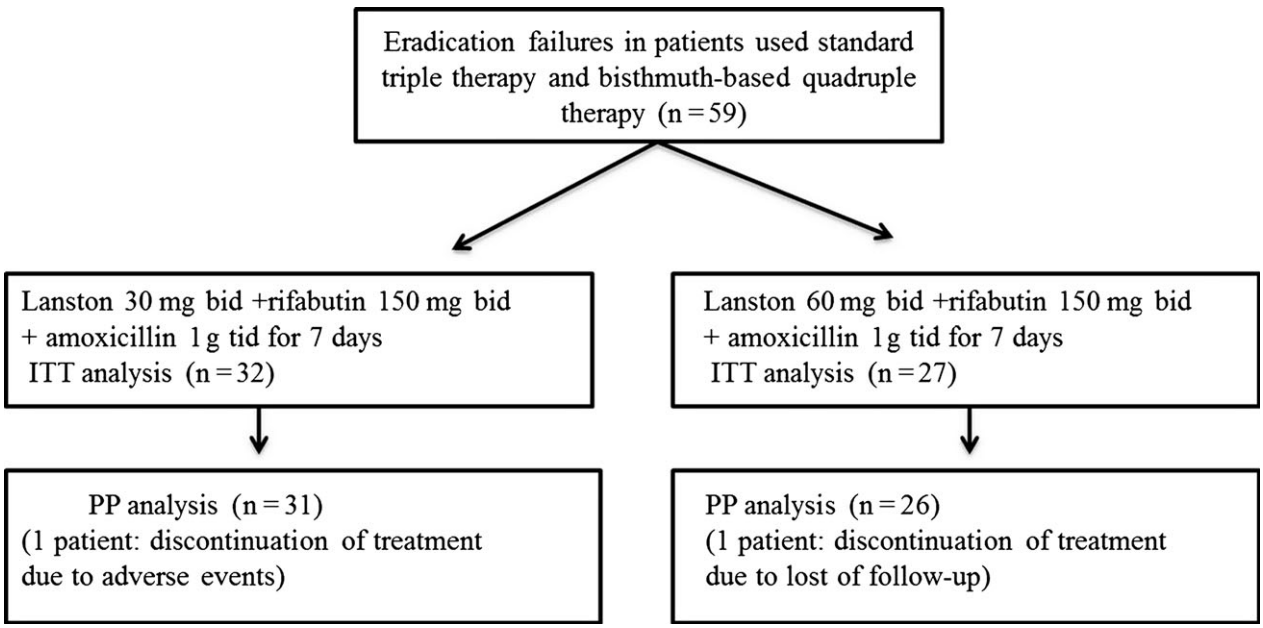

Figure 1 The flow diagram for eradication of *Helicobacter pylori*.

Table 1 Clinical characteristics of patients

	Lansoprazole 60 mg (n = 32)	Lansoprazole 120 mg (n = 27)	*p*-Value
Age (years, mean)	54.6	56.2	.595
Sex (M : F)	12 : 20	13/14	.444
Smoking	4 (12.5%)	5 (18.5%)	.983
Alcohol	7 (21.9%)	5 (18.5%)	.775
Disease			
Gastric ulcer	18 (56.3%)	8 (29.6%)	.132
Duodenal ulcer	5 (15.6%)	1 (3.7%)	
Functional dyspepsia	9 (28.1%)	18 (66.7)	

Table 2 Eradication rates of *Helicobacter pylori*

	Lansoprazole 60 mg (n = 32)	Lansoprazole 120 mg (n = 27)	*p*-Value
ITT (intention to treat)	25/32 (78.1%, 60.0–90.7)	26/27 (96.3%, 81.0–99.9)	.051
PP (per protocol)	25/31 (80.7%, 62.5–92.5)	26/27 (100%, 86.8–100)	.047

in 27 (100%) of the 27 patients in the PP analysis. There was statistically significant difference between the two groups in terms of the eradication rates in PP analysis (p = .047), whereas a marginally statistical significance was found in terms of the eradication rates in ITT analysis (p = .051; Table 2).

The most common adverse events were epigastric pain in the three patients (9.3%) versus one patient (3.7%), epigastric discomfort in two patients (6.2%) versus, one patient (3.7%), and nausea in one patient (3.1%) versus one patient (3.7%), in the groups A and B. There was no statistically significant difference between the two groups in terms of adverse events (Table 3). Reported side effects were mild, and treatment was well tolerated. No major changes in physical examination or in standard laboratory parameters were observed after treatment. As drug compliance and tolerability were optimal in all patients, we searched for other factors possibly associated with treatment failure (Table 4). Neither demographic data nor endoscopic lesions were predictive of treatment failure.

Table 3 Adverse effects

	Lansoprazole 60 mg (n = 32, %)	Lansoprazole 120 mg (n = 27, %)
Epigastric pain	3 (9.3)	1 (3.7)
Epigastric discomfort	2 (6.2)	1 (3.7)
General weakness	1 (3.1)	
Nausea	1 (3.1)	1 (3.7)
Urine color change	1 (3.1)	
Sleepy	1 (3.1)	
Lip discomfort	1 (3.1)	

Table 4 Eradication rates of *Helicobacter pylori* according to various clinical factors

	Eradication rates (%)	*p*-Value
Age		
<60	28/33 (84.8, 68.1–94.8)	.957
>60	23/26 (92.0, 69.8–97.5)	
Sex		
Male	22/24 (91.7, 73.0–99.0)	.686
Female	28/34 (82.4, 65.3–93.2)	
Smoking		
Smoker	8/9 (88.9, 73.2–94.1)	.983
Nonsmoker	42/49 (85.7, 51.7–99.7)	
Alcohol drinking		
Drinker	11/12 (91.7, 71.6–93.8)	.775
Nondrinker	39/46 (84.18, 61.5–99.7)	
Diseases		
Gastric ulcer	23/25 (92.0, 65.1–95.6)	.883
Duodenal ulcer	5/6 (83.3, 35.8–99.6)	
Gastritis	16/18 (88.9, 70.8–97.6)	
Side effects		
Positive	7/8 (87.5, 47.3–99.6)	.983
Negative	42/49 (85.7, 73.7–94.3)	

Discussion

Our study shows that as empirical third-line therapy, rifabutin-based high-dose PPI and amoxicillin combined therapy is more effective in patients with refractory *H. pylori* infection after two eradication failures with key antibiotics such as clarithromycin, metronidazole, and tetracycline previously prescribed. High-dose PPI and amoxicillin are recommended as one of several options for empirical rescue therapy for *H. pylori* infection in the absence of antimicrobial susceptibility testing. The dosing schedule of antibiotics is also important for the treatment of infectious diseases. Antibiotics with the beta-lactam ring, such as amoxicillin, have little postantibiotic effects on the gram-negative rods [22]. The frequent dosing of amoxicillin is required to sustain the levels of amoxicillin higher than the MIC level for a long time, which makes the bioavailability of amoxicillin enhanced in comparison with the twice-daily dosing from the point of view of pharmacology of antibiotics [23]. Miehlke et al. [24] reported in PP analysis, eradication rate of high-dose rabeprazole (40 mg trice) and amoxicillin 1.0 g trice for 14 days

was 75%. Four studies from Japan reported the efficacy of a second-line treatment with a PPI plus amoxicillin after the failure of the standard triple therapy [23,24,25]. Surprisingly, three of these studies (106 patients) reported optimal results (eradication rates of 87, 91 and 100%), dosing 10 mg of rabeprazole and 500 mg of amoxicillin four times daily, for 14 days. The fourth study (63 patients), with a 58% eradication, administered 20 mg of rabeprazole plus 1 g of amoxicillin twice a day, for 14 days. The differences between these studies may be explained by the different dosage scheme, especially on the pharmacokinetics of these drugs. An oral dose of 500 mg of amoxicillin is rapidly absorbed, with a peak in plasma concentrations between 1 and 2 hours, and approximately a 75% is excreted between 6 and 8 hours after its administration. A dosage of 500 mg every 6 hours can probably maintain higher plasma dosages of amoxicillin than a dosage of 1000 mg twice daily [26].

The large multicenter surveillance studies have confirmed that resistance of *H. pylori* to amoxicillin is in the order of 1% [27,28]. In Korea, primary amoxicillin resistance was seen in 2.2-5.6% (mean 2.3%, 8/350) [29,30]. Other clinical trials did not detect any pre- or post-treatment resistance to amoxicillin [31,32]. Also, it is known that the genotype of CYP2C19 is associated with the metabolism of the PPIs. Not knowing whether the patients are extensive or poor metabolizers, or their CYP2C19 polymorphisms, higher PPI doses or newer PPI types might be more effective [33–35]. Potent acid inhibition is important for the eradication of *H. pylori*. Potent inhibition increases the stability and antibiotics in gastric mucosa [34]. Furthermore, acid inhibition allows *H. pylori* to reach its growth phase, rendering the bacteria more sensitive to antibiotics. The distribution frequencies of people with the homEM genotype are 30–40% in Asian countries [36]. The usual doses PPIs used in the standard regimen are insufficient for patients with the homEM genotype, as well as that a higher dose of a PPI causes few adverse effects and is considered to be sufficiently safe [36]. The rifabutin-based high-dose PPI and amoxicillin combined therapy can resolve the problems of clarithromycin and metronidazole resistance and homozygous extensive metabolizers of CYP2C19 gene polymorphisms, the main reasons for eradication failure [37].

Rifabutin-based triple therapy was found to be highly effective and reliable as an alternative rescue therapy for the treatment of *H. pylori* infection after two failed eradication treatments. Borody et al. showed a 12 days of half the dose of rifabutin (150 mg daily) combined with a high dose of pantoprazole (80 mg thrice daily) and amoxicillin (1 g or 1.5 g thrice daily) produced higher eradication rates of 91 and 97%, respectively, as a rescue therapy, suggesting that the treatment regimen is considered highly effective as a rescue therapy. In the presence of low-dose rifabutin (150 mg), combined frequent high dosing of PPI and amoxicillin for 12 days is effective for rescue therapy [38]. Our present open single-center study showed that high dose of PPI (lansoprazole 60 mg twice daily) and amoxicillin (1 g trice daily) combined rifabutin therapy achieved significant better eradication rate (100%) than standard dose of PPI (lansoprazole 30 mg twice daily) 80.6% in PP analysis ($p = .047$) after failures in two courses of previous *H. pylori* eradication therapy. Primary rifabutin resistance in *H. pylori* isolates is low, ranging from 1.3% to 2.4%. Unlike other antibiotics, rifabutin is chemically stable at a wide pH range and is not likely affected by inadequate acid suppression [39]. The combination of rifabutin with either metronidazole or amoxicillin shows additive effects [40].

For treating *H. pylori* infection, the length of treatment for the rifabutin regimen has controversies, as does the influence this has on the treatment outcome. A mean *H. pylori* eradication rate of 75% (95% CI from 68 to 83%) for the 7-day regimen was calculated, while the 10- to 14-day regimen was similar or even slightly lower (71%; 95% CI, 63–79%) [21]. However, as previously reviewed, when a subanalysis was performed depending on the duration of the second-line rifabutin therapy, better results were observed with 10–12 days (92%) than with 7 days (69%). Finally, therapies between 12 and 14 days have yielded results similar to the 10-day course and are likely to increase the incidence of adverse event [21].

Our data suggest that in the presence of 7 days relatively short duration, frequent dosing of amoxicillin and a high-dose PPI can improve eradication rate and reducing side effects. It has been suggested that rifabutin efficacy decreases with increasing number of failed previous therapies, perhaps due to patients who had failed at least two courses of eradication therapy and may have harbored *H. pylori* strains that were more difficult to eradicate [41]. Overall, mean *H. pylori* eradication rate (intention-to-treat analysis) with rifabutin-containing regimens (1008 patients) was 73% (67–79%). Respective cure rates for second-line (223 patients), third-line (342 patients), and fourth-/fifth-line (95 patients) rifabutin therapies were 79% (67–92%), 66% (55–77%), and 70% (60–79%), respectively [41]. Antimicrobial susceptibility testing of *H. pylori*is was desirable before initiation of third-line therapy, although the culture-based antibiotic susceptibility testing for *H. pylori* is expensive, time-consuming, and not always available on a routine basis [42]. The

sensitivity of a bacterial culture is not 100%, and therefore, the antimicrobial susceptibility cannot be obtained in all cases. Therefore, rifabutin (together with a PPI and amoxicillin) can be administered as a rescue treatment without the need for a prior antibiogram [13].

The mean rate of adverse effects to rifabutin treatment in *H. pylori* studies has been approximately 22% [21]. In our study, this incidence was reported to be somewhat lower (15.5%), but in most cases, symptoms were well tolerated and no side effects were considered serious. In our study, most frequent side effects were epigatric pain (7.0%), epigastric discomfort (5.2%), and nausea (3.5%). Myelotoxicity is the most significant adverse event of rifabutin. Overall, this complication is rare and is far more likely when high dose (600 mg/day) and prolonged duration therapy is used. However, myelotoxicity was not reported in most of the studies evaluating rifabutin for *H. pylori* infection. Until now, all patients have recovered from leucopenia uneventful in few days [43,44]. Several concerns remained regarding rifabutin treatment. First, this drug is extremely expansive; second, severe leucopenia and thrombocytopenia can occur to a patient under treatment with rifabutin. Finally, there is some concern about widespread use of rifabutin, a member of class of established antimycobacterial drugs in patients with *H. pylori* infection [45]. Because multiresistant strains of *Mycobacterium tuberculosis* have increased in number, indications for these drugs should be chosen very carefully to avoid further acceleration of development of resistance. Rifabutin should be used only as rescue therapy after amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin have failed to eradicate to patients who have experienced failure of *H. pylori* [42]. The main limitation of our study is that it was a single-centered study and that no antibiotic testing has been performed.

In conclusion, rifabutin-based high-dose PPI-combined therapy as empirical rescue treatment is more effective than standard dose PPI-combined rifabutin-based therapy, safe and best tolerable in third-line therapy in the Korean population. The key to successful rescue therapy with rifabutin–amoxicillin–PPI regimen may be to increase doses of PPI and amoxicillin. Further randomized clinical trials with antimicrobial susceptibility tests are needed.

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