Digestive and Liver Disease 47 (2015) 108–113

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Two-week, high-dose proton pump inhibitor, moxifloxacin triple *Helicobacter pylori* therapy after failure of standard triple or non-bismuth quadruple treatments

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ARTICLE INFO

Article history:
Received 2 April 2014
Accepted 12 October 2014
Available online 11 November 2014

Keywords:
Eradication
Failure
Helicobacter pylori
Levofloxacin
Moxifloxacin
Quinolones
Rescue
Therapy

ABSTRACT

Background: Aim was to evaluate the efficacy and tolerability of a moxifloxacin-containing second-line triple regimen in patients whose previous *Helicobacter pylori* eradication treatment failed.
Methods: Prospective multicentre study including patients in whom a triple therapy or a non-bismuth-quadruple-therapy failed. Moxifloxacin (400 mg qd), amoxicillin (1 g bid), and esomeprazole (40 mg bid) were prescribed for 14 days. Eradication was confirmed by ^{13}C-urea-breath-test. Compliance was determined through questioning and recovery of empty medication envelopes.
Results: 250 patients were consecutively included (mean age 48 ± 15 years, 11% with ulcer). Previous (failed) therapy included: standard triple (n = 179), sequential (n = 27), and concomitant (n = 44); 97% of patients took all medications, 4 were lost to follow-up. Intention-to-treat and per-protocol eradication rates were 82.4% (95% CI, 77–87%) and 85.7% (95% CI, 81–90%). Cure rates were similar independently of diagnosis (ulcer, 77%; dyspepsia, 82%) and previous treatment (standard triple, 83%; sequential, 89%; concomitant, 77%). At multivariate analysis, only age was associated with eradication (OR = 0.957; 95% CI, 0.933–0.981). Adverse events were reported in 25.2% of patients: diarrhoea (9.6%), abdominal pain (9.6%), and nausea (9.2%).
Conclusion: 14-day moxifloxacin-containing triple therapy is an effective and safe second-line strategy in patients whose previous standard triple therapy or non-bismuth quadruple (sequential or concomitant) therapy has failed, providing a simple alternative to bismuth quadruple regimen.

1. Introduction

Helicobacter pylori infection is the main known cause of gastritis, gastroduodenal ulcer disease, and gastric cancer [1]. However, despite more than 30 years of experience in *H. pylori* treatment, the ideal regimen to treat this infection remains undefined. Consensus conferences have recommended therapeutic regimens that achieve cure rates higher than 80% on an intention-to-treat basis [2]. However, large clinical trials and meta-analyses have shown that the most commonly used first-line therapies – a proton pump inhibitor (PPI) plus 2 antibiotics – can fail in ≥20% of patients, and, in clinical practice, this rate might be even higher [1,3]. Moreover, during the last few years, the efficacy of standard triple regimens has been decreasing, and several studies have reported

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http://dx.doi.org/10.1016/j.dld.2014.10.009
1590-8658/

intention-to-treat eradication rates lower than 75% and even lower than 50% [4]. Antibiotic resistance to clarithromycin has been identified as one of the major factors affecting our ability to cure *H. pylori* infection, and the rate of resistance to this antibiotic seems to be increasing in many geographic areas [5].

A rescue regimen comprising a quadruple combination of a PPI, bismuth, tetracycline, and metronidazole has been used as the optimal second-line approach based on the relatively good results reported [6,7]. However, administration of the regimen is complex and adverse events are relatively common [6,7]. Furthermore, the quadruple regimen still fails to eradicate *H. pylori* in approximately 20–30% of cases. Finally, bismuth salts are no longer available worldwide. Therefore, management of first-line eradication failures is becoming challenging.

Non-bismuth quadruple "sequential" and "concomitant" regimens, including a PPI, amoxicillin, clarithromycin and a nitroimidazole, are increasingly used as first-line treatments for *H. pylori* infection [8,9]. However, eradication with rescue regimens may be challenging after failure of key antibiotics such as clarithromycin and nitroimidazoles.

Recent findings indicate that fluoroquinolones such as levofloxacin could prove to be an efficacious alternative to standard antibiotics, not only as first-line therapies but also, and more interestingly, as second-line regimens [10–12]. We previously obtained "intermediate" results (74% eradication rate) with a combination of a PPI, amoxicillin, and levofloxacin given for 10 days in multicenter studies performed in Spain [13,14]. On the other hand, recent studies suggest that the efficacy of levofloxacin-containing therapy is decreasing, most likely due to increased primary quinolone resistance [15].

Moxifloxacin is a second-generation fluoroquinolone with a wide antibacterial spectrum [16]. Studies in vitro have shown that moxifloxacin has an improved coverage of Gram-positive and anaerobic bacteria while retaining good activity against Gram-negative bacteria [16]. Moxifloxacin has a higher in vitro activity against gram-positive and anaerobic pathogens compared with levofloxacin [17]. In vitro studies have shown excellent susceptibility of *H. pylori* strains to moxifloxacin [18], and clinical trials have confirmed its higher effectiveness – as a first-line therapy – compared with standard clarithromycin-based triple therapy [19]. Furthermore, few studies have suggested that the emergence of bacterial resistance appears to be less common for moxifloxacin than for other fluoroquinolones, and that moxifloxacin may be less affected by quinolone resistance than levofloxacin in *H. pylori* [18] and other bacterial infections [20,21].

Therefore, the aim of the present study was to evaluate the efficacy and tolerability of a second-line triple regimen containing moxifloxacin in patients whose previous *H. pylori* eradication treatment failed.

2. Methods

2.1. Patients

This was a prospective multicenter study (21 Hospitals, 19 Spanish and 2 Italian) including consecutive patients in whose first-line therapy [standard triple therapy (PPI, clarithromycin, and amoxicillin) or a non-bismuth quadruple therapy (PPI, clarithromycin, amoxicillin and metronidazole), either sequentially or concomitantly] had failed to eradicate *H. pylori* infection. Previous failure was defined as a positive ^{13}C-urea breath test result 4–8 weeks after completion of treatment. The exclusion criteria were as follows: (1) age under 18 years, (2) presence of clinically significant associated conditions (insulin-dependent diabetes mellitus, neoplastic diseases, coagulation disorders, and hepatic, cardiorespiratory, or renal diseases), (3) previous gastric surgery, and (4) allergy to any of the drugs used in the study. The protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

2.2. Therapy

A second eradication regimen with moxifloxacin (400 mg o.d.), amoxicillin (1 g b.i.d.), and esomeprazole (40 mg b.i.d.) was prescribed for 14 days. Esomeprazol and amoxicillin were administered together after breakfast and dinner, and moxifloxacin after dinner. Patients were informed about potential side events (mainly metallic taste, nausea, vomiting, abdominal pain and diarrhoea) during the treatment period. Compliance with therapy was defined as intake of 100% of the medication prescribed and was determined from a questionnaire and recovery of empty envelopes of medications. The incidence of adverse events was evaluated by means of a specific questionnaire administered at the time the success or failure of *H. pylori* eradication treatment was confirmed.

2.3. Diagnostic methods to confirm eradication

Eradication of *H. pylori* was defined as a negative ^{13}C-urea breath test result (with citric acid and 100 mg of urea, using a previously reported protocol [22]) performed 4–8 weeks after completion of re-treatment in each centre. The test was carried out by nurses who were unaware of the therapy administered and the patients' *H. pylori* status. As endoscopy – and consequently culture – was not performed after therapy, antibiotic susceptibility was unknown and, therefore, the moxifloxacin eradication regimen was chosen empirically.

2.4. Outcomes

Primary outcome was eradication rate, measured as percentage of confirmed eradicated patients as reported in the previous section, by intention-to-treat analysis. Secondary outcomes were compliance (percentage of patients taking 100% of medications), safety (percentage of appearance, type and severity of adverse events), and per-protocol eradication rate. Eradication rates were stratified according to the first-line failed therapy, and the geographical region. Adverse events were classified depending on the intensity of symptoms evaluated by the corresponding physician. Adverse events were classified as mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (not allowing normal daily routine), and serious (death, hospitalization, disability, congenial anomaly, and/or requires intervention to prevent permanent damage).

2.5. Statistical analysis

The 95% confidence interval (95% CI) was calculated for categorical variables and the mean ± standard deviation for quantitative variables. Analysis of the efficacy of *H. pylori* eradication was performed on an intention-to-treat basis (including all eligible patients enrolled in the study regardless of compliance with the study protocol; patients with non-evaluable data were assumed to have been unsuccessfully treated) and on a per-protocol basis (excluding patients whose compliance with therapy was poor and patients with non-evaluable data after therapy).

A multiple logistic regression analysis was performed. The dependent variable was eradication of *H. pylori*, and the independent variables were age, sex, smoking (smokers and non-smokers), diagnosis (peptic ulcer or functional/uninvestigated dyspepsia), and type of first-line (failed) therapy. We used a backward modelling strategy, and the log-likelihood ratio was the statistic for model comparison.

Sample size was determined for an expected efficacy of 80% and a specified precision of ±5%. A sample size of 240 patients was necessary. As the probability of loss to follow-up was estimated at around 5%, the final size of the sample was 250 patients.

3. Results

3.1. Demographic variables

The study sample comprised 250 patients (21 centres, inclusion per centre ranged from 2 to 48, median inclusion was 6), of whom 89% had functional or non-investigated dyspepsia, and 11% peptic ulcer disease. Mean age was 48 ± 15 years, 58% were women, and 15% were smokers.

3.2. Previous treatments

Previous (failed) therapy included: standard triple therapy (PPI–clarithromycin–amoxicillin; 179 patients, 71%), sequential therapy (PPI–amoxicillin for 5 days, plus PPI–clarithromycin–metronidazole for another 5 days; 27 patients, 11%), and concomitant therapy (PPI–amoxicillin–clarithromycin–metronidazole for 10 days; 44 patients, 18%).

3.3. Compliance with the protocol and loss to follow-up

Four patients (1.6%) did not return for their follow-up visit. All but 8 patients (97%) complied with the protocol. All cases of non-compliance were due to adverse events. A CONSORT flow diagram of subjects' progress through the phases of the study is shown in Fig. 1.

3.4. Efficacy of eradication therapy

Intention-to-treat eradication was achieved in 206/250 patients (82.4; 95% CI = 77–87%). Per-protocol eradication was achieved in 204/238 patients (85.7%; 95% CI = 81–90%). Cure rates were similar when compared depending on the diagnosis (peptic ulcer 77% vs. functional/non-investigated dyspepsia 82%) and previous treatment; standard triple therapy 83% (149/179) vs. sequential 89% (24/27) vs. concomitant 77% (34/44). In the multivariate analysis, age was the only variable associated with eradication success (the higher the age, the lower the eradication rate; OR = 0.957; 95% CI = 0.933–0.981). A "per geographic region" multiple proportion analysis was performed and no statistically significant differences were found (88% vs. 85% vs. 83% vs. 74% and vs. 73%; $p > 0.05$); evaluating results in a "per-centre" analysis no heterogeneity of results was found ($Chi^2 = 3.22$, $p = 1.00$; $I^2 = 0\%$). Per-centre and region grouping data is shown in Table 1.

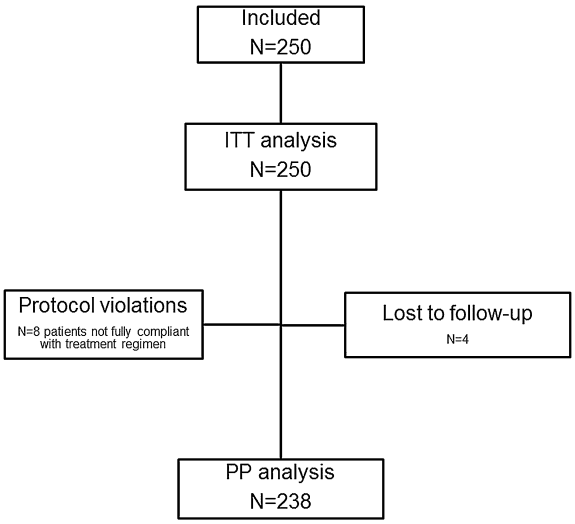

Fig. 1. CONSORT flow diagram showing progress of patients through the trial. ITT: intention-to-treat analysis; PP: per-protocol analysis.

Table 1
Safety/adverse events of treatment.

Adverse events	Total (%)	Intense (%)
Diarrhoea	24 (9.6)	4 (1.6)
Abdominal pain	24 (9.6)	5 (2.0)
Nausea	23 (9.5)	3 (1.2)
Metallic taste	13 (5.2)	1 (0.4)
Asthenia/anorexia	10 (4.0)	2 (0.8)
Vomiting	11 (4.4)	4 (1.6)
Vaginal candidiasis	2 (0.8)	0 (0)
Oral candidiasis	1 (0.4)	0 (0)
Rash	1 (0.4)	0 (0)
Insomnia	1 (0.4)	0 (0)
Syncope	1 (0.4)	0 (0)
Aphthous stomatitis	1 (0.4)	0 (0)
Dysphagia	1 (0.4)	0 (0)
Headache	1 (0.4)	0 (0)
Myalgia	1 (0.4)	0 (0)
Coated tongue	1 (0.4)	0 (0)
Total number of patients with adverse events	63 (25.2%)	19 (7.6)

3.5. Tolerance to eradication therapy

Adverse events were reported in 25.2% of patients (95% CI = 20–31%), most commonly diarrhoea (9.6%), abdominal pain (9.6%), nausea (9.2%), metallic taste (5.2%), vomiting (4.4%), and asthenia (4%) (Table 2). Symptoms were limited to the duration of treatment in most patients. In 19 cases (7.6%), the adverse events were classified as "intense", but none of them was classified as a serious adverse event.

Table 2
Eradication rate per geographic region and centre.

Hospital	Patients	Success	Eradication rate	Weight
Central-1	28	25	89%	5.7
Central-2	26	21	81%	5.6
Central-3	2	2	100%	4.0
Central-4	26	24	92%	5.8
Central-5	2	2	100%	4.0
	84	74	88%	
Northern-1	3	2	67%	3.7
Northern-2	4	2	50%	3.9
Northern-3	14	12	86%	5.4
Northern-4	4	3	75%	4.1
Northern-5	2	1	50%	3.2
	27	20	74%	
Eastern-1	21	15	71%	5.4
Eastern-2	5	3	60%	4.2
Eastern-3	2	2	100%	4.0
Eastern-4	17	13	76%	5.4
	45	33	73%	
Southern-1	6	5	83%	4.7
Southern-2	14	11	79%	5.3
Southern-3	10	8	80%	5.1
Southern-4	6	6	100%	5.4
Southern-5	4	3	75%	4.1
	40	33	83%	
Italian-1	42	36	86%	5.8
Italian-2	12	10	83%	5.3
	54	46	85%	
	250	206	82%	
	Heterogeneity:		$I^2 = 0.0\%$	$p = 1.00$

4. Discussion

In this large multicenter study we have shown that 14-day moxifloxacin-containing therapy is an effective second-line strategy in patients whose previous *H. pylori* therapy has failed, achieving an eradication rate >80% both by per-protocol and by intention-to-treat.

Moxifloxacin is a second-generation fluoroquinolone with a broad spectrum of activity compared with the first generation [16]. Initially, the combination of a PPI, amoxicillin, and moxifloxacin as the first-line regimen was associated with favourable results [23–29]. Later on, other authors studied this same regimen in patients with one previous eradication failure (standard triple therapy) and reported variable results [30–34], with eradication rates ranging from 67% to 76%. However, the sample size of these studies was low, all of them including less than 200 patients. To the best of our knowledge, our study (including 250 patients) is the largest to evaluate a moxifloxacin-containing rescue regimen. On the other hand, all previous rescue studies have been conducted in Korea and China, but none had been performed in Western countries.

Non-bismuth quadruple "sequential" and "concomitant" regimens, including a PPI, amoxicillin, clarithromycin and a nitroimidazole, are increasingly used as first-line treatments for *H. pylori* infection [8,9]. Eradication with rescue regimens may be challenging after failure of key antibiotics such as clarithromycin and nitroimidazoles. To the best of our knowledge, our study is the first one evaluating the moxifloxacin rescue regimen after these non-bismuth therapies. Cure rates were similar when compared depending on the previous treatment (standard triple therapy 83% vs. sequential 89% vs. concomitant 77%). Therefore, the moxifloxacin-containing triple therapy constitutes an encouraging second-line strategy in patients with previous non-bismuth quadruple "sequential" or "concomitant" treatment failure, which is in agreement with the results previously obtained with levofloxacin [35–39].

Our eradication rate (86% by per-protocol and 82% by intention-to-treat) may be considered encouraging, especially when it is taken into account that this rescue regimen was prescribed empirically after eradication failure with key antibiotics such as amoxicillin and clarithromycin. The relatively high cure rate – higher than in our previously published studies with levofloxacin in Spain and than in other studies conducted by other authors including moxifloxacin – may be due to several reasons: differences in antibiotic (quinolone) resistances, the prescription of high-dose new generation PPI (esomeprazole), and/or the long treatment duration (14 days).

With respect to antibiotic susceptibility, resistance of *H. pylori* to fluoroquinolones is increasing worldwide. Unfortunately, resistance to quinolones in general, and to levofloxacin in particular, is easily acquired, and in countries with a high consumption of these drugs, the resistance rate is increasing, having reached already relatively high rates [40]. In a recent systematic review of data on resistance of *H. pylori* to antibiotics in different countries, the overall levofloxacin resistance rate was found to be 16%, although the figures varied significantly from Europe (24%) to Asia, America, and Africa [41]. A recent multicenter study investigated the rate of primary antibiotic resistance of *H. pylori* in 2008 and 2009 in 18 European countries and found the rate for levofloxacin to be 13% in Spain and 27% in Italy [5]. The rate of levofloxacin resistance during this period (2008–2009) in Spain was investigated as part of the aforementioned European multicenter study and was shown to be 14% [42].

Resistance to fluoroquinolones appears to be primarily because of alterations in the gyrA gene [18,43–46] and hence could theoretically confer cross-resistance across a variety of fluoroquinolones. Accordingly, cross-resistance between various quinolones was found in several studies [40,43–45]. The prevalence of resistance to moxifloxacin in particular has been determined in only a limited number of studies, varying from 1% (in Indonesia) [47] to more than 40% (in China) [40], with intermediate figures in other countries. The increase of moxifloxacin resistance reported in several studies [18,46] could be explained by cross-resistance across other fluoroquinolones like ciprofloxacin and levofloxacin [48]. However, in our previous Spanish study [13], the efficacy of the levofloxacin-containing regimen remained constant over time from the year 2006 to 2011; this constant eradication rate may reflect, perhaps, that in our country the quinolone resistance rate has not increased as fast as it has been described for clarithromycin resistance [4].

With respect to the duration of the quinolone regimens, 3 meta-analyses [10–12] found, as did 2 recent randomized clinical trials [15,49], higher cure rates with 10-day than with 7-day levofloxacin-containing regimens. Furthermore, a very recent study has compared the efficacy of 14-day and 10-day levofloxacin-containing triple therapy as second-line regimen, and a higher eradication rate was demonstrated with the longest regimen (85% vs. 68%) [50]; this study suggests that long-term (e.g. 14 day) levofloxacin treatment might, perhaps, achieve a similarly high *H. pylori* cure rate than that obtained with moxifloxacin in the present study, although head to head (moxifloxacin vs. levofloxacin) studies would be necessary to confirm this hypothesis. Specifically with moxifloxacin, two recent studies have demonstrated that a triple therapy with this quinolone for 10 days is more effective than the same treatment for 5 or 7 days [24,28]. In another study, increasing the duration of therapy was expected to increase the eradication rate, but the expected increased did not materialize, most likely because of coincident marked increase in the prevalence of resistance to moxifloxacin [32]. Finally, in a recent randomized study, 14 days of treatment significantly increased the eradication compared with 7-day regimen [51].

The prescription of esomeprazole at high doses (40 mg b.i.d.) may also have contributed to the effectiveness of our moxifloxacin regimen. A former meta-analysis showed that high-dose PPIs increase cure rates by around 6–10% in comparison with standard doses [52]. A sub analysis of these data showed that the maximal effect was seen in the studies comparing high doses of the more potent second-generation PPIs – namely, 40 mg of esomeprazole twice a day – with a standard dose of a first-line PPI also twice a day [52]. Furthermore, esomeprazole (and rabeprazole) have shown better *H. pylori* eradication rates than first-generation PPIs in a recent meta-analysis [53]; again, this clinical benefit was more pronounced in esomeprazole 40 mg b.i.d. regimens [53].

Several meta-analyses have compared the efficacy and safety of moxifloxacin-containing triple therapy vs. bismuth-containing quadruple therapy for the treatment of persistent *H. pylori* infection, and have demonstrated that the moxifloxacin regimen is more effective and better tolerated [12,54,55]. On the other hand, administration of the quadruple regimen is relatively complex, while moxifloxacin-containing regimens (with amoxicillin and PPIs administered twice daily and moxifloxacin once daily) represent an encouraging simpler alternative. In our study, compliance with the moxifloxacin regimen was excellent, with 97% of patients taking all the medications correctly.

Regarding safety, in contrast to other fluoroquinolones, moxifloxacin has low interactions with other drugs and a low incidence of adverse events [56]. The drug is well tolerated with only mild gastrointestinal disturbances as the most common adverse effects [57]. In safety data on oral moxifloxacin obtained from 30 Phase II/III studies, nausea and diarrhoea were reported in 7.1 and 5.2% of patients, respectively [58]. A meta-analysis of studies comparing moxifloxacin-containing regimen with clarithromycin-based triple therapy demonstrated better overall tolerance of the moxifloxacin treatment [19]. Adverse events were reported in a relatively high proportion (26%) of our patients, most commonly

diarrhoea, abdominal pain, and nausea/vomiting. However, only in 8% of the cases were adverse events classified as intense (none of them was severe), and caused treatment withdrawal only in 3%.

The major drawback of our study is that culture was not performed, and therefore information on the prevalence of moxifloxacin resistance is lacking. Additionally, the impact of antibiotic resistance to moxifloxacin in the rescue therapy could not be evaluated by this study. It has been established that primary resistance of *H. pylori* to moxifloxacin significantly reduces the eradication rate [23,24]. However, in vitro antimicrobial susceptibility to quinolones in general and to moxifloxacin in particular does not necessarily lead to eradication in vivo (and vice versa) [40]. Our results suggest that systematically performing culture after a first failure may not be necessary. Therefore, assessing the sensitivity of *H. pylori* to antibiotics only after failure of the second treatment may be indicated in clinical practice [6], as has been recommended by the Maastricht IV consensus report [2]. Another limitation is that the median number of the enrolled patients in different centres is as low as 6, with some centres enrolling only 2 cases. Therefore, readers should be cautious, as a *beta* error is not completely ruled out.

Finally, the higher cost of moxifloxacin compared with levofloxacin might be a disadvantage and restrict its use in *H. pylori* eradication. In Spain, t he unitary cost of moxifloxacin more than doubles levofloxacin (4.53€ vs. 1.92€) which makes the overall cost per regimen a 63% more expensive (comparing both as 14 day treatment including esomeprazole). Therefore, a detailed cost-effectiveness study would be needed to conclude whether the benefit of moxifloxacin regarding efficacy is neutralized or even reverted due to its significantly higher cost.

In summary, a 14-day moxifloxacin-containing therapy is an effective and safe second-line strategy in patients whose previous standard triple therapy or non-bismuth quadruple (sequential or concomitant) therapy has failed, providing a simple alternative to bismuth quadruple regimen.

Conflict of interest

None declared.

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