Retrospective Study

Efficacy of 14-d vs 7-d moxifloxacin-based triple regimens for second-line Helicobacter pylori eradication

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Methods: Between 2011 and 2013, we conducted a retrospective review of the medical records of 160 patients who had experienced failure of their first-line proton pump inhibitor-based eradication therapy and subsequently received the moxifloxacin-based triple therapy as a second-line eradication treatment regimen. The patients who were treated with the moxifloxacin-based triple therapy (oral 20 mg rabeprazole b.i.d., 1000 mg amoxicillin b.i.d., and 400 mg moxifloxacin q.d.) for 7 d were assigned to the RAM-7 group (n = 79) while those who took them for 14 days were assigned to RAM-14 group (n = 81). The eradication rates for both groups were determined by intention-to-treat (ITT) and per-protocol (PP) analyses. Successful eradication therapy for Helicobacter pylori infection was defined as the documentation of a negative 13C-urea breath test 4 wk after the end of the eradication treatment.

Results: The overall ITT eradication rate was 76.2% (122/160). The final ITT eradication rates were 70.8% (56/79; 95%CI: 63.3%-77.1%) in the RAM-7 group and 81.4% (66/81; 95%CI: 74.6%-88.3%) in the RAM-14 group (P = 0.034). The overall PP eradication rate was 84.1% (122/145), and the final PP eradication rates were 77.7% (56/72; 95%CI: 70.2%-85.3%) in the RAM-7 group and 90.4% (66/73; 95%CI: 82.8%-98.1%) in the RAM-14 group (P = 0.017). The H. pylori-eradication rates in the RAM-14 group were significantly higher compared with that of the RAM-7 group according to both the ITT (P = 0.034) and the PP analyses (P = 0.017). Both groups exhibited good treatment compliance (RAM-7/RAM-14 group: 100%/100%). The adverse event rates were

Abstract

AIM: To evaluate the efficacy of the 14-d moxifloxacin-based triple therapy for the second-line eradication of Helicobacter pylori (H. pylori) infection.

METHODS: Between 2011 and 2013, we conducted a retrospective review of the medical records of 160 patients who had experienced failure of their first-line proton pump inhibitor-based eradication therapy and subsequently received the moxifloxacin-based triple therapy as a second-line eradication treatment regimen. The patients who were treated with the moxifloxacin-based triple therapy (oral 20 mg rabeprazole b.i.d., 1000 mg amoxicillin b.i.d., and 400 mg moxifloxacin q.d.) for 7 d were assigned to the RAM-7 group (n = 79) while those who took them for 14 days were assigned to RAM-14 group (n = 81). The eradication rates for both groups were determined by intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis compared the treatment groups as originally allocated while the PP analysis including only those patients who had completed the treatment as originally allocated. Successful eradication therapy for H. pylori infection was defined as the documentation of a negative 13C-urea breath test 4 wk after the end of the eradication treatment.

RESULTS: The overall ITT eradication rate was 76.2% (122/160). The final ITT eradication rates were 70.8% (56/79; 95%CI: 63.3%-77.1%) in the RAM-7 group and 81.4% (66/81; 95%CI: 74.6%-88.3%) in the RAM-14 group (P = 0.034). The overall PP eradication rate was 84.1% (122/145), and the final PP eradication rates were 77.7% (56/72; 95%CI: 70.2%-85.3%) in the RAM-7 group and 90.4% (66/73; 95%CI: 82.8%-98.1%) in the RAM-14 group (P = 0.017). The H. pylori-eradication rates in the RAM-14 group were significantly higher compared with that of the RAM-7 group according to both the ITT (P = 0.034) and the PP analyses (P = 0.017). Both groups exhibited good treatment compliance (RAM-7/RAM-14 group: 100%/100%). The adverse event rates were
19.4% (14/72) and 20.5% (15/73) in the RAM-7 and RAM-14 groups, respectively (P = 0.441). Adverse events occurred in 14 of the 72 patients (19.4%) in the RAM-7 group and in 15 of the 73 patients (20.5%) in the RAM-14 group. No statistically significant differences (P = 0.441) were observed.

**CONCLUSION**: The 14-d moxifloxacin-based triple therapy is a significantly more effective second-line eradication treatment as compared to the 7-d alternative for *H. pylori* infection in South Korea.

**Key words**: *Helicobacter pylori*; Treatment failure; Second-line treatment; Moxifloxacin; Eradication rate

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Core tip: This study aimed to evaluate the efficacy of the 14-d moxifloxacin-based triple therapy compared to the corresponding 7-d regimen for second-line *Helicobacter pylori* (*H. pylori*) eradication in South Korea. The *H. pylori*-eradication rates in the RAM-14 group were significantly higher compared to the RAM-7 group for both the intention-to-treat and per-protocol analysis. The high eradication rate, excellent compliance, and safety of the 14-d regimen suggest its potential suitability as an alternative to the standard bismuth-based quadruple therapy. The 14-d moxifloxacin-based triple therapy is a significantly more effective second-line eradication treatment than the 7-d alternative for *H. pylori* infection in Korean patients.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infection is the single most important factor causing chronic atrophic gastritis, peptic ulcer disease, gastric cancer as well as gastric mucosa associated lymphoid tissue lymphoma[1]. The eradication of *H. pylori* infection effectively reduces the incidence of peptic ulcer and gastric cancer, and prevents their recurrence[2]. The most important first-line treatment for the eradication of *H. pylori* is currently the standard triple therapy composed of a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole[3,4]. Although many studies have reported excellent results with this therapy, eradication rates vary widely between 70% and 95%(5,6), with a tendency to decrease due to increasing antibiotic resistance[7,8]. For those patients who failed their first-line eradication therapy, second-line eradication therapy for persistent *H. pylori* infection is required.

Many alternative, second-line treatment regimens have been studied. Currently, most experts recommend a bismuth-based quadruple therapeutic regimen, consisting of a PPI, bismuth salt, metronidazole, and tetracycline, that is administered for 7-14 d[9,10]. However, a recent meta-analysis revealed a mean failure rate of nearly 25% and higher with this therapy[6,10].

In the Maastricht IV/Florence Consensus[11], a fluoroquinolone-based triple therapy such as moxifloxacin or levofloxacin was used as second-line treatment after failure of the standard triple and the bismuth-based quadruple therapies. Moxifloxacin is a second-generation fluoroquinolone widely used to treat respiratory and skin infections[11]. Unlike other fluoroquinolones, moxifloxacin has a low incidence of adverse events and fewer interactions with other drugs. Gastrointestinal disturbances such as diarrhea and nausea are the most common reported adverse events of moxifloxacin[12]. Recent studies have reported satisfactory eradication rates with moxifloxacin-based triple therapy for first-line *H. pylori* treatment[13,14]. This therapy has also shown excellent eradication rates as a second-line treatment regimen[15,16] with significantly better compliance and adverse event rates compared with the bismuth-based quadruple therapy. However, the eradication rate did not increase over the course of a prolonged, 7-10-d treatment period[16], due to increased resistance to moxifloxacin[17]. We hypothesized that a longer duration of treatment with moxifloxacin-based triple therapy might increase the efficacy of *H. pylori* eradication.

The aim of the present study was to compare the *H. pylori*-eradication, treatment compliance, and adverse event rates, between second-line 14-d moxifloxacin-based triple therapy and the 7-d alternative among Korean patients.

**MATERIALS AND METHODS**

**Patient selection**

This study was conducted at Seoul National University Bundang Hospital between January 2011 and December 2013. The medical records of 160 patients who had experienced failure of first-line PPI-based eradication therapy and subsequently received moxifloxacin-based triple therapy as second-line eradication treatment for *H. pylori* infection were reviewed in this retrospective study. Eradication failure was defined on the basis of at least one of the following three tests: (1) a positive 13C-urea breath test (13C-UBT); (2) histological evidence of *H. pylori* by modified Giemsa staining in the lesser and greater curvature of the body and antrum; and (3) a positive rapid urease test (CLO test; Delta West, Bentley, Australia) by gastric mucosal biopsy from the lesser curvature of the body and antrum. None of the patients had previously received *H. pylori*-eradication therapy before the administration of first-line treatment.
Patients were also excluded if they had received PPIs, 
H$_2$ receptor antagonists or antibiotics in the previous 
4 wk, or if they had used NSAIDs or steroids in the 2 
wk prior to the $^{13}$C-UBT. The other exclusion criteria 
were as follows: (1) age below 18 years; (2) previous 
gastric surgery or endoscopic mucosal dissection for 
gastric cancer; (3) advanced gastric cancer; (4) severe 
concurrent disease (hepatic, renal, respiratory, or 
cardiovascular systems); (5) pregnancy; and (6) any 
condition probably associated with poor compliance 
(e.g., alcoholism or drug addiction). The study protocol 
was approved by the Ethics Committee at Seoul 
National University Bundang Hospital (IRB number: 
B-1406/256-105).

**First-line eradication regimens for H. pylori**

Patients received standard and orally administered 
triple-, bismuth-based quadruple-, or sequential 
therapy as first-line treatment for the eradication 
of *H. pylori*. The standard triple therapy included 
1 g amoxicillin taken twice a day (b.i.d.), 500 mg 
clarithromycin b.i.d., and 20 mg rabeprazole (or 40 mg 
esomeprazole) b.i.d. for 7 d. Bismuth-based quadruple 
therapy consisting of 300 mg of tripotassium dicitrato 
bismuthate taken 4 times a day (q.i.d.), 500 mg of 
tetracycline q.i.d., 500 mg of metronidazole 3 times 
a day (t.i.d.), and 20 mg rabeprazole (or 40 mg 
esomeprazole) b.i.d. for 10 d. Sequential therapy was 
given for 2 wk, and included 1 g amoxicillin and 20 
mg rabeprazole (or 40 mg esomeprazole) b.i.d. for the 
first week, followed by 500 mg clarithromycin, 500 
mg metronidazole, and 20 mg rabeprazole (or 40 mg 
esomeprazole) b.i.d for the second week.

**Study design**

The patients were classified into two groups. Those 
who received moxifloxacin-based triple therapy 
(oral 20 mg rabeprazole b.i.d., 1000 mg amoxicillin 
b.i.d., and 400 mg moxifloxacin q.d.) for 7 d were 
assigned to the RAM-7 group while those who received 
moxifloxacin-based triple therapy for 14 d were 
assigned to the RAM-14 group. Treatment compliance 
was evaluated indirectly by remnant pill counting and 
directly through a discussion with a physician one 
week after completion of the treatment. Compliance 
was defined as good when drug intake was at least 
85%. At the same time, all of the patients were 
asked questions about adverse events. Successful 
eradication therapy for *H. pylori* infection was defined 
as a negative $^{13}$C-UBT test 4 wk after the cessation 
of eradication treatment. Data that was recorded 
included demographics (age, gender distribution, 
smoking status, alcohol use), previous history of peptic 
ulcer, endoscopic findings, reasons for drop-outs, and 
the type of first-line regimen that was administered.

$^{13}$C-urea breath test

Before the $^{13}$C-UBT, patients were instructed to stop 
taking medications (i.e., bismuth, antibiotics for 4 wk; 
PPIs for 2 wk) that could affect the results, and fast 
for a minimum of 4 h. After washing the patient’s oral 
cavity through gargling, a pre-dose breath sample was 
obtained. Then, 100 mg of $^{13}$C-urea powder (UBiTkit™, 
Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) was 
dissolved in 100 mL of water and administered orally. 
Breath samplings were taken with special breath 
collection bags while patients were in the sitting position, 
both before drug administration (baseline) and 20 min 
after the powder medication. The samples were analyzed 
using an isotope-selective, non-dispersive infrared 
spectrometer (UBiT-IR 300™; Otsuka Pharmaceutical Co. 
Ltd, Tokyo, Japan).

**Statistical analysis**

The primary and secondary outcomes of the present 
study were the *H. pylori*-eradication rates and the 
treatment-related adverse events, respectively. The 
eradication rates were determined by intention-
to-treat (ITT) and per-protocol (PP) analyses. ITT 
analysis compared the treatment groups including 
all of the patients as originally allocated while the PP 
analysis compared the treatment groups including only 
those patients who had completed the treatment as 
originally allocated. The mean ± SD were calculated 
for the quantitative variables. The student’s *t* test was 
used to evaluate the continuous variables, and the 
$\chi^2$ test and Fisher’s exact test were utilized to assess 
the non-continuous variables. Additionally, univariate 
and multivariate analyses were conducted to assess 
the effects of factors on the eradication rate. All of 
the statistical analyses were performed using the 
Predictive Analytics Software (PASW) 20.0 version for 
Windows (SPSS Inc., IBM, Chicago, IL, United States). 
A *P*-value of less than 0.05 was defined as statistically 
significant.

**RESULTS**

**Characteristics of patients**

A schematic diagram of the study is provided in Figure 
1. A total of 160 patients who had experienced failure 
of first-line eradication therapy for *H. pylori* were 
enrolled (mean age, 63 years; range: 24-86 years). Of 
the 160 patients, 145 (90.6) completed their allocated 
regimens. The remaining 15 (7% or 4.3% were from 
the RAM-7 group and 8% or 5.1% were from the 
RAM-14 group) patients (9.4) were excluded from 
the study because of loss to follow-up. No patient was 
excluded from either group for non-compliance (taking 
< 85% of the assigned tablets) or for treatment 
discontinuation due to adverse events. A total of 72 
RAM-7 and 73 RAM-14 patients were included in 
the final PP analysis. The enrolled patients’ baseline 
demographic and clinical data are provided in Table 
1. There were no statistical differences in age, gender 
distribution, smoking status, alcohol use, previous
H. pylori eradication rates and compliance

Table 2 shows the rates of eradication of *H. pylori* infection according to the ITT and PP analyses. The overall ITT eradication rate was 76.2% (122/160). The final ITT eradication rates were 70.8% (56/79; 95%CI: 63.3%-77.1%) in the RAM-7 group and 81.4% (66/81; 95%CI: 74.6%-88.3%) in the RAM-14 group ($p = 0.034$, Table 2). The overall PP eradication rate was 84.1% (122/145), and the final PP eradication rates were 77.7% (56/72; 95%CI: 70.2%-85.3%) in the RAM-7 group and 90.4% (66/73; 95%CI: 82.8%-98.1%) in the RAM-14 group ($p = 0.017$). The *H. pylori*-eradication rates in the RAM-14 group were significantly higher than in the RAM­7 group according to both the ITT ($p = 0.034$) and the PP analyses ($p = 0.017$). The treatment compliance was 100% in both groups (Table 2).

Figure 1  Flow schematic of the study included in intention-to-treat and per-protocol analyses. ITT: Intention-to-treat; PP: Per-protocol; RAM-7: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 7 d; RAM-14: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 14 d.

Table 2  *Helicobacter pylori* eradication rates and compliance

|            | RAM-7 | RAM-14 | $p$ value |
|------------|-------|--------|-----------|
| ITT analysis |       |        |           |
| Eradication rate, n (%) | 56 (70.8) | 66 (81.4) | 0.034 |
| 95%CI       | 63.3%-77.1% | 74.6%-88.3% |      |
| PP analysis |       |        |           |
| Eradication rate, n (%) | 56 (77.7) | 66 (90.4) | 0.017 |
| 95%CI       | 70.2%-85.3% | 82.8%-98.1% |      |
| Compliance | 100% | 100% | -         |

RAM-7: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 7 d; RAM-14: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 14 d; ITT: Intention-to-treat; PP: Per-protocol.

between the two groups ($P > 0.05$).

**H. pylori eradication rates and compliance**

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history of peptic ulcer, endoscopic findings, reasons for drop out, or the first-line regimen administered
Table 3  Adverse events n (%)  

| Adverse events       | RAM-7 (n = 72) | RAM-14 (n = 73) | P value |
|----------------------|----------------|-----------------|---------|
| Epigastric discomfort| 3 (4.1)        | 5 (6.8)         | 0.874   |
| Constipation         | 0 (0.0)        | 1 (1.4)         | 0.411   |
| Diarrhea             | 4 (5.5)        | 6 (8.2)         | 0.991   |
| Dizziness            | 1 (1.4)        | 1 (1.4)         | 0.667   |
| Headache             | 0 (0.0)        | 1 (1.4)         | 0.667   |
| Nausea or vomiting   | 6 (8.3)        | 1 (1.4)         | 0.415   |
| Skin rash            | 0 (0.0)        | 0 (0.0)         | -       |
| Total                | 14 (19.4)      | 15 (20.5)       | 0.441   |

RAM-7: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 7 d; RAM-14: Rabeprazole/amoxicillin/moxifloxacin triple therapy x 14 d; ITT: Intention-to-treat; PP: Per-protocol.

Adverse events
Table 3 lists the adverse events that occurred in the two groups. Adverse events occurred in 14 of the 72 patients (19.4) in the RAM-7 group and in 15 of the 73 patients (20.5) in the RAM-14 group. No statistically significant differences (P = 0.441) were observed. The most common adverse events were nausea/vomiting (6/72, 8.3) and diarrhea (4/72, 5.5) in the RAM-7 group, and diarrhea (6/73, 8.2) and epigastric discomfort (5/73, 6.8) in the RAM-14 group. The differences between groups were not statistically significant (P > 0.05). Most of the adverse events were mild-to-moderate in intensity and none were serious enough to warrant discontinuation of treatment in either group.

DISCUSSION

Determination of the appropriate second-line eradication treatment for *H. pylori* infection remains uncertain. Many guidelines recommend a bismuth-based quadruple therapy (bismuth, PPI, metronidazole, and tetracycline) as second-line treatment after failure of first-line eradication therapy\(^{3,5}\). However, eradication failure rates of more than 20% have been found with this regimen in several countries (including South Korea) primarily because of bacterial resistance\(^{2,8}\). Additionally, poor patient compliance due to the occurrence of adverse events or complicated dosing schedules has also been implicated in treatment failures\(^{16,18,19}\).

In order to address these problems, various alternative treatment options designed to prevent the development of bacterial resistance and promote treatment compliance have been reported\(^{19-21}\). Other regimens that have reported low rates of bacterial resistance to antibiotics and adverse events have also been investigated. Fluoroquinolone-based regimens, for example, have been studied as first-line or salvage treatments. First-generation fluoroquinolones including pefloxacin and norfloxacin, have shown low eradication rates\(^{22,23}\), while better rates have been recorded in second-generation fluoroquinolones such as levofloxacin and moxifloxacin. As first-line treatment, levofloxacin-based triple therapy revealed eradication rates of up to 90%\(^{24,25}\), with higher rates reported in moxifloxacin-based triple therapy\(^{13,14}\).

As first-line treatment, the *H. pylori*-eradication rate of moxifloxacin-based triple therapy was reported between 84.1% and 89%, which is higher than that of standard triple therapy\(^{26,27}\). As a second-line treatment, good efficacy with eradication rates as high as 90%, have been previously demonstrated\(^{15}\). Although bismuth-based quadruple therapy has generally been considered as the second-line treatment of choice\(^{28}\), moxifloxacin-based therapy is often preferred because of poor compliance to the former regimen resulting from adverse events, complicated dosing schedules, and low eradication rates\(^{18}\). Other studies indicate that levofloxacin-based triple therapy administered for 10 d as a rescue treatment was more effective (compared to the 7-d regimen) than bismuth-based quadruple therapy\(^{29,30}\). In a separate study in Turkey, moxifloxacin-based triple therapy, has been evaluated as first-line treatment on a 14-d basis\(^{31,32}\) with eradication rates determined at only 42%-53% on ITT and 47%-53.3% on PP analyses, respectively. These results might be related to the different regional and institutional usages of fluoroquinolones\(^{33}\).

In this study, we compared the eradication rates of the 14-d with the 7-d regimens of the moxifloxacin-based triple therapy as second-line modalities for the treatment of *H. pylori* infection. We believe that these longer treatment durations would increase eradication efficacies without increasing or decreasing adverse-event or drug-compliance rates, respectively. The ITT and PP analyses revealed eradication rates of 70.8% and 77.7%, respectively, for the RAM-7 group and 81.4% and 90.4% respectively, for the RAM-14 group. Although statistically significant differences in eradication rates were reported, there were no statistically significant differences in adverse events or treatment compliance (P > 0.05) with the moxifloxacin-based therapy. Thus, a longer duration of moxifloxacin-based triple therapy (14 d) was found to be more effective as a salvage second-line eradication treatment compared to a shorter duration of therapy in patients whose first-line treatment had failed, without increasing or decreasing the adverse-event or drug-compliance rate, respectively.

The most common adverse events of moxifloxacin therapy are gastrointestinal disturbances such as diarrhea and nausea which were also observed in our present study. The total adverse-event rate for the 14-d moxifloxacin-based triple treatment was 20.5% (15/73), which was similar to that for the 7-d moxifloxacin-based triple treatment (19.4%, 14/72), although the difference was not statistically significant. In both groups, mild to moderate adverse events were reported. None was serious enough to require medication discontinuation or interfered with regular life. On the other hand, the medication discontinuation
rate and the incidence of adverse events of 14-d bismuth-based quadruple therapy have been reported to be 7.5%-23% and 38.2%-65%[3,34], respectively, which were higher than the results obtained in our study. In other words, the adverse events of longer-duration moxifloxacin-based triple therapy (14 d) occur at a similar frequency to those of shorter-duration therapy (7 d) in the present study.

One limitation of our study is the lack of any analysis of antibiotic resistance relative to the eradication rates and treatment regimens. The efficacy and timing of antibiotic susceptibility testing after eradication therapy failure remain uncertain. Some researchers have argued that antibiotic susceptibility testing is unnecessary after first-line eradication therapy, because it is neither practical nor cost-effective for primary care practices[11,18]. For this reason, bacterial culture and antibiotic susceptibility testing were not performed in this study. Nevertheless, we believe such testing to be particularly necessary after two or more eradication failures.

In conclusion, 14-d moxifloxacin-based triple therapy is a more highly effective second-line eradication treatment than 7-d moxifloxacin-based triple therapy for H. pylori infection. The high eradication rate, excellent compliance, and safety of the 14-d regimen suggest its potential suitability as an alternative to the standard bismuth-based quadruple therapy. Further large prospective studies are required in order to determine the proper treatment duration and assess the efficacy and timing of antibiotic susceptibility testing after eradication therapy failure.

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