Should quinolones come first in *Helicobacter pylori* therapy?

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***Abstract*:** New generations of fluoroquinolones, like levofloxacin and moxifloxacin, exhibit a broad-spectrum activity against Gram-positive and Gram-negative bacteria, and have been successfully introduced into the treatment of *Helicobacter pylori* infection. Based on a large body of evidence, current guidelines recommend the use of levofloxacin- or moxifloxacin-containing proton-pump inhibitor (PPI) triple therapies in second-line or rescue treatment of *H. pylori* infection. The efficacy of standard PPI triple therapies has substantially declined during the last decade, mainly due to increasing resistance against the key antibiotics clarithromycin and metronidazole. Therefore, alternative strategies for first-line therapy of *H. pylori* infection have been evaluated in a considerable number of clinical trials including sequential regimens, nonbismuth quadruple regimens, and quinolone-containing PPI triple therapy regimens. The aim of this paper is to summarize the current body of evidence of levofloxacin- and moxifloxacin-containing regimens in first-line treatment of *H. pylori* infection, and to discuss the risks and benefits of these strategies in the light of increasing resistance of *H. pylori* to quinolones.

***Keywords*:** *Helicobacter pylori*, levofloxacin, moxifloxacin, quinolones, sitafloxacin, therapy, treatment

Introduction

Indications for a *Helicobacter pylori* eradication therapy are defined in several consensus guidelines. These indications include peptic ulcer disease, low-grade gastric mucosa-associated lymphoid tissue lymphoma, atrophic gastritis, and after resection of early gastric cancer. Furthermore, eradication therapy is considered an option in functional dyspepsia, in first-degree relatives of gastric cancer patients, or before starting a long-term therapy with nonsteroidal anti-inflammatory drugs or acetylsalicylic acid [Malfertheiner *et al.* 2007].

Conventional first-line eradication therapies may fail in up to 30% of patients, leading to a significant increase of antimicrobial resistance [Della Monica *et al.* 2002; Fennerty *et al.* 1999], particularly against the key antibiotics clarithromycin and/or metronidazole [Heep *et al.* 2000; Wang *et al.* 2000].

Current European and American guidelines recommend a combination of proton-pump-inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole for 7–14 days in first-line therapy. Furthermore, 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 for clarithromycin resistance are relatively high. Another option in first-line therapy is a quadruple therapy consisting of a PPI, amoxicillin, clarithromycin, and metronidazole [Chey and Wong, 2007; Malfertheiner *et al.* 2007].

The bismuth-based quadruple therapy containing a PPI or ranitidine, bismuth subsalicylate, metronidazole, and tetracycline is partially also recommended in first-line and second-line treatment for at least 10 days. However, the bismuth component is not available in many countries and the rate of side effects is relatively high [Chey and Wong, 2007; Malfertheiner *et al.* 2007].

Another possibility in second-line therapy is a combination of a quinolone and amoxicillin. For third-line treatment, a combination of

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rifabutin and amoxicillin is suggested. In general, susceptibility testing is strongly recommended after second therapy failure [Fischbach *et al.* 2009].

Quinolones in *H. pylori* eradication therapy

New generations of quinolones, like levofloxacin and moxifloxacin, with broad-spectrum activity against Gram-positive and Gram-negative bacteria are mainly used in infections of the respiratory and urogenital tract. The increasing use of quinolones in different countries is probably responsible for the rising resistance to these antibiotics of different classes of bacteria, including *H. pylori* [Glocker *et al.* 2007]. In *H. pylori*, single point mutations in the *gyrA* gene, the quinolone resistance-determining region, cause resistance to this class of antibiotics [Tankovic *et al.* 2003].

Cross-resistance between various quinolones was found in several studies [Wang *et al.* 2010; Bogaerts *et al.* 2006]. Although minimal inhibitory concentrations vary between the different generations, strains were still considered as resistant for all quinolones [Cattoir *et al.* 2007; Tankovic *et al.* 2003].

In Germany, the rate for quinolone-resistant *H. pylori* is about 10%, rising to 17% after previous treatment failures [Glocker *et al.* 2007]. Similar figures have recently been reported from other countries such as the UK [Chisholm and Owen, 2009], Italy [Romano *et al.* 2008], Japan [Miyachi *et al.* 2006], and Taiwan [Hung *et al.* 2009].

Quinolones are well-tolerated antibiotics with mainly mild adverse effects, like reactions of the gastrointestinal tract, the central nervous system, and the skin. Rare serious side effects are phototoxicity, cardiotoxicity, arthropathy, and tendinitis; they often lead to serious tolerability problems [De Sarro and De Sarro, 2001].

Fluoroquinolone use was found to be a risk factor for *Clostridium difficile*-associated diarrhea (CDAD) [Mera *et al.* 2010; McCusker *et al.* 2003]. It is still under discussion whether this association may only reflect the wide use of quinolones in patients predisposed for the occurrence of CDAD because of other reasons (age, comorbidity, etc.) [Deshpande *et al.* 2008].

In vitro experiments showed good antimicrobial activity for new fluoroquinolones such as levofloxacin and moxifloxacin [Bauernfeind, 1997] against a variety of Gram-positive and Gram-negative organisms including *H. pylori*, which were resistant to the established antibiotics.

A study from India showed an eradication success of up to 77% for a 2-week dual therapy with PPI and norfloxacin [Gupta *et al.* 1997]. Another Indian study compared three different regimens, containing a PPI, secnidazole, a nitroimidazole, and clarithromycin, amoxicillin or pefloxacin, an analog of norfloxacin not approved by the Food and Drug Administration. The combination with pefloxacin achieved an eradication success of 71% [Ahuja *et al.* 1998].

The first study on a levofloxacin-containing triple therapy in *H. pylori* first-line therapy by Cammarota and colleagues showed more promising results [Cammarota *et al.* 2000]. First data on second-line treatment were published by Wong and colleagues comparing a combination of a PPI, levofloxacin, and rifabutin with bismuth-containing quadruple therapy achieving high eradication rates in both groups of 92% and 91% [Wong *et al.* 2003].

Several studies on levofloxacin in second-line treatment followed, mostly randomized controlled trials, also comparing a levofloxacin-based regimen with the guideline-recommended second-line quadruple therapy. In the majority of these studies, levofloxacin 500 mg/day was administered in combination with a PPI and amoxicillin for either 7 or 10 days.

A meta-analysis by Gisbert and Morena showed an overall *H. pylori* eradication rate for the levofloxacin-based therapies of 81% (95% confidence interval (CI): 78–85%) *versus* 70% (95% CI: 66–74%) with the quadruple regimen, a difference of statistical significance [Gisbert and Morena, 2006]. Eradication rates of a levofloxacin-based regimen with a treatment duration of 10 days were higher than those of a 7-day treatment course (81% [95% CI: 78–84%] for 10 days *versus* 73% [95% CI: 68–79%] for 7 days of treatment; $p < 0.01$). Overall side effects of levofloxacin-based triple therapies appeared in 19% (95% CI: 15–22%) *versus* 44% (95% CI: 40–49%) of the patients receiving a bismuth-based quadruple therapy. Regarding severe adverse effects, a higher incidence in the quadruple regimen was also noticeable (0.8% *versus*

8.4%; 95% CI: 0.06–0.67). The meta-analysis showed no difference in side effects between a levofloxacin-based treatment of 7 or 10 days duration [Gisbert and Morena, 2006]. Similar results were reported in a second meta-analysis [Saad *et al.* 2006]. Later clinical studies would further confirm these figures [Di Caro *et al.* 2009; Gisbert *et al.* 2008].

The new fluoroquinolone moxifloxacin was not launched until 1999 for the treatment of respiratory tract infections with a comparable antibacterial spectrum as levofloxacin but with fewer phototoxic and central nervous system-excitatory effects [De Sarro and De Sarro, 2001]. In early studies, promising eradication rates of about 90% in the first-line therapy of *H. pylori* were reported [Nista *et al.* 2005; Di Caro *et al.* 2002a].

Data on moxifloxacin-containing second-line therapy are rare. First studies were published by a Korean group, first comparing a triple therapy containing moxifloxacin 400 mg/day, amoxicillin, and a PPI with a bismuth-based quadruple therapy, both for 7 days. Eradication rates were 75.6% with the moxifloxacin triple therapy, and 54.5% with the quadruple therapy by intention-to-treat (ITT) analysis. In a second study, both regimens were extended to 10 days (moxifloxacin-based triple) and 14 days (quadruple therapy), achieving eradication rates of 72% in both groups. In both studies, the moxifloxacin regimen was superior in terms of side-effect rates and patient compliance [Kang *et al.* 2007; Cheon *et al.* 2006].

Comparing a moxifloxacin-containing triple therapy plus a PPI and metronidazole with a bismuth-based quadruple therapy for 7 days, eradication rates of 73% and 54% were reported from Croatia [Bago *et al.* 2009]. In Korea, treatment success of a second-line triple therapy (moxifloxacin, amoxicillin, and esomeprazole) was prospectively observed over a period of 5 years. Although treatment duration was extended from 7 to 10 days and later to 14 days, eradication rates declined (2004: 75%; 2005–2006: 72%; 2007–2008: 68% in ITT analysis). That effect is most likely due to the rapidly increasing prevalence of resistance to moxifloxacin of the enrolled patients in the same period (2004: 6%; 2005–2006: 12%; 2007–2008: 28%) [Yoon *et al.* 2009]. A study from our group showed an overall eradication rate of 78% for the combination of a PPI, moxifloxacin, and rifabutin for 7 days in rescue therapy of *H. pylori* infection [Miehlke *et al.* 2008]. From a currently ongoing randomized multicenter trial, we have recently reported an eradication rate of 80% and 91% following a 7-day or 14-day treatment, respectively, with esomeprazole, moxifloxacin, and amoxicillin by interim analysis [Berning *et al.* 2009].

Levofloxacin in first-line therapy

The first prospective study with 100 patients compared two different levofloxacin-containing triple therapies together with rabeprazole and either amoxicillin or tinidazole [Cammarota *et al.* 2000]. The dosage of levofloxacin was 500 mg once a day. Both groups achieved high eradication rates with 92% and 90% in ITT analysis. Only mild adverse side effects occurred in a low rate in both therapy regimens. Hereafter, the same group published a study comparing a triple therapy consisting of levofloxacin, amoxicillin, and rabeprazole for 7 days with a dual therapy consisting of levofloxacin and rabeprazole for 5, 7, or 10 days. According to their preliminary findings, an eradication rate of 90% was reached for the triple therapy, while the dual therapies did not achieve acceptable eradication rates (50–70%), irrespective of the therapy extension [Di Caro *et al.* 2002b]. This study was followed by a large randomized trial with 300 patients who were treated with either a standard therapy, consisting of a PPI, clarithromycin, metronidazol, or amoxicillin, or a levofloxacin-containing triple therapy, this time combined with clarithromycin. Again, a high eradication rate of 87% in the levofloxacin-containing therapy was achieved, significantly higher than the standard regimens with eradication rates of 72% and 75% [Nista *et al.* 2006].

Another Italian group could not achieve similar eradication rates in a study comparing a triple therapy containing levofloxacin, azithromycin, and a PPI with a standard triple therapy with amoxicillin, clarithromycin, and a PPI. Here, both regimens lead to eradication rates of 65% in ITT analysis, whereas the tolerability was significantly higher for the levofloxacin-containing therapy [Iacopini *et al.* 2005].

A study from Germany randomized 61 patients to either levofloxacin, amoxicillin, and esomeprazole or a standard triple therapy. Levofloxacin was prescribed in a higher dosage of 2×500 mg. The eradication rate was 87% after levofloxacin triple therapy and 84% following

standard triple therapy. Of interest, antibiotic susceptibility testing was performed prior to enrollment. In three patients treated with levofloxacin triple therapy, a double resistance of *H. pylori* to clarithromycin and metronidazole was found. A single resistance of *H. pylori* to clarithromycin was found in another two patients. All five patients were treated successfully with the study regimen. This suggests that a resistance to clarithromycin and metronidazole seems not to affect the efficacy of levofloxacin triple therapy. A pretreatment levofloxacin resistance was found in two patients (3%), one in each group. The eradication therapy succeeded in both patients [Antos *et al.* 2006].

An Italian study with 130 patients compared a triple therapy containing levofloxacin (2×250 mg) and amoxicillin with standard triple therapy containing clarithromycin and amoxicillin. By ITT analysis, eradication rates of 91% for the levofloxacin triple regimen and 77% for the standard therapy were achieved. Unfortunately, no specifications about the local resistance situation were applied [Rispo *et al.* 2007].

In 2007 and 2009 Gisbert and colleagues from Spain published two prospective uncontrolled studies with 64 and 75 patients, respectively, evaluating the combination of levofloxacin 2×500 mg and amoxicillin together with ranitidine bismuth citrate or a PPI for 10 days. Eradication rates in both studies were similar at 84% and 83%. Both combinations were tolerated well. Based on a previous study in the same geographical area, the authors assumed for this patient population a low resistance rate to quinolones of about 6% [Gisbert *et al.* 2009, 2007]. In a recently published study, the same group compared two triple therapies containing levofloxacin or clarithromycin with another two sequential regimens also containing levofloxacin or clarithromycin. The standard regimen with a low ITT eradication rate of 64% was inferior to the levofloxacin-containing triple therapy as well as to both sequential regimens, most likely due to a high resistance rate to clarithromycin and metronidazole in this population. Unfortunately, no pretreatment susceptibility testing was available. The eradication rate for the combination of levofloxacin, amoxicillin, and omeprazole for 10 days was reported to be 83%, just as in the sequential regimen omeprazole, amoxicillin for 5 days, followed by omeprazole, levofloxacin, and metronidazole for another 5 days [Molina-Infante *et al.* 2010].

A prospective study with 123 patients from The Netherlands, treating in first-, second and third-line, achieved very high eradication rates of 96% and 93% for levofloxacin-containing (2×500 mg) triple therapies together with amoxicillin or clarithomycin in the first-line subpopulation. As a possible reason for the high cure rate, the authors presumed a low quinolone resistance in The Netherlands because of a lower use of quinolones compared with other countries [Schrauwen *et al.* 2009].

A large crossover multicenter trial from Taiwan, which compared a standard triple therapy with a triple regimen containing levofloxacin and amoxicillin, showed an advantage for the standard triple therapy (84% *versus* 74%) in a population with low resistance to clarithromycin and levofloxacin (both <10%). After unsuccessful treatment, patients were retreated in a crossover fashion for 10 days. In this case, the strategy starting with the standard triple therapy and, if required, retreating with the levofloxacin-containing triple regimen was superior compared with the reverse approach (93% *versus* 85% overall eradication success in ITT) [Liou *et al.* 2010].

Moxifloxacin in first-line therapy

Data about moxifloxacin in the first-line treatment of *H. pylori* arise mainly from Italy with mostly good eradication rates. The first study was published in 2002 by Di Caro and colleagues who treated a total of 120 patients with either moxifloxacin alone, lansoprazole and moxifloxacin, or lansoprazole, moxifloxacin, and clarithromycin for 1 week. In the triple combination, an eradication rate of 90% could be achieved, while the other groups reached much lower eradication rates [Di Caro *et al.* 2002a].

In 2005, the same group compared two different moxifloxacin-containing triple therapies (esomeprazole + moxifloxacin + amoxicillin and esomeprazole + moxifloxacin + tinidazole) with respective clarithromycin-containing therapies. Eradication rates of about 88–90% were obtained in the moxifloxacin-containing regimens, while the regimens including clarithromycin succeeded in only 73–75% of patients. In both single-center randomized studies, treatment duration was 7 days, moxifloxacin dosage 400 mg/day [Nista *et al.* 2005].

Similar findings were reported by a Croatian group using the same moxifloxacin dosage and treatment duration. In a randomized controlled trial with 128 patients, PPI triple therapies containing moxifloxacin and amoxicillin or metronidazol were tested against standard triple therapies. Moxifloxacin-containing triple therapies showed significantly higher eradication rates (86–93% *versus* 70–78%), and were better tolerated than standard triple therapies containing clarithromycin. Primary resistance to moxifloxacin was found in 5.9% of cases. *H. pylori* eradication rates were significantly higher in patients infected with quinolone-sensitive strains compared with those infected with quinolone-resistant strains following PPI triple therapy with moxifloxacin and amoxicillin (91.1% *versus* 66.7%), or with moxifloxacin and metronidazole (98.1% *versus* 75%) in first-line treatment [Bago *et al.* 2007]. Another recent randomized study of the same group including 150 patients, reported an ITT eradication rate of 76% and 84% after 7 and 10 days of first-line therapy with lansoprazole, moxifloxacin, and amoxicillin, respectively [Bago *et al.* 2010]. Again, primary resistance of *H. pylori* to moxifloxacin, which was found in 6% of cases, significantly reduced the eradication rate (98% and 66% in moxifloxacin-sensitive and -resistant strains).

Two small Turkish studies showed surprisingly low eradication rates of 53–67% [Kilic *et al.* 2008] and 42% [Sezgin *et al.* 2007] for the combination of a PPI or ranitidine bismuth citrate, moxifloxacin, and amoxicillin given for 14 days. However, the authors refer to low eradication rates for standard triple therapy of about 50–63% in their population. Unfortunately, pretreatment resistance rates were not available. Therefore, the reasons for these low eradication rates remain unknown, but are likely caused by a high resistance to antibiotics in the population.

A recent study from Italy compared four different groups all treated with moxifloxacin, amoxicillin, and esomeprazole. Three groups were treated with high-dose moxifloxacin (2×400 mg/day) for 10, 7 and 5 days, one with 400 mg/day moxifloxacin for 10 days. Eradication rates were 90% for moxifloxacin 2×400 mg/day (10 days) and 80% for both moxifloxacin 2×400 mg/day (7 days) and moxifloxacin 1×400 mg/day (10 days). Despite a higher dosage of moxifloxacin, all groups showed only mild adverse effects with no statistical difference between the different regimens [Sacco *et al.* 2009].

Discussion

Based on a large body of published clinical trials, a quinolone-based PPI triple therapy is effective and safe, and shows similar or better outcome parameters compared with the standard PPI first-line therapy. Compared with bismuth-based quadruple therapy, PPI triple regimens containing levofloxacin or moxifloxacin are better tolerated, and more effective if used for at least 10 days. Treatment duration of 7 or 10 days appears to make no difference with regard to side effects or patient compliance.

The "American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection" and the German level 3 guideline "*Helicobacter pylori* and Gastroduodenal Ulcer Disease" both recommend a combination of PPI, levofloxacin 500 mg/day, or moxifloxacin 400 mg/day, and amoxicillin 2×1 g/day as an option for second-line treatment [Fischbach *et al.* 2009; Chey and Wong, 2007]. The underlying data come from numerous studies, mostly comparing this regimen with the conventional second-line therapy, a quadruple of PPI, bismuth subsalicylate, metronidazole, and tetracycline. An advantage in *H. pylori* eradication rate and tolerability was clearly shown [Gisbert and Morena, 2006]. More data on moxifloxacin or other fluoroquinolones in second-line anti-*H. pylori* treatment has been accumulated more recently. Similar to the studies involving levofloxacin, they show advantages in terms of eradication and side-effect rates compared with the bismuth-containing quadruple therapy [Bago *et al.* 2009; Kang *et al.* 2007; Cheon *et al.* 2006].

So far, a total of about 900 patients from 11 studies have been treated with different levofloxacin-containing triple regimen in first-line therapy. The eradication rates, with the exception of one study, ranged from 74% to 96% (Table 1). Similar findings were reported for moxifloxacin in first-line therapy (Table 2) [Bago *et al.* 2010; Sacco *et al.* 2009; Kilic *et al.* 2008; Bago *et al.* 2007; Sezgin *et al.* 2007; Nista *et al.* 2005; Di Caro *et al.* 2002a].

Is this enough data to recommend a quinolone-based triple therapy in first-line therapy of *H. pylori* infection? As mentioned before, primary quinolone resistance in *H. pylori* is reported to be

Table 1. Levofloxacin-based first-line treatment regimens in *H. pylori* infection.

First author Year	Study design	Patients (*n*)	Regimens	Treatment duration (days)	Eradication rates, intention to treat (%) (*n*)	Side effects (%)
Cammarota [2000]	Prospective randomized	100	RAB 20 mg od, LEV 500 mg od, AMO 1000 mg bid	7	92 (46/50)	8
			RAB 20 mg od, LEV 500 mg od, TIN 500 mg bid		90 (45/50)	10
Di Caro *et al.* [2002b]	Prospective randomized	160	RAB 20 mg od, LEV 500 mg od	5	50 (20/40)	0
			RAB 20 mg od, LEV 500 mg od	7	70 (28/40)	0
			RAB 20 mg od, LEV 500 mg od	10	65 (26/40)	15
			RAB 20 mg od, LEV 500 mg od, AMO 1000 mg bid	7	90 (36/40)	30
Iacopini [2005]	Prospective randomized	164	ESO 20 mg od, LEV 500 mg od, AZI 500 mg od	7	65 (54/83)	12
			ESO 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	65 (53/81)	30
Nista [2006]	Prospective randomized	300	ESO 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	75 (75/100)	20
			ESO 20 mg bid, CLA 500 mg bid, MET 500 mg bid	7	72 (72/100)	18
			ESO 20 mg bid, CLA 500 mg bid, LEV 5000 mg bid	7	87 (87/100)	13
Antos [2006]	Prospective randomized	61	ESO 40 mg bid, LEV 500 mg bid, AMO 1000 mg bid	7	87 (26/30)	52
			ESO 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	84 (26/31)	41
Gisbert [2007]	Prospective	64	RBC 400 mg bid, LEV 500 mg bid, AMO 1000 mg bid	10	84 (54/64)	10
Rispo [2007]	Prospective randomized	130	ESO 20 mg bid, LEV 250 mg bid, AMO 1000 mg bid	7	91 (59/65)	*
			ESO 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	77 (50/65)	
Schrauwen [2009]	Prospective	104[$]	ESO 40 mg bid, LEV 500 mg bid, AMO 1000 mg bid	7	96 (43/45)[$]	29[‡]
			ESO 40 mg bid, LEV 500 mg bid, CLA 500 mg bid	7	93 (55/59)[$]	41[‡]
Castro-Fernández [2009]	Prospective	135	OME 20 mg bid[§], LEV 500 mg bid, AMO 1000 mg bid	10	72 (97/135)	12
Gisbert [2009]	Prospective	75	OME 20 mg bid, LEV 500 mg bid, AMO 1000 mg bid	10	83 (62/75)	13
Molina-Infante [2010]	Prospective randomized	460	OME 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	10	64 (74/115)	25
			OME 20 mg bid, LEV 500 mg bid, AMO 1000 mg bid	10	80 (93/115)	27
			OME 20 mg bid (1–10), AMO 1000 mg bid (1–5), CLA 500 mg bid (6–10), MET 500 mg bid (6–10)	10	77 (88/115)	25
			OME 20 mg bid (1–10), AMO 1000 mg bid (1–5), LEV 500 mg bid (6–10), MET 500 mg bid (6–10)	10	83 (95/115)	25
Liou [2010]	Prospective randomized	432	LAN 30 mg bid, LEV 750 mg od, AMO 1000 mg bid	7	74 (161/217)	*
			LAN 30 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	84 (180/215)	

*No data; [$]only data from first-line therapies; [‡]data allowing no discrimination between first- and second-line; [§]or other PPI bid.
AMO, amoxicillin; AZI, azithromycin; bid, twice daily; CLA, clarithromycin; ESO, esomeprazole; LAN, lansoprazole; LEV, levofloxacin; MET, metronidazole; od, once daily; OME, omeprazole; RAB, rabeprazole; RBC, ranitidine bismuth citrate; TIN, tinidazole.

Table 2. Moxiflocaxin-based first-line treatment regimens in *H. pylori* infection.

First author Year	Study design	Patients (*n*)	Regimens	Treatment duration (days)	Eradication rate, intention to treat (%) (*n*)	Side effects (%)
Di Caro *et al.* [2002a]	Prospective randomized	120	MOX 400 mg od	7	23 (9/40)	8
			LAN 30 mg od, MOX 400 mg od	7	33 (13/40)	13
			LAN 30 mg od, MOX 400 mg od, CLA 500 mg bid	7	90 (36/40)	13
Nista [2005]	Prospective randomized	320	ESO 20 mg bd, MOX 400 mg od, AMO 1000 mg bid	7	88 (70/80)	13
			ESO 20 mg bid, MOX 400 mg od, TIN 500 mg bid	7	90 (72/80)	14
			ESO 20 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	73 (58/80)	33
			ESO 20 mg bid, CLA 500 mg bid, TIN 500 mg bid	7	75 (60/80)	36
Bago [2007]	Prospective randomized	277	LAN 30 mg bid, MOX 400 mg od, MET 400 mg bid	7	94 (58/62)	8
			LAN 30 mg bid, MOX 400 mg od, AMO 1000 mg bid	7	86 (57/66)	5
			LAN 30 mg bid, CLA 500 mg bid, MET 400 mg bid	7	70 (50/71)	18
			LAN 30 mg bid, CLA 500 mg bid, AMO 1000 mg bid	7	78 (61/78)	9
Sezgin [2007]	Prospective	71	PAN 40 mg bid, MOX 400 mg od, AMO 1000 mg bid	14	42 (30/71)	30
Kilic [2008]	Prospective randomized	120	RBC 400 mg bid, CLA 500 mg bid, AMO 1000 mg bid	14	77 (23/30)	37
			RBC 400 mg bid, MOX 400 mg od, AMO 1000 mg bid	14	67 (20/30)	42
			ESO 40 mg bid, CLA 500 mg bid, AMO 1000 mg bid	14	63 (19/30)	57
			ESO 40 mg bid, MOX 400 mg od, AMO 1000 mg bid	14	53 (16/30)	70
Sacco [2009]	Prospective randomized	399	ESO 20 mg bid, MOX 400 mg bid, AMO 1000 mg bid	10	90 (85/94)	12
			ESO 20 mg bid, MOX 400 mg bid, AMO 1000 mg bid	7	80 (82/102)	16
			ESO 20 mg bid, MOX 400 mg bid, AMO 1000 mg bid	5	71 (70/98)	12
			ESO 20 mg bid, MOX 400 mg od, AMO 1000 mg bid	10	80 (84/105)	13
Bago [2010]	Prospective randomized	150	LAN 30 mg bid, MOX 400 mg od, AMO 1000 mg bid	7	76 (57/75)	15
			LAN 30 mg bid, MOX 400 mg od, AMO 1000 mg bid	10	84 (63/75)	24

*No data.
AMO, amoxicillin; bid, twice daily; CLA, clarithromycin; ESO, esomeprazole; LAN, lansoprazole; MET, metronidazole; MOX, moxifloxacin; od, once daily; PAN, pantoprazole; RBC, ranitidine bismuth citrate; TIN, tinidazole.

relatively low in populations where quinolone consumption is low. Unfortunately, these figures seem to have increased over the last years [Chang *et al.* 2009; Hung *et al.* 2009; Glocker *et al.* 2007]. In other countries with high use of quinolones, a primary resistance of about 20% and higher has already been reported [Zullo *et al.* 2007]. Previous quinolone use in other indications caused an abrupt rise of levofloxacin-resistance in *H. pylori* from 2% in quinolone-naïve native Americans to 17% after one course of quinolone treatment, and up to 60% after two or more courses [Carothers *et al.* 2007]. In addition, there appear to be higher rates of levofloxacin resistance in older patients [Zullo *et al.* 2007]. After failure of a levofloxacin-

based eradication therapy, levofloxacin resistance rates increased to 30%. Unfortunately, failure of classical first-line regimens not containing quinolones did also increase the rate of levofloxacin resistance [Romano *et al.* 2008; Glocker *et al.* 2007; Perna *et al.* 2007].

The impact of primary quinolone resistance on the efficacy of quinolone-containing first-line therapy has not been thoroughly investigated so far. An Italian study with 40 patients receiving a second-line treatment with a PPI, levofloxacin, and amoxicillin showed a much lower eradication rate in quinolone-resistant strains (75% *versus* 33.3%; $p = 0.074$) in a population with 30% of patients infected by levofloxacin-resistant strains [Perna *et al.* 2007]. Gatta and colleagues reported an eradication rate of 55.5% (10 out of 18 patients with known levofloxacin resistance, mostly multi-resistant also to clarithromycin and metronidazole) [Gatta *et al.* 2005]. On the other hand, another Italian study investigating the benefit of susceptibility test-driven therapy in first- and second-line levofloxacin-based eradication therapy demonstrated cure rates of over 90% in first-line therapy for tailored therapy regimen as well as for empirical therapy. In second-line therapy, there was a significant difference favoring the susceptibility test-driven therapy (97% *versus* 81%; $p < 0.01$). The resistance rate for levofloxacin was 10% for patients who had never received an *H. pylori* treatment before and 12% after one failure [Marzio *et al.* 2006]. The eradication success of levofloxacin-based triple therapy seems not to be affected by clarithromycin and/or metronidazole resistance [Antos *et al.* 2006; Gatta *et al.* 2005; Bilardi *et al.* 2004]. 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% *versus* 98%) [Bago *et al.* 2010].

Therefore, in populations with clarithromycin resistance greater than 15–20% and low quinolone resistance rates, a PPI triple therapy with levofloxacin or moxifloxacin might be considered. For this strategy, an acceptable threshold of 10% for quinolone resistance is currently being discussed [Gisbert *et al.* 2007; Marzio *et al.* 2006]. 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 in other indications should not be treated with quinolone-containing eradication regimens.

For quinolone-containing PPI triple therapy, a treatment duration of 10 days showed an advantage over 7 days in second-line or rescue regimen [Gisbert and Morena, 2006], but for first-line treatment of *H. pylori* infection there is not enough evidence. Most of the studies were performed with a treatment duration of only 7 days (Table 1), suggesting this to be sufficient. So far, in second-line treatment, no difference in eradication success was demonstrated with a levofloxacin dosage of 500 mg/day *versus* 250 mg twice a day [Saad *et al.* 2006], as well as with levofloxacin 500 mg/day *versus* 500 mg twice a day [Di Caro *et al.* 2009]. Again, in first-line treatment similar data do not exist, so that a single levofloxacin dose of 500 mg/day according to second-line guideline recommendations can currently be considered optimal.

At present, the combination of levofloxacin/moxifloxcin and amoxicillin should be preferred over clarithromycin, since most data were published on an amoxicillin-containing PPI triple regimen. Such a combination should also be favored because of the extremely low rates of first and secondary resistance to amoxicillin. In the special case of patients with intolerance to penicillin, a PPI triple therapy containing a quinolone and rifabutin could be an alternative [Gisbert *et al.* 2010, 2006].

Both sequential regimens with standard antibiotics and concomitant nonbismuth quadruple therapies have shown promising results in first-line therapy of *H. pylori* infection providing eradication rates of 90% and higher [Essa *et al.* 2009; Jafri *et al.* 2008]. Therefore, these regimens are currently recommended as valuable alternatives for first-line therapy by the German guidelines [Fischbach *et al.* 2009]. A recent study from Spain, however, could not confirm a benefit of a sequential regimen containing levofloxacin compared with a levofloxacin triple therapy or conventional sequential therapy [Molina-Infante *et al.* 2010]. Thus, a sequential regimen

containing levofloxacin cannot be recommended at the moment.

In summary, large randomized controlled trials are certainly needed to explore further the role of quinolones in first-line treatment, especially in times of increasing resistance to quinolones in *H. pylori* infection. The relationship between primary quinolone resistance and eradication success as well as the development of secondary resistance after treatment failure deserves permanent attention.

Conclusion

A quinolone-based triple therapy is a safe and well-tolerated option in anti-*H. pylori* therapy. In second-line or rescue treatment, the combination of a PPI, levofloxacin or moxifloxacin, and amoxicillin is a valid option, especially in countries where bismuth salts are unavailable. In first-line therapy, a quinolone-based triple therapy can not generally be recommended at the moment. 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 levofloxacin or moxifloxacin, and amoxicillin for 7–10 days could be a valuable alternative, especially in quinolone- naïve patients.

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