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High efficacy of gemifloxacin-containing therapy in *Helicobacter Pylori* eradication

A pilot empirical second-line rescue therapy

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Abstract

Background: *Helicobacter pylori (H pylori*) is a common gastric pathogen which is associated with chronic gastritis, peptic ulcer, and gastric cancer. It has worldwide distribution with higher incidence in developing countries. Gemifloxacin is a fluoroquinolone antibiotic with documented in vitro activity against *H pylori.* Considering that there is no clinical data to verify gemifloxacin efficacy in *H pylori* eradication, this pilot clinical trial was designed.

Methods: This prospective pilot study was performed during February 2014 to February 2015. A regimen of gemifloxacin (320 mg single dose) plus twice daily doses of amoxicillin1g, bismuth 240 mg, and omeprazole 20 mg for 14 days were prescribed for *H pylori* infected patients in whom a first-line standard quadruple therapy (clarithromycin–amoxicillin–bismuth–omeprazole) had failed. To confirm *H pylori* eradication a 13C-urea breath test was performed 4 weeks after treatment.

Compliance and incidence of adverse effects were evaluated by questionnaires.

Results: A total of 120 patients were enrolled consecutively; out of which 106 patients achieved *H pylori* eradication; per-protocol and intention-to-treat eradication rates were 91.4% (95% CI: 85.5–97.6) and 88.3% (95% CI: 75.4–92.4) respectively. Three patients (2.5%) failed to take at least 80% of the drugs and excluded from the final analysis. Adverse effects were reported in 42% of patients, most commonly including nausea (15%) and diarrhea (13.3%), which was intense in 1 patient and led to the discontinuation of treatment. In total, 96.7% (116/120) of the patients took the medications correctly.

Conclusion: This study revealed that gemifloxacin-containing quadruple therapy provides high *H pylori* eradication rate (≥90% PP cure rate), and this agent can be included in the list of second-line *H pylori* therapeutic regimens.

Abbreviations: *H pylori* = *Helicobacter pylori*, ITT = intention to treat, PP = per-protocol.

Keywords: gemifloxacin, *H pylori*, *Helicobacter pylori* eradication

1. Introduction

Helicobacter pylori (H pylori) is a prevalent gastric pathogen and considered as the most common etiologic agent of infection-related cancers, which represent 5.5% of the global cancer burden.[1] *H pylori* infection causes a spectrum of both gastric and extra gastrointestinal diseases: acute and chronic gastritis, peptic ulcer disease, gastric atrophy, intestinal metaplasia, MALT lymphoma, and gastric adenocarcinoma.[2]

In spite of decreasing *H pylori* prevalence in developed countries, the problem still remains in developing countries. Low socioeconomic status, lower level of education, and poor hygiene are among the most important risk factors for the colonization, and beginning in early childhood in these areas.[3] Up to 90% of the adults are infected with *H pylori* in Iran.[4,5]

There is a prominent difference in the efficacy of first-line and second-line *H pylori* eradication regimens between Western Asian countries and western regimens, mainly due to the variable prevalence of resistant organisms in these regions.[6]

Over the last decades an increasing resistance rate has been happened in Western Asia. Clarithromycin resistance rates have increased from 1.4% in 1997 to 26.5% in 2013 In Iran.

Primary *H pylori* resistance to antibiotics such as Metronidazole, Amoxicillin, and Tetracycline has grown as well.[6]

The Maastricht IV Consensus suggested that the standard triple therapy should now be avoided unless in areas where local clarithromycin resistance is low (<15–20%) or culture confirms susceptibility to clarithromycin.[7,8] In addition, it has also been reported that a regimen focusing on a broad-spectrum fluoroquinolone that inhibits deoxy ribonucleic acid (DNA) gyrase was effective in the first- and second-line treatment.[9–11]

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However a dramatic increase in levofloxacin resistance has been found in various different countries.[12,13] Gemifloxacin, a newer quinolone, has excellent in vitro anti *H pylori* activity compared with levofloxacin. It also has a nearly five times lower MIC level against *H pylori* than levofloxacin.[14–16]

To our best knowledge, no data is available to evaluate a gemifloxacin-containing regimen for *H pylori* eradication. In our study, we aimed to assess the efficacy and tolerability of gemifloxacin-containing sequential regimen in the second-line treatment of *H pylori* infection in Iran, where there is high resistance rates to levofloxacin, as well as clarithromycin.

2. Methods

After obtaining the approval of institutional review board (IRB) and the university ethical committee (91-01-36-4703) all the consecutive *H pylori* positive patients were recruited in this prospective, open label clinical trial (ID: IRCT2012101311101N1) during a 1-year period from early February 2014 to February 2015 at 3 university health-care settings affiliated to Shiraz University of Medical Sciences.

Signed informed consent was obtained in accordance with the Helsinki Declaration and all the patients were well informed about the condition of the study and their rights.

2.1. Patients

Consecutive patients in whom first-line quadruple therapy (clarithromycin–amoxicillin–bismuth-omeprazole) had failed to eradicate *H pylori* infection were eligible for this trial. Two antral biopsy specimens were obtained by endoscopy, from all the patients. According to endoscopic findings, patients were categorized into 3 groups: (1) nonulcerative–nonerosive, (2) erosive, (3) ulcerative.[17] The biopsy samples were evaluated by the rapid urease test and gram staining for the presence of *H pylori*. If one of these results was negative, samples were cultured using the standard protocol.[18,19] The presence of *H pylori* was confirmed as positive if two of these tests (Gram staining, rapid urease test, and culture) resulted positive: patients were excluded from the study if any one of the following criteria was present: (1) Patients under 18 or >80 years of age; (2) pregnancy and lactation; (3) history of previous gastric surgery; (4) severe systemic disease including advanced liver disease or renal failure, gastric malignancy, adenocarcinoma, and lymphoma; (5) History of known hypersensitivity to amoxicillin, metronidazole, or quinolones and PPI (Omeprazole); (6) contraindication to treatment drugs; (7) consumption of antibiotics in the past 4 weeks.

2.2. H pylori treatment protocol

Recruited patients were treated with gemifloxacin 320 mg single dose plus twice daily doses of amoxicillin1g, bismuth 240 mg, and omeprazole 20 mg for 14 days.

Omeprazole and bismuth were given 30 minutes before meals, and all the remaining antibiotics were given after meals.

2.3. H pylori eradication assessment

Four weeks after the end of the treatment, 13C-urea breath test (13C-UBT), a noninvasive nonradioactive method with standard protocol,[20] was performed to confirm the status of *H pylori* eradication and treatment success. The patients were instructed to use neither any antibiotic nor PPI and H2 blocker during these 4 weeks to avoid any conflict with UBT result.

2.4. Compliance and adverse effects assessment

Patients were evaluated by questionnaires at completion of the therapy to assess adherence to the therapeutic regimen and adverse events.

Low compliance was defined as taking $\leq$80% of the pills; such patients and those lost to follow-up were excluded from the per protocol analysis.

2.5. Susceptibility test

As assessing the sensitivity of *H pylori* to antibiotics may be indicated in clinical practice only after the failure of the second treatment[21] the in vitro susceptibility testing was performed for those patients who needed culture for the confirmation of *H pylori* presence. For in vitro susceptibility testing of the *H pylori* strains, a suspension equal to the McFarland tube no. 3 was prepared for each isolate. Brain heart infusion broth (Merck, Germany) plates, supplemented with fetal calf serum (Gibco), were inoculated by confluent swabbing of the surface with the adjusted inoculum suspensions.

E-test strips (Biomerieux, France) were tested against metronidazole, clarithromycin, fluoroquinolone (levofloxacin, and gemifloxacin), and amoxicillin placed onto the dried surface of the inoculated agar plates. The minimum inhibitory concentration (MIC) was determined by the agar dilution test. The resistance breakpoints for amoxicillin, clarithromycin, fluoroquinolone and metronidazole were defined as $\geq$2, $\geq$1, $\geq$ 1, and $\geq$8 mg/mL, respectively.

The plates were then incubated at 37 °C under microaerophilic conditions. The MICs were read after 48 to 72 hours of incubation on the basis of the inter section of the elliptical zone of growth inhibition using the MIC scale on the E-test strip, as per the manufacturer's instructions.[18,19]

2.6. Statistical analysis and sample size estimation

The Fisher exact test was used for calculation of sample size with estimated eradication rate of 95% considering an 80% power level and 5% significance level.

The minimum sample size was 108 based on these assumptions. With the expectation of a drop-out rate of 10% (precision $\pm$10%), the sample size should include at least 118 patients.

The primary aim of this study was to determine the eradication potency of gemifloxacin-containing regimen as a second-line rescue therapy for *H pylori* infection. The secondary goal was to assess the patients' adherence to the treatment and possible adverse effects.

Both per-protocol (PP) and intention to treat (ITT) analyses were performed. ITT analysis included all of the patients who were enrolled in the study including dropouts or the patents that used the medication out of the protocols. Even 95% confidence intervals (CIs) were calculated by normal approximation.

Descriptive analyses were presented as mean ($\pm$standard deviation) for quantitative variables and absolute numbers (percentages) for qualitative variables.

The Mann–Whitney test for quantitative variables and Fisher's exact test for qualitative variables were used. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Characteristics of the patients

Among 548 evaluated patients, a total of 120 patients with *H pylori* infection who failed the first-line *H pylori* eradication therapy were enrolled in the study, out of which 116 patients completed the course of *H pylori* treatment (Fig. 1).

The mean age of the participants was 42.25 ± 16.61 years. Also, 68 (56.7) patients were female. There was no significant difference between gender distribution ($P = 0.49$) (Table 1).

3.2. Prevalence of antibiotic resistance

H pylori strains were achieved for the agar dilution test from77 (64.2%) patients. Among the primary resistance patterns, metronidazole resistance was the highest (55 strains or 71.4%), followed by clarithromycin (47 strains or 61.0%), levofloxacin (11 strains or 14.3%), Amoxicillin (6 strains or 5.4%), and gemifloxacin (5 strains or 4.5%) (Table 2).

There were some strains with multiple resistances to >1 antibiotic (47 strains or 61%).

3.3. Eradication rates

The eradication rate was 91.4% (106/116; 95% CI: 85.5–97.6) in the PP analysis and 88.3% (106/120; 95% CI: 75.4–92.4) in the ITT analysis.

Table 1

The characteristics of the patients.

Variable	Enrolled patients (N = 120)	P
Sex; N (%)		
Male	52 (43.3)	0.49
Female	68 (56.7)	
Age, y; mean ± SD	42.25 ± 16.61	
Endoscopic finding		
N (%)		
Nonulcerative–nonerosive	14 (11.7)	0.001
Erosive	45 (37.5)	
Ulcerative	61 (50.8)	

SD = standard deviation.

Table 2

Pattern of antibiotic resistance.

Antibiotics	MIC range	Resistance strains n = 77 (%)
Metronidazole	≤ 0.061–≥256	55 (71.4)
Clarithromycin	≤ 0.016– ≥256	47 (61.0)
Levofloxacin	≤ 0.020–≥ 32	11 (14.3)
Amoxicillin	≤ 0.016–32	6 (7.8)
Gemifloxacin	≤ 0.002–32	5 (6.5)

MIC = minimum inhibitory concentration.

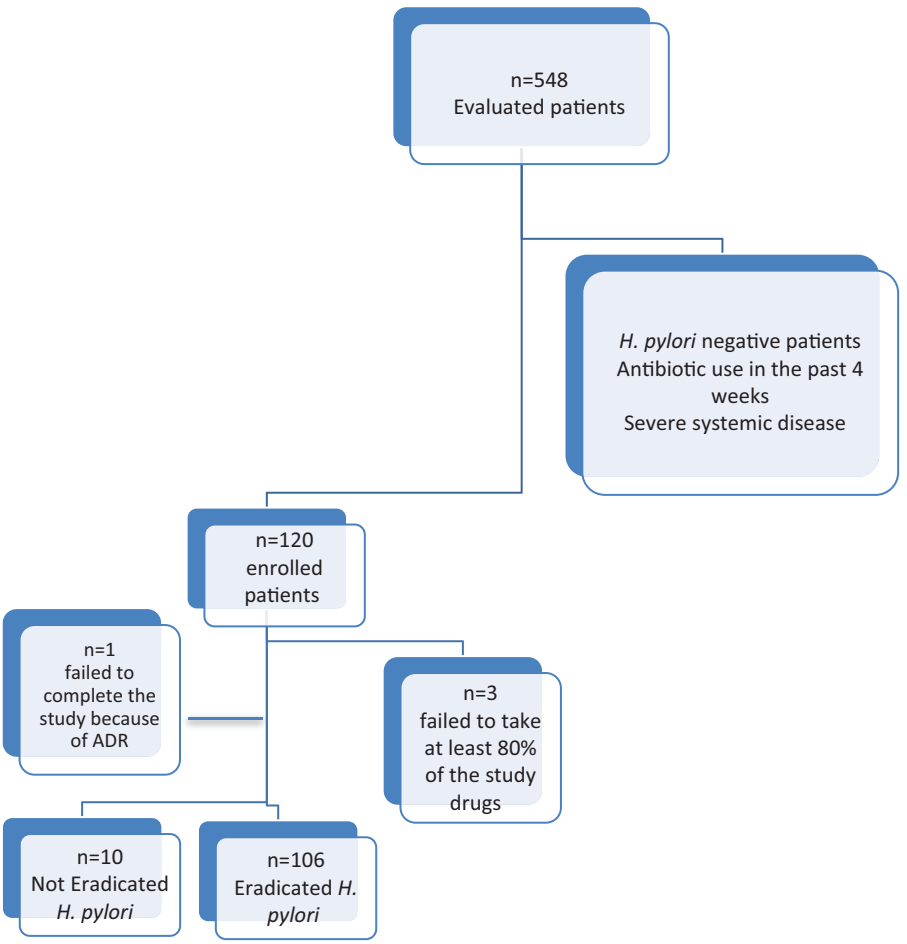

Figure 1. Flow diagram for the patient selection process. ADR = adverse drug reaction.

Table 3

Eradication rates according to endoscopic findings.

Variable	Eradication rate % (ITT analysis)	*P*
Nonulcerative		
Nonerosive	85.7 (12/14)	
Erosive	84.5 (38/45)	< 0.001
Ulcerative	91.8 (56/61)	

ITT = intention to treat.

Subgroup analysis revealed that 61 (92.6% PP and 89.7% ITT) female patients and 45 (88.5% PP and 86.5% ITT) male patients achieved eradication, which showed no significant statistical difference for both PP eradication and ITT rate ($P=1$ and 0.737, respectively). The ITT eradication rates were 91.8% (56/61) and 84.7% (50/59) in patients with and without ulcerative lesion, respectively ($P<0.001$, Table 3).

3.4. Side effects and compliance

Side effects were reported in 42% of patients, most commonly nausea (15%) and diarrhea (13.3%), and it was intense in only 1 patient, which led to discontinuation of the treatment (Table 4).

Three (2.5%) patients failed to take at least 80% of the study drugs because of poor compliance (Fig. 1). In total, 96.7% (116/120) of patients took the medications correctly

Table 4

Adverse effects ofgemifloxacin-containing therapy.

Adverse events	Number = 120 (%)
Any adverse effects	54 (45)
Nausea	18 (15)
Diarrhea	16 (13.3)
Skin rash	11 (9.2)
Abdominal pain	7 (5.8)
Bloating	9 (7.5)
Headache	13 (10.8)
Dizziness	9 (7.5)

4. Discussion

The prevalence of *H pylori* infection is reported to be as low as 30% in the developed countries, whereas it is found in at least 80% of people in developing and underdeveloped countries.[5]

The prevalence of *H pylori* infection among Iranian population varies from 30% up to 90% in different provinces.[5,22,23]*H pylori* serology was reported to be positive in 50% of Iranian children in 1 study.[24]

As well as higher prevalence rate of *H pylori* infection in Iran and many other developing countries, eradication rate of *H pylori* is much lower than that of western countries. Based on this, the treatment regimens suggested in western studies may not be ideal in Iran; thus, local surveys must be used in determination of treatment regimens and the duration of treatment.[6]

Due to the low eradication rate, an optimal therapeutic regimen has not yet been defined; moreover, triple therapies are not generally successful in Iran and quadruple therapy for a minimum duration of 2 weeks is considered as the best treatment schedule. Some of suggested quadruple regimens include clarithromycin, metronidazole, and furazolidone based.[25]

Considering the diverse effectiveness of different regimens in West Asian countries, patterns of antibiotic resistance of each country must be used to choose the ideal therapeutic option. Antibiotic resistance of *H pylori* has a strong influence on the selection of eradication therapy regimen. In recent years, resistances to antibiotics including metronidazole and clarithromycin have increased in Iran.[26] Talebi et al[27] have reported that in the north of Iran the resistance of *H pylori* to metronidazole, clarithromycin, tetracycline, and amoxicillin is 73.4%, 30%, 9%, and 6.8%, respectively. Another study in the north-west provinces of Iran found that the resistance of *H pylori* was 76.8% for metronidazole, 14.3% for clarithromycin, 18.7% for tetracycline, 28.6% for amoxicillin, 33.0% for ciprofloxacin, and 11.6% for nitrofurantoin.[28] In our report the resistance rate was 71.4%, 61.0%, 14.3%, 7.8%, and 6.5% for metronidazole, clarithromycin, levofloxacin, Amoxicillin, and gemifloxacin, respectively. According to our results, there is a dramatic increase in the clarithromycin resistance rate in comparison with other reports.

Recommendations for the management of *H pylori* infection are still evolving, and vary according to the demographic features. Higher prevalence rate of *H pylori* infection in Iran and many other developing countries and lower eradication rate by western regimen necessitates local surveys.[26] Because of the increasing rate of resistant strains to first-line antibiotics, there is a considerable interest in identifying alternative therapeutic regimens. Florouquinolones are a class of antibiotics with wide use for the treatment of respiratory, urinary tract, and gastrointestinal infections with excellent in vitro activity against *H pylori* compared with levofloxacin.[14,15] Chang et al[16] in an in vitro study revealed that gemifloxacin has greater in vitro antimicrobial activity in compression with levofloxacin against *H pylori*.

As a part of first-line quadruple therapy eradication regimen, combination of PPI, amoxicillin, levofloxacin, and rifaximin were successful in 80% (PP)[29] and quadruple therapy regimen with levofloxacin, tetracycline, bismuth, and PPI had 87% PP and 78% ITT eradication rate.[30]

The extensive use of quinolones for *H pylori* eradication worldwide increased the concern about the relationship between prior quinolone use and the subsequent emergence of *M. tuberculosis* resistant to quinolone.[31]

Gemifloxacin, a newer quinolone with poor activity against *M. tuberculosis*, can overcome this problem. Besides there is a dramatic increase in levofloxacin resistance in various different countries and there is a prompt need to choose a more potent quinolone in order to prevent the development of quinolone resistance during *H pylori* eradication. Gemifloxacin is showed to be superior to levofloxacin in antimicrobial activity against *H pylori* isolates and even overcame some levofloxacin resistance.[16]

We found that the eradication rate of *H pylori* infection in patients with ulcerative lesion (91.8%) was significantly higher when compared to patients without ulcer (84.7%). Similar result is shown in a meta-analysis conducted by Huang and Hunt[32], which there was a 9.2% difference in the eradication rate between peptic ulcer and nonpeptic ulcer disease. This finding was also confirmed in another meta-analysis of randomized-controlled trials in the treatment of *H pylori* infection.[33] In Broutet et al[34] study, the risk factors associated with the failure of *H pylori* eradication treatment in 2751 patients reviewed and found that the eradication rate of patients with ulcer was higher than patients without ulcer (78.1% vs 66.3%). Our study using a gemifloxacin-based regimen has confirmed the observation of an inferior eradication rate in patients with ulcer than those without ulcer.

As far as we know, there is no clinical study in the evaluation of *H pylori* eradication rate by gemifloxacin. This is the first study to show the excellent PP eradication rate (>90%) and good

tolerability of this rescuetherapy in second-line treatment of *H pylori* infection.

This therapeutic regimen had minor side effects such as dyspepsia which is a common problem in all therapeutic regimens. Gemifloxacin was tolerated well by the patients, overall.

There were some limitations in our experiment. First, it was an uncontrolled study, because our objective was mainly to identify a highly effective (90%) rescue regimen in our country. Besides, evaluation of more regimens needed more cases which would take a long time for case enrolment. Second, Gemifloxacin genotypic resistances were not done.

In conclusion, the results of this study revealed that Gemifloxacin has good efficacy and tolerability in combination with other therapeutic agents and could be introduced to the list of the second line *H pylori* therapeutic regimens. Gemifloxacin is given once daily and may be a better option where the patients' noncompliance is a major issue. This drug may be considered to be used in each conventional step of *H pylori* treatment and, more importantly, in failure cases it could be included in second-line rescue therapy regimen.

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