The efficacy of moxifloxacin-based triple therapy in treatment of *Helicobacter pylori* infection: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Recent evidence shows that moxifloxacin could exert an antimicrobial effect against *Helicobacter pylori* in both *in vitro* and *in vivo* models. To systematically evaluate whether moxifloxacin-containing triple therapy could improve eradication rates and reduce side effects in first-line or second-line anti-*H. pylori* treatment, eligible articles were identified by searches of electronic databases. We included all randomized trials comparing moxifloxacin-based triple therapy with standard triple or quadruple therapy during *H. pylori* eradication treatment. Statistical analysis was performed with Review Manager 5.0.10. Subanalysis/sensitivity analysis was also performed. We identified seven randomized trials (n = 1263). Pooled *H. pylori* eradication rates were 79.03% (95%CI: 75.73-82.07) and 68.33% (95%CI: 64.44-72.04) for patients with moxifloxacin-based triple therapy or with standard triple or quadruple therapy, respectively (intention-to-treat analysis). The odds ratio (OR) was 1.82 (95%CI: 1.17-2.81), the occurrence of total side effects was 15.23% (95%CI: 12.58-18.20) and 27.17% (95%CI: 23.64-30.92) for groups with or without moxifloxacin, and the summary OR was 0.45 (95%CI: 0.26-0.77). In subgroup analyses, we noted that the second-line eradication rate in the moxifloxacin group was significantly higher than that in the quadruple therapy group (73.33 *vs* 60.17%, OR: 1.78, 95%CI: 1.16-2.73, P<0.001). However, there was no difference in first-line eradication treatment. Findings from this meta-analysis suggest that moxifloxacin-based triple therapy is more effective and better tolerated than standard triple or quadruple therapy. Therefore, a moxifloxacin-based triple regimen should be used in the second-line treatment of *H. pylori* infection.

Key words: Moxifloxacin; *Helicobacter pylori*; Eradication rate; Side effects; Meta-analysis

Introduction

Helicobacter pylori infection is a common and significant public health problem; it can be found in 70-90% of the population in developing countries and in 25-50% in developed countries (1). Eradication of *H. pylori* is the recommended treatment for gastric and duodenal ulcers, gastric cancer, atrophic gastritis, mucosa-associated lymphoma tissue lymphoma, and other *H. pylori*-related complications (2-4). According to the Maastricht consensus, the first-line therapy for *H. pylori* eradication is a combination of proton pump inhibitors (PPI) or ranitidine bismuth citrate and clarithromycin plus either amoxicillin or metronidazole (5). In first-line therapies, eradication rates using combinations of PPI-based triple therapies range from 75 to 98%, with most of them near 80% (6-8). This signifies that up to 20% of patients are expected to be treatment failures, a value which, as already observed

(9), could be even higher in areas with a high prevalence of resistant *H. pylori* strains. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salts, and a PPI; however, a pooled analysis of 40 trials demonstrated an average eradication rate of 76% for quadruple therapy when used as second-line therapy (10). Furthermore, this regimen requires the administration of four drugs with a complex scheme, and is associated with a relatively high incidence of adverse effects (11).

Moxifloxacin is a second-generation fluoroquinolone with an antibacterial spectrum that includes all major upper and lower respiratory tract pathogens, including beta-lactamase and macrolide-resistant pneumococci, and is currently widely used to treat infections of the respiratory tract, skin, and skin structures (12). Recently,

several reports have demonstrated that moxifloxacin-based regimens provide excellent first-line therapies and rescue regimens for *H. pylori* eradication (13-16). Two meta-analyses showed the advantages of moxifloxacin-containing triple therapy for first-line and second-line treatment of *H. pylori* infection; however, some trials included in the two meta-analyses were of low quality, and the trials using moxifloxacin-containing triple therapy were not thoroughly analyzed (17,18).

Therefore, we systematically reviewed the *H. pylori* eradication efficacy and tolerance of moxifloxacin-based triple therapy as first-line and second-line treatments of *H. pylori* infection. By summarizing the data from high-quality randomized controlled trials, meta-analysis provides greater statistical power and a more precise estimate of eradication rates with moxifloxacin-based triple therapy in patients with *H. pylori* infection. This analysis also provides a more precise comparison of the frequency of side effects associated with the regimens. As a first-line therapy, we compared moxifloxacin-based regimens with standard triple therapy, while as a second-line therapy, we compared moxifloxacin-based regimens with quadruple therapy.

Material and Methods

Selection of studies

Studies evaluating moxifloxacin-based triple therapy for the eradication of *H. pylori* were considered. For the meta-analysis, the selection criteria were as follows: i) articles had to report comparative randomized-controlled trials; ii) they had to include at least two treatment arms consisting of triple therapy (a PPI and two antibiotics) or quadruple therapy (i.e., PPI, bismuth, and two antibiotics or ranitidine bismuth citrate plus these same antibiotics) and a moxifloxacin-involved regimen; iii) the study population consisted of subjects first treated and retreated; iv) the data of successful eradication and/or side effects in *H. pylori* eradication were available.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Controlled Trials Register (Issue 1, 2012), PubMed (1966 to March 2012), Embase (1980 to March 2012), and the Science Citation Index (1945 to March 2012). A search strategy was constructed using a combination of the following words: *Helicobacter pylori* or *H. pylori* and moxifloxacin or avelox. Only articles published in English were included. Reference lists from the trials selected by electronic searching were manually searched to identify further relevant trials. We also conducted a manual search of abstracts from 1995 to 2012 (March) from the following congresses: International Workshop of the European Helicobacter Study Group, American Digestive Disease Week, and United European Gastroenterology Week. Abstracts of the articles selected in each of these multiple

searches were reviewed, and those meeting the inclusion criteria were recorded. References of reviews on *H. pylori* treatment with moxifloxacin and from the articles selected for the study were also examined for articles meeting the inclusion criteria. Authors of some identified trials were asked whether they knew of additional studies, including unpublished randomized ones. In the case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used.

Data extraction

Standardized data abstraction sheets were prepared. Data were extracted for study quality, dose and duration of moxifloxacin treatment, and anti-*H. pylori* regimens, as well as for the number of enrolled subjects, diagnostic methods of testing *H. pylori* infection before enrolling and after completing the study, and score systems for assessing side effects. Meanwhile, key outcomes data such as eradication rates, occurrence of diarrhea, nausea, taste disturbance, and abdominal pain were abstracted from all included studies. All articles were examined independently for eligibility by two reviewers. Disagreements were resolved by consulting a third reviewer. Quality was assessed using Jadad scoring based on three items: randomization, double blinding, and description of withdrawals/dropouts. We considered that trials were of low quality if their scores were less than 3.

Data synthesis

Data were entered into the Cochrane Collaboration Review Manager program RevMan 5.0.10 (released on May 16, 2008, The Nordic Cochrane Centre, The Cochrane Collaboration, Rigs Hospitalet, Denmark). The outcome measure examined was the odds ratio (OR) of improving *H. pylori* eradication rates and reducing side effects with moxifloxacin-based triple therapy *vs* standard triple or quadruple therapy. Categorical variables were compared with the chi-square test, and $P < 0.05$ was considered to be statistically significant. Eradication rates and side effects were analyzed based on a fixed-effects model using the methods of Mantel-Haenszel both by an intention-to-treat and by a per-protocol. Heterogeneity among the studies was assessed by the chi-square test. Statistical significance of heterogeneity was set at 0.10. If the heterogeneity was significant, subanalysis was used. Where the heterogeneity was not obvious and $P > 0.10$, we employed the fixed-effect model; otherwise, we used the random-effect model.

### Subanalysis/sensitivity analysis

In the meta-analysis, subanalyses of *H. pylori* eradication efficacy were planned *a priori* depending on: i) the type of drugs co-prescribed with moxifloxacin (the combination with amoxicillin or metronidazole and a PPI is the most widely prescribed), ii) the country of the

subjects, iii) the *H. pylori* eradication times, and iv) the quality of the studies (based on the quality score proposed by JADAD; see appropriate section). In the sensitivity analysis, we evaluated the influence of low quality studies by estimating the ORs in the absence of one or more studies (we used JADAD scores to assess the quality of studies; if the JADAD score of the study was below 3, we could tell that the study was of low quality). Finally, we used funnel plot asymmetry to detect any publication bias in the meta-analysis and Egger's regression test to measure funnel plot asymmetry. If the funnel plot was almost symmetrical, we could say that there was no obvious publication bias.

Results

Description of the studies

The bibliographical search yielded a total of 59 studies. Of these studies, 14 were excluded owing to publication type, (i.e., seven reviews, three comments, and four letters). We excluded another 19 articles (10 non-clinical trials and 9 unrelated articles) after examining the title and abstract, the remaining 26 potentially relevant articles were retrieved for more detailed assessment. From these 26 articles, we excluded another 11, because there was no control group. Eight study groups were also excluded because of comparisons of different courses, or containing moxifloxacin in two regimens, or the absence of an eligible control group. Finally, seven randomized controlled trails (RCTs) (13-16,19-21) met the inclusion criteria (Figure 1). The characteristics of the seven trials included in this meta-analysis are summarized in Table 1, including quality scores.
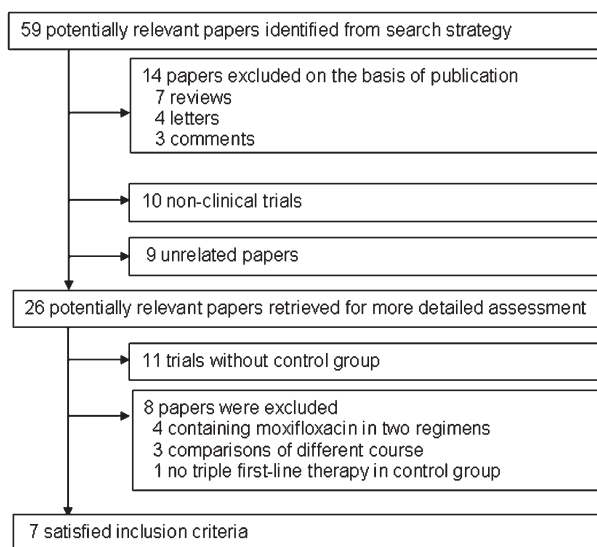
Figure 1. Flow diagram of search strategy and study selection.

Eradication rates

Seven studies that described *H. pylori* eradication rates were selected for the meta-analysis. Of these selected studies, five reported significantly improved eradication rates, and the remaining two studies had similar efficacies for *H. pylori* eradication. The pooled intention-to-treat data showed that 524 of 663 patients with moxifloxacin-based triple regimens (79.03%; 95%CI: 75.73-82.07) and 410 of 600 patients given regimens without moxifloxacin (68.33%; 95%CI: 64.44-72.04) achieved eradication. The OR was 1.82 (95%CI: 1.17-2.81; Supplementary Figure S1). Overall, per-protocol eradication rates were 84.24% (95%CI: 81.14-87.02) and 75.79% (95%CI: 71.95-79.34) for moxifloxacin-based triple regimen and regimen without moxifloxacin, respectively (OR: 1.65; 95%CI: 0.95-2.86).

Side effects

Total side effects were initially included in the meta-analysis because data for occurrence of total side effects could be obtained from all the RCTs. Of these studies, three trials reported a significantly lower incidence of gastrointestinal side effects with moxifloxacin. Side effects in moxifloxacin-based regimens were less than in regimens without moxifloxacin: 15.23% (95%CI: 12.58-18.20) and 27.17% (95%CI: 23.64-30.92), respectively; the summary OR was 0.45 (95%CI: 0.26-0.77) (Supplementary Figure S2).

Subanalysis/sensitivity analysis

Subanalyses for the meta-analysis were planned depending on choice of antibiotics, eradication times, and the country in which subjects were treated. We divided all eligible trials into moxifloxacin+amoxicillin (M+A) and moxifloxacin+metronidazole/tinidazole (M+Me/T) subgroups, first treatment and rescue treatment subgroups, or Asia and Europe subgroups. For antibiotics subanalysis, the M+A subgroup had no significant difference. However, the M+Me/T subgroup had a significant difference, with summary ORs 1.50 (95%CI: 0.95-2.38) and 3.00 (95%CI: 1.84-4.89), respectively (Supplementary Figure 3). For time of eradication subanalysis, the first time subgroup had no difference and the rescue subgroup had significant difference, with summary ORs 1.80 (95%CI: 0.71-4.55) and 1.78 (95%CI: 1.16-2.73), respectively (Supplementary Figure S4). For subanalysis by country of subjects, the Asia subgroup had no difference and the Europe subgroup had a significant difference, with summary ORs 1.27 (95%CI: 0.71-2.29) and 2.71 (95%CI: 1.87-3.93), respectively (Supplementary Figure 5).

In the sensitivity analysis, we first excluded two low quality studies, and eradication rates had no significant changes (OR: 2.11; 95%CI: 1.43-3.10); then we excluded the largest study, and eradication rates also had no significant changes (OR: 1.67; 95%CI: 1.02-2.73).

Table 1. Characteristics of the 7 studies in this meta-analysis comparing *H. pylori* eradication efficacy with moxifloxacin-based triple therapy *vs* standard triple or quadruple therapy.

| Reference/country	Number (moxifloxacin/control)	Diagnosis	Diagnostic methods	Moxifloxacin regimen (duration)	% Eradication (No. of patients)	% Adverse effects (No. of patients)	Triple or quadruple regimen (duration)	% Eradication (No. of patients)	% Adverse effects (No. of patients)	Q
Cheon (15) Korea	85 (41/44)	Peptic ulcer, gastric adenoma or cancer, non-ulcer dyspepsia	UBT,RUT or histology/UBT (4 weeks later)	E (20 mg bid) A (1 g bid) M (400 mg qd) (7 days)	ITT 75.6 (31/41) PP 83.8 (31/37)	9.8 (4/41)	E (20 mg bid) B (300 mg qd) Me (500 mg tid) T (500 mg qd) (14 days)	ITT 54.5 (24/44) PP 72.7 (24/33)	27.3 (12/44)	2
Kang (19) Korea	192 (139/53)	Peptic ulcer, dysplasia or gastric cancer non-ulcer dyspepsia	UBT,RUT or histology/UBT (4 weeks later)	E (20 mg bid) A (1 g bid) M (400 mg qd) (10 days)	ITT 71.9 (100/139) PP 82.6 (100/121)	12.2 (17/139)	E (20 mg bid) B (300 mg qd) Me (500 mg tid) T (500 mg qd) (14 days)	ITT 71.7 (38/53) PP 90.5 (38/42)	39.6 (21/53)	4
Bago (16) Croatia	160 (82/78)	Non-ulcer dyspepsia	UBT/UBT (6 weeks later)	O (20 mg bid) M (400 mg qd) Me (500 mg tid) (7 days)	ITT 73.2 (60/82) PP 78.9 (60/76)	14.6 (12/82)	O (20 mg bid) B (120 mg qd) Me (500 mg tid) T (500 mg qd) (7 days)	ITT 53.8 (42/78) PP 64.6 (42/65)	23.1 (18/78)	3
Zheng (20) China	109 (53/56)	Peptic ulcer, chronic gastritis	UBT/UBT (4 weeks later)	R (10 mg bid) A (1 g bid) M (400 mg qd) (7 days)	ITT 75.5 (40/53) PP 83.3 (40/48)	9.4 (5/53)	R (10 mg bid) B (150 mg tid) C (500 mg bid) Me (400 mg bid) (7 days)	ITT 62.5 (35/56) PP 71.4 (35/49)	16.1 (9/56)	4
Nista (13) Italy	320 (160/160)	Non-ulcer dyspepsia	histology+UBT/ UBT (6 weeks later)	E (20 mg bid) A (1 g bid) T (500 mg bid) M (400 mg qd) (7 days)	ITT 88.8 (142/160) PP 90.4 (142/157)	13.1 (21/160)	E (20 mg bid) A (1 g bid) T (500 mg bid) C (500 mg bid) (7 days)	ITT 73.8 (118/160) PP 78.7 (118/150)	34.4 (55/160)	3
Bago (14) Croatia	277 (128/149)	Non-ulcer dyspepsia	histology+RUT or culture/ histology+RUT or culture (4-6 weeks later)	L (30 mg bid) A (1 g bid) Me (400 mg bid) M (400 mg qd) (7 days)	ITT 89.8 (115/128) PP 93.5 (115/123)	6.3 (8/128)	L (30 mg bid) A (1 g bid) Me (400 mg bid) C (500 mg bid) (7 days)	ITT 74.5 (111/149) PP 78.2 (111/142)	13.4 (20/149)	5
Kilic (21) Turkey	120 (60/60)	Non-ulcer dyspepsia	histology or RUT/UBT(8 weeks later)	RBC (400 mg bid) E (40 mg bid) A (1 g bid) M (400 mg qd) (14 days)	ITT 60 (36/60) PP 60 (36/60)	56.7 (34/60)	RBC (400 mg bid) E (40 mg bid) A (1 g bid) C (500 mg bid) (14 days)	ITT 70 (42/60) PP 70 (42/60)	46.7 (28/60)	2

C: clarithromycin; A: amoxicillin; R: rabeprazole; T: tinidazole; O: omeprazole; L: lansoprazole; E: esomeprazole; RBC: ranitidine bismuth citrate; B: bismuth subcitrate; M: moxifloxacin; Me: metronidazole; UBT: ^{13}C-urea breath test; RUT: rapid urease test; ITT: intention-to-treat analysis; PP: per-protocol analysis; Q: quality score; qd: one time a day; bid: two times a day; tid: three times a day.

Publication bias

We found the funnel plot had a slightly asymmetrical distribution (Figure 2), but Egger's regression test suggested no significant asymmetry of the funnel plot (P = 0.860), indicating no evidence of substantial publication bias.

Discussion

Optimizing *H. pylori* eradication therapy remains an ongoing challenge worldwide. Conventional first-line eradication therapies may fail in up to 30% of patients, leading to a significant increase in antimicrobial resistance (22), particularly against the key antibiotics clarithromycin and/or metronidazole (23,24). A sequential treatment containing PPI plus amoxicillin for 5 days followed by an additional 5 days of a PPI, clarithromycin, and metronidazole/tinidazole is suggested as an alternative, although most available data were collected in Italy where the rates
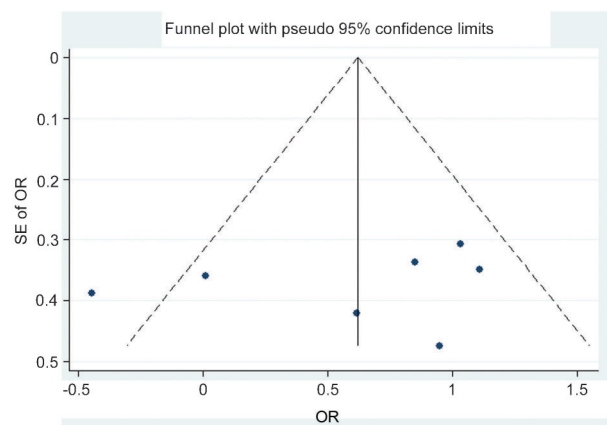
Figure 2. Funnel plot of included studies for eradication rates.

for clarithromycin resistance are relatively high. Another option in first-line therapy is a quadruple therapy consisting of a PPI, amoxicillin, clarithromycin, and metronidazole (5,25). The bismuth-based quadruple therapy containing a PPI or ranitidine, bismuth subsalicylate, metronidazole, and tetracycline is also partially recommended in first-line and second-line treatment for at least 10 days. (5,25). Another possibility in second-line therapy is a combination of a quinolone and amoxicillin. For third-line treatment, a combination of rifabutin and amoxicillin is suggested. In general, susceptibility testing is strongly recommended after second therapy failure (26).

Second-generation fluoroquinolones (levofloxacyn, moxifloxacin) have proved to have an antibacterial effect to *H. pylori*, especially in terms of safety and simplicity of dosing schedule. Moxifloxacin-containing triple therapies have achieved eradication rates up to 90% in first-line treatments and over 70% in second-line therapies. The results of our meta-analysis demonstrated higher *H. pylori* eradication rates with a moxifloxacin-based triple regimen than standard triple or quadruple regimens (79.03 *vs* 68.33%, P<0.01), with OR 1.82 (95%CI: 1.17-2.81). We also found that, in first-line treatment, the eradication rate of a moxifloxacin-based triple regimen was not different from that of a standard triple regimen. But in second-line treatment, the eradication rate of a moxifloxacin-based triple regimen was significantly different from that of a quadruple regimen (73.33 *vs* 60.17%, P<0.01). Regarding the choice of antibiotics for combination with moxifloxacin, we found that the M + Me/T subgroup had a higher cure rate (P<0.01). It is possible that moxifloxacin and metronidazole or tinidazole exert a synergistic effect against *H. pylori*.

Based on a large body of published clinical trials and the result of our meta-analysis, a moxifloxacin-based PPI triple therapy is effective and safe, and shows better outcome parameters compared with the standard PPI first-line and second-line therapies. Compared with bismuth-based quadruple therapy, PPI triple regimens containing moxifloxacin are better tolerated and more effective. However, is this enough data to recommend a quinolone-based triple therapy in first-line therapy of *H. pylori* infection?

As mentioned earlier, primary quinolone resistance in *H. pylori* is reported to be relatively low in populations where quinolone consumption is low. Unfortunately, these values seem to have increased over the last years (27,28). In other countries with high use of quinolones, a primary resistance of about 20% and higher has already been reported (29). In *H. pylori*, single point mutations in the gyrA gene, the quinolone resistance-determining region, cause resistance to this class of antibiotics (30). In Germany, the rate for quinolone-resistant *H. pylori* is about 10%, rising to 17% after previous treatment failures (31). Similar values have recently been reported from other countries such as the United Kingdom (32), Italy (33), Japan (34), and Taiwan (28).

A recent study from Croatia including 150 patients with primary quinolone resistance (6%) demonstrated a significant reduction of eradication success of moxifloxacin-containing PPI triple therapy in patients infected with quinolone-resistant *H. pylori* strains (66 *vs* 98%) (35). Therefore, in populations with clarithromycin resistance greater than 15-20% and low quinolone resistance rates, a PPI triple therapy with moxifloxacin might be considered. For this strategy, an acceptable threshold of 10% for quinolone resistance is currently being discussed (36,37). This seems to be a reasonable suggestion at present, since most of the studies in first-line, quinolone-based therapy have been performed in populations with quinolone resistance lower than 10%. That again points out the importance of permanent surveillance of quinolone resistance within a given population in order to adapt recommendations appropriately. Patients who have been previously exposed to quinolones for other indications should not be treated with quinolone-containing eradication regimens.

Several methodological weaknesses may limit the validity and generalizability of this meta-analysis. First, there are no studies involving patients from North America or Africa. The studies included were conducted in Italy, Croatia, Turkey, Korea, and China. It is well established that antibiotic resistance profiles of *H. pylori* vary among different geographical regions for which a pharmacogenomic difference could exist (38). Such resistance profiles are likely to significantly impact the efficacy of moxifloxacin-based triple therapy, and thus may limit the generalizability of these results to African or American populations. Second, heterogeneity among trials can be another limitation of the meta-analysis; there were many factors causing heterogeneity, such as different regimens of drugs and duration. Third, ethnic differences might be another cause of heterogeneity, which may lead to different responses to *H. pylori* eradication therapy. Therefore, more high-quality, multicenter, randomized, controlled trials from other countries and regions are necessary.

In summary, moxifloxacin-based triple therapy is a safe and well-tolerated option in anti-*H. pylori* therapy. In second-line treatment, the combination of a PPI, moxifloxacin, and metronidazole or tinidazole is a valid option, especially in countries where bismuth salts are unavailable. In first-line therapy, a moxifloxacin-based triple therapy cannot generally be recommended. However, under specific circumstances, this combination might be considered as an individual first-line treatment option. Thus, in a population with low primary quinolone resistance and high primary clarithromycin resistance, a PPI triple therapy with moxifloxacin and metronidazole or tinidazole could be a valuable alternative.

Supplementary Material

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Acknowledgments

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