Clinical research

Comparison of moxifloxacin-based therapies and standard bismuth-based quadruple therapy for first-line treatment of *Helicobacter pylori* infection

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Abstract

Introduction: *Helicobacter pylori* antibiotic resistance continues to be an important issue for decisions regarding eradication treatment. The aim of our study was to compare the efficacy of two bismuth-containing quadruple regimens: one including moxifloxacin, and the other including metronidazole, tetracycline and triple therapy with moxifloxacin as a first-line regimen.
Material and methods: A total of 332 patients received three different regimens: (a) moxifloxacin-containing bismuth quadruple therapy, BMAR (bismuth subsalicylate 562 mg, BID, moxifloxacin 500 mg QD, amoxicillin 1 g, BID, rabeprazole 20 mg, BID); (b) standard bismuth quadruple therapy, BTMR (bismuth subsalicylate 562 mg, BID, tetracycline 500 mg, QID, metronidazole 500 mg, TID, rabeprazole 20 mg, BID, for 2 weeks); or (c) moxifloxacin-containing triple therapy, MAR (moxifloxacin 500 mg, QD, amoxicillin 1 g, BID and rabeprazole 20 mg, BID).
Results: The eradication rates of the three groups using ITT analysis were BMAR 93.6%, BTMR 78.4% and MAR 90.8%. Rates were 98.9%, 87% and 99.1%, respectively, using PP analysis. The eradication rate was significantly higher in the BMAR group than in the other groups based on ITT analysis ($p < 0.001$). There was no significant difference between the BMAR and MAR groups based on PP analysis ($p > 0.05$); however, the eradication rate was significantly higher in both of the groups than in the BTMR group ($p < 0.001$).
Conclusions: Moxifloxacin-containing regimens are efficacious choices for first-line therapy of *H. pylori* eradication. Adding bismuth therapy to moxifloxacin-based therapies only increases adverse events without increasing the eradication rate.

Key words: *Helicobacter pylori*, moxifloxacin, eradication.

Introduction

Helicobacter pylori is the most common bacterial infection worldwide and a leading cause of gastritis and gastroduodenal ulcer disease [1]. *Helicobacter pylori* infection is an important risk factor for gastric cancer and gastric MALT lymphoma. According to the literature, *H. pylori* appears to be responsible for 780,000 new cancers worldwide [2]. In addition to these gastric effects, *H. pylori* infection is associated with dys-

lipidaemia, resulting in atherosclerosis [3]. Overall, several data suggest that *H. pylori* infection-related complications significantly increase morbidity and mortality. Therefore, it is important to diagnose and treat this infection appropriately.

Currently advised therapeutic regimens differ among countries according to antibiotic resistance profiles of *H. pylori*. In countries where clarithromycin resistance is low (< 15%), clarithromycin-containing therapy is recommended. Turkey is a country with high clarithromycin resistance rates [4]. According to Maastricht V guidelines, bismuth-containing quadruple therapies are the first-line treatment options in *H. pylori* infection in Turkey. In addition to this option, fluoroquinolone-based therapies including levofloxacin and moxifloxacin are increasingly preferred by physicians according to the patient's allergy status to other antibiotics, concomitant kidney and liver function abnormalities and resistance to first-line non-fluoroquinolone-based therapies.

The objective of this study was to evaluate the effectiveness and safety of moxifloxacin-containing triple and moxifloxacin-based quadruple therapies in a tertiary state hospital in Turkey.

Material and methods

Study design and patient selection

Our study had a retrospective design. Consecutive patients who were diagnosed with *H. pylori* gastritis after endoscopic biopsy were enrolled between September 2017 and December 2017. The main indications for endoscopy were uninvestigated dyspepsia, dyspepsia with alarming features, resistant dyspepsia that did not respond to proton pump inhibitors (PPIs) and iron deficiency anaemia during this period. Four biopsy specimens (two from the corpus and two from the antrum) were obtained during all endoscopic procedures. *Helicobacter pylori* and gastritis were shown by Giemsa and haematoxylin and eosin staining in pathologic evaluation. Patient files and data systems were analysed to evaluate history, compliance with treatment and side-effects. Exclusion criteria were being younger than 18 years old, receiving medications such as bismuth preparations, treatment with proton pump inhibitors or antibiotics up to 4 weeks before upper endoscopy, history of *H. pylori* eradication treatment, malignant or severe disease, history of gastric surgery, pregnancy or lactation, and known allergy to antibiotics.

Treatment protocols

Three different treatment protocols were given to the patients by four gastroenterologists independently of one another: (a) moxifloxacin-containing bismuth quadruple therapy, BMAR (bismuth subsalicylate 562 mg, BID, moxifloxacin 500 mg, once daily BID, amoxicillin 1 g, BID, rabeprazole 20 mg, BID for 2 weeks) (n = 101 patients); (b) standard bismuth-containing quadruple therapy, BTMR (bismuth subsalicylate 562 mg, BID, tetracycline 500 mg, QID, metronidazole 500 mg, TID, rabeprazole 20 mg, BID, for 2 weeks) (n = 111 patients); or (c) moxifloxacin-containing triple therapy, MAR (moxifloxacin 500 mg, QD, amoxicillin 1 g, BID, rabeprazole 20 mg, BID, for 2 weeks) (n = 120 patients). *Helicobacter pylori* eradication was determined using the stool antigen test with an enzyme immunoassay utilizing a monoclonal antibody. The test was performed at least 4 weeks after the end of therapy.

Statistical analysis

Data were analysed using the computer program SPSS 23.0 (IBM, USA). Equality of variances was evaluated using Levene's test. One-way ANOVA was used for comparison of more than two group means for continuous data. The χ^2 test was used to compare demographic data, eradication rates, side-effects and symptoms among the treatment groups. In the assessment of treatment, per-protocol (PP) and intention-to-treat (ITT) analyses were used. In the ITT analysis, all participants were included. In the PP analysis, participants who did not follow the study protocol or dropped out of the study were excluded. Data were presented as the means ± standard deviation or number and percentage. Differences were considered significant at $p < 0.05$.

Results

A total of 332 patients were enrolled in the study: 120 in the MAR group, 111 in the BTMR group and 101 in the BMAR group. Overall, 159 patients were male and 173 patients were female. At the first admission, the most frequent complaint was dyspepsia (255/332, 75.3%), followed by abdominal pain (209/332, 62.9%) and reflux (166/332, 50%). After the endoscopic evaluation, the most common endoscopic finding was gastritis (277/332, 83.4%). Relevant demographic and endoscopic data are displayed in Tables I and II.

The efficacies of eradication regimens are shown in Table III. On ITT analysis, eradication rates were 94/101 (93.6%, 95% CI: 88.1–98.0) for the BMAR group, 87/111 (78.4%, 95% CI: 70.7–86.0) for the BTMR group and 109/120 (90.8%, 95% CI: 85.7–96.0) for the MAR group. On PP analysis, eradication rates were 94/95 (98.9%, 95% CI: 96.9–100.0) for BMAR, 87/100 (87%, 95% CI: 80.4–93.6) for BTMR and 109/110 (99.1%, 95% CI: 97.3–100.0) for MAR. When all treatment groups were compared to each other separately based on

Table I. Baseline patient characteristics

Parameter	BMAR	BTMR	MAR	*P*-value
Number of patients (ITT)	101	111	120	> 0.05
Age (mean ±SD) [years]	45.6 ±16.38	45.3 ±12.71	44.3 ±13.96	> 0.05
BMI (mean ± SD) [kg/m^2]	30.0 ±3.15[a]	27.8 ±4.56[b]	29.9 ±3.19[a]	< 0.001, < 0.001*
Sex % (M/F)	48/53	55/56	56/64	> 0.05
Smoking habit % (Y/N)	19.8/80.2	24.3/75.7	20.0/80.0	> 0.05

*[a,b]Protocols within a row without a common superscript differ. *p < 0.001 between BMAR and BTMR, p < 0.001 between BTMR and MAR, and p > 0.05 between BMAR and MAR. BMAR – bismuth subsalicylate 562 mg BID, moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID; BTMR – bismuth subsalicylate 5 62 mg BID, tetracycline 500 mg QID, metronidazole 500 mg TID, rabeprazole 20 mg BID; MAR – moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID.*

Table II. *Helicobacter pylori* eradication rates after various treatment regimens

Parameter	BMAR	BTMR	MAR	*P*-value
Intention-to-treat analysis:	94/101[a]	87/111[b]	109/120[c]	< 0.001*
n (%)	93.1	78.4	90.8	
95% CI	88.1–98.0	70.7–86.0	85.7–96.0	
Per-protocol analysis:	94/95[a]	87/100[a]	109/110[a]	0.006, < 0.001[¥]
n (%)	98.9	87.0	99.1	
95% CI	96.9–100.0	80.4–93.6	97.3–100.0	
Compliance:	95/101	100/111	110/120	> 0.05
n (%)	94.1	90.1	91.7	
95% CI	89.4–98.7	84.5–95.6	86.7–96.6	

*[a,b,c] Protocols within a row without a common superscript differ. *p < 0.001 between BMAR and BTMR, p < 0.001 between BTMR and MAR, and p < 0.001 between BMAR and MAR. [¥]p = 0.006 between BMAR and BTMR, p < 0.001 between BTMR and MAR, and p > 0.05 between BMAR and MAR. BMAR – bismuth subsalicylate 562 mg BID, moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID; BTMR – bismuth subsalicylate 562 mg BID, tetracycline 500 mg QID, metronidazole 500 mg TID, rabeprazole 20 mg BID, MAR – moxifloxacin 500 mg QD, amoxicillin 1 g, BID, rabeprazole 20 mg BID. CI – confidence interval.*

Table III. Initial symptoms and pre-treatment endoscopy findings of patients

Initial symptoms and endoscopy findings	BMAR *n*, %	BTMR *n*, %	MAR *n*, %	*P*-value
Dyspepsia	72, 71.3	91, 82.0	87, 72.5	> 0.05
Abdominal pain	57, 56.4	73, 65.8	79, 65.8	> 0.05
Reflux	57, 56.4[a]	46, 41.4[b]	63, 52.3[ab]	0.041, > 0.05, > 0.05
Premature fullness	25, 24.8[a]	17, 15.3[ab]	10, 8.3[b]	> 0.05, > 0.05, 0.002
Weight loss	8, 7.9	3, 2.7	4, 3.3	> 0.05
Loss of appetite	13, 12.9	11, 9.9	11, 9.2	> 0.05
Gastritis	79, 78.2[a]	107, 96.4[b]	91, 75.8[a]	< 0.001, < 0.001, > 0.05
Erosive gastritis	8, 7.9	9, 8.1	9, 7.5	> 0.05
Gastric ulcer	5, 5.0	6, 5.4	6, 5.0	> 0.05
Duodenal ulcer	11, 10.9	10, 9.0	10, 8.3	> 0.05
Oesophagitis	3, 3.0	9, 8.1	10, 8.3	> 0.05
Gastric polyp	9, 8.9	3, 2.7	6, 5.0	> 0.05
Duodenitis	10, 9.9[a]	31, 27.9[b]	8, 6.7[a]	0.002, < 0.001, > 0.05
LES dysfunction	31, 30.7	49, 44.1[a]	28, 23.3[b]	> 0.05, 0.001, > 0.05
Hernia	7, 6.9	5, 4.5	5, 4.2	> 0.05

*[a,b]Protocols within a row without a common superscript differ. *Three p-values were given for three comparisons: between BMAR and BTMR, between BTMR and MAR, and between BMAR and MAR respectively. BMAR – bismuth subsalicylate 562 mg BID, moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID; BTMR – bismuth subsalicylate 562 mg BID, tetracycline 500 mg QID, metronidazole 500 mg TID, rabeprazole 20 mg BID, MAR – moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID.*

Table IV. Relief of symptoms after treatment with three different treatment regimens

Parameter	Symptoms after treatment (Y/N)	
	n	%
BMAR	28/73	27.7/72.3
BTMR	38/73	34.2/65.8
MAR	36/84	30.0/70.0
P-value	> 0.05	

BMAR – bismuth subsalicylate 562 mg BID, moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID; BTMR – bismuth subsalicylate 562 mg BID, tetracycline 500 mg QID, metronidazole 500 mg TID, rabeprazole 20 mg BID; MAR – moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID.

H. pylori eradication rates by ITT analysis, there was a statistically significant difference among the BMAR, BTMR and MAR groups. Eradication rates were significantly higher in the BMAR group than in the other two groups. The eradication rate was significantly higher in the MAR group than in the BTMR group. On PP analysis, higher eradication rates were seen in the MAR and BMAR groups than in the BTMR group. There was no significant difference between the MAR and BMAR groups on PP analysis. Although there were significantly different eradication rates among the three groups, relief of symptoms did not improve significantly among the groups (Table IV).

In each group of patients, regardless of eradication regimen, various side-effects were seen. Overall, nausea (95/332, 28.6%) and darkened stools (90/332, 27.1%) were the two most common side-effects, and both were common to patients who were treated with bismuth-containing regimens. Bismuth-containing regimens were associated with significantly more side-effects than was the MAR regimen. All side-effects, their frequencies and comparisons among groups are shown in Table V.

Discussion

Our study showed that moxifloxacin-containing regimens had higher eradication rates compared to standard bismuth-based quadruple therapy. The Maastricht consensus conference declared that eradication rates > 80% and > 90% in ITT and PP analyses are effective therapeutic rates [5]. Our results demonstrated that moxifloxacin-containing triple and quadruple therapies had similar eradication rates, over 90%. This result was compatible with results reported in the literature. It is well known that the eradication rate is 90% in the first-line treatment and 70% in the second-line treatment with moxifloxacin-containing triple therapies [6].

Despite high eradication rates, moxifloxacin-containing regimens are generally used as

Table V. Side effects of different treatment regimens

Side effects	BMAR	BTMR	MAR	*P*-value*
Side effects of treatment % (Y/N)	57.4/42.6[a]	52.3/47.7[a]	30.0/70.0[b]	> 0.05, 0.008, < 0.001
Nausea (*n*, %)	38, 37.6[a]	41, 36.9[a]	16, 13.3[b]	> 0.05, < 0.001, < 0.001
Vomiting (*n*, %)	9, 8.9[a]	11, 9.9[a]	0, 0.0[b]	> 0.05, 0.001, 0.003
Metallic taste (*n*, %)	2, 2.0[a]	18, 16.2[b]	3, 2.5[a]	0.001, 0.001, > 0.05
Itchiness (*n*, %)	9, 8.9	7, 6.3	7, 5.8	> 0.05 for all
Skin rash (*n*, %)	8, 7.9	7, 6.3	7, 5.8	> 0.05 for all
Constipation (*n*, %)	0, 0.0	1, 0.9	0, 0.0	> 0.05 for all
Diarrhoea (*n*, %)	15, 14.9[a]	4, 3.6[b]	12, 10.0[ab]	0.009, > 0.05, > 0.05
Dysphagia (*n*, %)	3, 3.0	18, 16.2	1, 0.8	0.003, < 0.001, > 0.05
Chest pain (*n*, %)	3, 3.0	6, 5.4	1, 0.8	> 0.05 for all
Darkened stool (*n*, %)	45, 44.6[a]	42, 37.8[a]	3, 2.5[b]	> 0.05, < 0.001, < 0.001
Black tongue (*n*, %)	11, 10.9[a]	23, 20.7[a]	0, 0.0[b]	> 0.05, < 0.001, 0.001
Vaginal discharge (*n*, %)	4, 4.0	0, 0.0	4, 3.3	> 0.05 for all
Headache (*n*, %)	9, 8.9	4, 3.6	7, 5.8	> 0.05 for all
Abdominal pain (*n*, %)	9, 8.9	10, 9.0	8, 6.7	> 0.05 for all

*[a,b]Protocols within a row without a common superscript differ. *Three p-values were given for three comparisons: between BMAR and BTMR, between BTMR and MAR, and between BMAR and MAR. BMAR – bismuth subsalicylate 562 mg BID, moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID; BTMR – bismuth subsalicylate 562 mg BID, tetracycline 500 mg QID, metronidazole 500 mg TID, rabeprazole 20 mg BID, MAR – moxifloxacin 500 mg QD, amoxicillin 1 g BID, rabeprazole 20 mg BID.*

second-line treatments [7]. Currently, first-line treatments are usually standard quadruple therapies with bismuth salts, metronidazole and tetracycline in areas where clarithromycin resistance is high [8]. In the literature, early studies evaluating the efficacy of moxifloxacin-based therapies for first-line treatment of *H. pylori* reported a 90% eradication rate [9]. Nista and colleagues compared moxifloxacin-based triple therapies with clarithromycin-based triple therapy and found that moxifloxacin-based therapy provided high eradication rates [10]. Similarly, Wenzhen *et al.* found that moxifloxacin-based triple therapy was more effective than was clarithromycin-based triple therapy [11]. Rakici *et al.* compared levofloxacin- and moxifloxacin-based therapies and found that both regimens were more effective than were clarithromycin-based triple therapy [12]. Nevertheless, studies comparing bismuth-based standard quadruple therapies and moxifloxacin-based therapies as first-line therapy have been lacking. To our knowledge, the present study is the first to compare bismuth-based standard quadruple therapy with moxifloxacin-based therapies. For the first time, we demonstrated that moxifloxacin-based therapies provide optimum eradication rates compared to bismuth-based standard quadruple therapy.

It remains unanswered which moxifloxacin-based regimen is better, what the optimal dosage of moxifloxacin is, and what the optimum therapeutic choice is: sequential, hybrid or concomitant. Sacco *et al*. investigated the optimal dosage and duration of moxifloxacin-based triple therapies and found that 400 mg for 10 days was the best first-line treatment [13]. We used two different moxifloxacin-based regimens, one including additional bismuth, and we found no difference in terms of eradication rates in PP analyses. It is well known that bismuth salts are highly effective against *H. pylori* with high rates of adverse reactions and low patient compliance [14, 15]. Thus, we conclude that adding bismuth therapy to moxifloxacin is not necessary and is not an effective treatment option.

Resistance of *H. pylori* to various antibiotics remains an important therapeutic difficulty [16, 17]. In addition to its use in eradication, increasing use of second-generation fluoroquinolones such as levofloxacin and moxifloxacin is responsible for resistance [18]. In addition, antibiotic resistance profiles vary among countries. The oldest studies reported a 5% resistance rate for moxifloxacin [19]. A recent study from China showed that moxifloxacin resistance was 17.2% [20]. Shao *et al.* found a higher resistance rate of nearly 38.5% [21]. In Turkey, studies investigating the resistance to moxifloxacin are lacking. Kocazeybek *et al.* found that the rate of resistance to levofloxacin was 23.7%; it is possible that the resistance rate of moxifloxacin is similar to that of levofloxacin [4]. Overall, resistance to second-line fluoroquinolones is increasing, and this trend is an important limitation for first-line moxifloxacin-based regimens.

Our study has some limitations. The retrospective design is one. Assessing the optimum efficacy of *H. pylori* treatment protocols, prospective and randomized trials are necessary. Although our study had a retrospective design, the number of patients in each treatment arm was sufficient to compare treatment protocols. Another limitation is that the determination of adverse events of eradication regimens was performed by investigating patient files and the hospital data system.

It is an important issue to decide on an eradication protocol for *H. pylori* infection. Increasing antibiotic resistance makes *H. pylori* treatment more difficult. Culture-based antibiotic therapy is not feasible in most countries or in most hospitals. First-line eradication regimens generally reflect regional antibiotic resistance profiles. In Turkey, the recommended first-line eradication regimen is standard bismuth-based quadruple therapy with tetracycline and metronidazole. Various antibiotics are used as first-line eradication regimens in various countries, and moxifloxacin is one of them. Although we demonstrated that moxifloxacin-based eradication therapies were more effective than the standard bismuth-based quadruple therapy for the first time, increasing antibiotic resistance to moxifloxacin inhibits its use as a first-line treatment.

Conflict of interest

The authors declare no conflict of interest.

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