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MINIREVIEWS

Quinolone-based first, second and third-line therapies for *Helicobacter pylori*

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Abstract

Helicobacter pylori (*H. pylori*) is a very common bacterium that infects about 50% of the world population in urban areas and over 90% of people living in rural and developing countries. Fluoroquinolones, a class of antimicrobials, have been extensively used in eradication regimens for *H. pylori*. Levofloxacin is the most commonly used, and in second-line regimens, is one of the most effective options. However, an increasing resistance rate of *H. pylori* to fluoroquinolones is being observed, that will likely affect their effectiveness in the near future. Other novel fluoroquinolone molecules, such as moxifloxacin, sitafloxacin, gatifloxacin and gemifloxacin, have been proposed and showed encouraging results *in vitro*, although data on their clinical use are still limited. Further studies in large sample trials are needed to confirm their safety and efficacy profile in clinical practice.

Key words: *Helicobacter pylori*; Eradication regimens; Fluoroquinolones; Antibiotic resistance; Levofloxacin; Rescue treatments

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Core tip: In the present minireview, we analyzed current evidence about the use of fluoroquinolones in first, second and third-line eradication regimens for *Helicobacter pylori* (*H. pylori*). The increasing resistances to levofloxacin are a worrying issue, that confirm the need to use this drug with proper care. We analyzed the current use of fluoroquinolones in first-line and rescue regimens, underlining possible pitfalls and mistakes that could be avoided in clinical practice. Novel molecules have been investigated, that could offer an interesting tool to combat *H. pylori*.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a very common bacterium that infects about 50% of the world population in urban areas and over 90% of people living in rural and developing countries[1,2]. The imperative to treat *H. pylori* infection lies in the fact that it is a known risk factor for benign[3] (chronic gastritis and peptic ulcer disease) and malignant [adenocarcinoma and mucosa-associated lymphoid tissue lymphoma] gastric disorders[4]. Indeed, bacterial eradication may change the natural course of these diseases and prevent their malignant evolution[5].

Currently, first-line therapies (triple, sequential or concomitant regimens) are able to achieve eradication in about 80% of cases but when these fail, a second-line regimen is necessary. In this case, Maastricht Ⅳ guidelines advise a levofloxacin-containing triple therapy or a bismuth-based quadruple regimen[6]. Since bismuth is not available worldwide and in some countries an excessive number of tablets of tetracycline formulations may be needed to obtain a therapeutic effect[7], fluoroquinolone-containing triple therapies are being adopted with increasing frequency several fluoroquinolone-based protocols, mainly including levofloxacin, have been proposed and tested in different combinations as first, second and third-line treatment for *H. pylori* eradication[8].

Aim of this review is to depict an all-encompassing scenario of the use of fluoroquinolones for *H. pylori* eradication.

FLUOROQUINOLONES: MAIN CHARACTERISTICS IN THE *H. PYLORI* CONTEXT

The fluoroquinolone drug class is active against both gram-positive and gram-negative bacteria. It acts by inhibiting DNA gyrase, a type Ⅱ topoisomerase, as well as topoisomerase Ⅳ, an enzyme necessary to separate replicated bacterial DNA, thus inducing a block of cell division[9]. This mechanism explains its effectiveness against *H. pylori*. However, the resistance of this bacterium to fluoroquinolones is due to point mutations in the *gyrA* region[10].

The antibiotics belonging to this class that have been applied for *H. pylori* eradication are moxifloxacin, sitafloxacin and levofloxacin, which is the most commonly employed. Although guidelines recommend its use in second-line regimens, several studies have used this antibiotic in first-line treatment. This last application may theorically not be correctly indicated because of the risk of further increasing antibiotic resistances[11] due to plasmid-mediated horizontally transferable genes[12]. An example of this unfavorable trend has been observed in Asian countries, where the resistance rates are largely above 10%: 18.4% in Vietnam[13], 20.6% in China[14] and 63.3% in Pakistan[15]. Only Malaysia registered 0%[16] and Japan 8.2%[17].

In Europe, the global resistance to levofloxacin, according to a recent multicentric epidemiologic study, is 14.1%[12], with values ranging from 11.7% in Ireland[18] to 29.1% in Germany[19]. This last percentage should be paid particular attention, if we consider that in 2003 a resistance rate of only 3.3% was detected in France[20]. In Italy a single study found resistance in 10.6% of the strains[21]; this result was confirmed by a recent overview that observed a rate of 11.8% in already treated patients[22].

THE USE OF LEVOFLOXACIN IN *H. PYLORI* ERADICATION REGIMENS

Second line treatments

Levofloxacin has been mainly employed after failure of a first-line regimen, usually in combination with amoxicillin [levofloxacin-based triple therapy (LTT)] for a variable period lasting from 7 to 10 d[23]. Current literature demonstrates that LTT is still more effective than bismuth-containing quadruple therapy. In a meta-analysis by Di Caro *et al*[24] the overall eradication rates were 76.5% in the LTT group and 67.4% in the quadruple regimen group. The superiority of LTT was more evident when it was administered for 10 d (88.7%) as compared to 7 d (70.6%). In a similar meta-analysis by Gisbert *et al*[25], a better tolerability profile of LTT in second-line treatment as compared to the quadruple regimen protocol including bismuth was reported: adverse events occurred in 0.8% and 8.4% of the two groups, respectively.

Other levofloxacin-based alternative regimens have been proposed as second-line therapies after the failure of clarithromycin-based first-line regimens. The "Sequential with levofloxacin" schedule (SQL) has been used in some trials[26]; amoxicillin is given for the first 5 d and levofloxacin plus metronidazole for the remaining 5 d, but the reported success rate is variable, ranging from 65.4% to 82.5%[27,28]. Prolonging the administration of LTT up to 14 d has been proposed as a strategy to improve the effectiveness. Indeed, in a study from Taiwan, 14-d LTT had a success rate of 90.5%, much better than the 10-d LTT (73.6%)[29].

First line treatments

The application of levofloxacin in first-line regimens shows a satisfactory outcome. To date, eleven studies[30-40], reported in Table 1, have investigated LTT as first-line treatment. The pooled success rate was 79.1%, with a 95%CI of 77.7%-80.5%. Studies comparing two different proton pump inhibitors (PPI) in this setting showed an equivalent power[32].

Some studies, therefore, had a disappointing eradication rate for LTT, close to 70%. For these reasons, other levofloxacin-based first-line regimens have been proposed: sequential (SQL) and concomitant (CL). SQL was able to eradicate the bacterium in 96% of cases in an Italian study[41], and a similar rate (95.6%)

Table 1 Studies investigating first-line levofloxacin-based triple therapies

Ref.	Year	Country	PPI	Eradicated/enrolled patients	Duration (d)	ITT rate
Qian *et al*[30]	2012	China	Esomeprazole	269/345	7	78.1%
Cuadrado-Lavín *et al*[31]	2012	Spain	Omeprazole	207/250	10	82.8%
Pan *et al*[32]	2010	China	Esomeprazole/rabeprazole	173/199	7	87.1%
Assem *et al*[33]	2010	Egypt	Esomeprazole	381/450	7	84.7%
Erçin *et al*[34]	2010	Turkey	Lansoprazole	66/91	14	72.0%
Liou *et al*[35]	2010	Taiwan	Lansoprazole	320/432	7	74.0%
Chen *et al*[36]	2010	China	Esomeprazole	222/300	7	74.0%
Molina-Infante *et al*[37]	2010	Spain	Omeprazole	380/460	10	82.6%
Castro-Fernández *et al*[38]	2009	Spain	All PPI	97/135	10	71.8%
Rispo *et al*[39]	2007	Italy	Esomeprazole	118/130	7	90.8%
Lee *et al*[40]	2006	South Korea	All PPI	186/267	7	69.8%
Total				2419/3059		79.1%

The dose of levofloxacin was 500 mg b.i.d and amoxicillin 1 g b.i.d for all studies. PPI: Proton pump inhibitor; ITT: Intention to treat.

was found in a Turkish study[42]. The lowest rate was recorded in a Spanish trial: 82.6%[37]. Only one Italian study tested a 5-d concomitant therapy[43], including levofloxacin 500 mg b.i.d, tinidazole 500 mg b.i.d and amoxicillin 1 g b.i.d. This trial found an eradication rate of 92.2% at intention-to-treat (ITT) and 96.5% at per-protocol (PP) analysis, similar to the control group, that received classical 10-d sequential therapy, which eradicated the bacterium in 93.3% and 95.5% of cases at ITT and PP, respectively. This study prompts two considerations. The first, that conventional first-line therapies are as effective as levofloxacin-containing regimens. The second, that the large difference between ITT and PP in the concomitant regimen is a consequence of a large number of drop-outs, suggesting that this therapy may be less well tolerated than the classical sequential therapy, most probably due to the major antibiotics "charge" ("load"?). Finally, the data in Table 1 do not demonstrate a better outcome of first-line levofloxacin triple therapy than sequential or concomitant treatments. Based on these considerations, the use of levofloxacin in first-line regimens may not be advantageous, taking into account its limited benefits. Moreover, in case of failure, the clinician may encounter some problems in the choice of a rescue therapy, since this good therapeutic option has already been used[44]. Further support of the recommendation to avoid using levofloxacin in first-line regimens may be provided by the evident, rapid increase of worldwide resistances, as reported above.

Third line regimens

Current guidelines propose a culture-based approach when several attempts to eradicate *H. pylori* fail[6]. Unluckily, antimicrobial susceptibility testing is not widely and promptly available. Because of this limitation, several studies have assessed the effectiveness of empirical third-line protocols including levofloxacin. Gisbert *et al*[45] reported, in a prospective multicentre study, that in third-line therapy, 10-d LTT achieved eradication in 66% of cases in 2006. In Italy, third-line LTT was effective in 83% and 75%, in two studies performed about 10 years ago[46,47]. Presumably, these satisfactory results cannot be replicated nowadays due to the increased rate of quinolone resistances. Moreover, when compared to a rifabutin-based triple therapy, LTT was shown to be less effective (71.4% *vs* 57.1%, respectively)[48] even if the combination with tetracycline can improve the LTT success rate. A "quadruple" regimen including bismuth, levofloxacin and tetracycline was effective in 78.9% in a study from Taiwan[49]. This peculiar combination has been tested as second-line therapy in two other trials with an excellent outcome in Turkey and Taiwan (90.6% and 95.8%, respectively)[50,51]. However, the use of a quadruple regimen in second-line therapy strongly restricts its therapeutic potential for third-line use.

NOVEL MOLECULES: MOXIFLOXACIN, SITAFLOXACIN AND GEMIFLOXACIN

Moxifloxacin is a fourth generation fluoroquinolone. Currently, it is indicated for respiratory infections. However, it has been proposed to treat *H. pylori* infection in some Asian and European trials. The first study was conducted in Germany in 2011, and achieved a 95% success rate in second-line therapy, consisting of a 14-d triple (moxifloxacin plus amoxicillin) regimen[52]. More recently, a multicenter European trial carried out in 250 subjects demonstrated that a second-line 14-d moxifloxacin-based triple regimen was effective in 82.4% of cases[53]. In South Korea, where the use of this drug is extensive, the same treatment was able to cure the infection only in 68.4%[54]. This result strongly supports the hypothesis that a wide consumption of fluoroquinolones may lead to a huge prevalence of resistances. Indeed, a subsequent study[55] from the same area confirmed a similar eradication rate (62.4%). A single Turkish study[56] investigated a quadruple regimen (moxifloxacin, bismuth and tetracycline) in second-line and demonstrated satisfactory results, with a success rate of 82.1%.

Sitafloxacin is another fourth generation fluoro-

quinolone which is currently marketed only in Japan and few other Far East Asian countries. For this reason, only five studies have been performed to investigate its application for *H. pylori* treatment[57-60]. These trials showed that a triple therapy with amoxicillin and sitafloxacin in third-line obtained a success rate ranging from 70% to 90.9%. Nevertheless, further studies are required to assess the effectiveness of this drug[17].

Gemifloxacin is a new quinolone which may be a promising alternative to overcome the problem of *H. pylori* levofloxacin resistances. A recent study from Taiwan showed that gemifloxacin demonstrates inhibitory concentration values only slightly lower than levofloxacin for its antimicrobial activity against *H. pylori* isolates, as well as sensitivity in levofloxacin-resistant strains[61]. Therefore, gemifloxacin may be a powerful quinolone to combat *H. pylori* and offers a future alternative for resistant strains. However, current studies have investigated the effectiveness of gemifloxacin only *in vitro*[62-64], and clinical trials are needed to translate these results to humans. Finally, gatifloxacin has been employed only in few pilot studies as a third-line regimen, showing a success rate ranging from 75% to 84.4%[65,66], but with discordant results when used in first-line[67,68].

CONCLUSION

Fluoroquinolones-based protocols offer encouraging strategies for the eradication of *H. pylori* infection. According to the current evidence and the Maastricht Ⅳ consensus, they should be used as first-line or "rescue" treatment, depending on geographic areas, since *H. pylori* resistance to these antibiotics is increasing. However, the use of levofloxacin in a first-line regimen has limited benefits and it restricts the therapeutic options in case of failure. Therefore, this antibiotic should generally be confined to second-line treatment. In third-line its use is mainly empirical. Despite the relatively few studies, new fluoroquinolones could offer promising alternative options for resistant strains. Moxifloxacin, sitafloxacin, gatifloxacin and gemifloxacin have been less investigated but may be the most encouraging molecules.

The extension of therapy duration to 14 d improves the eradication rates, but this strategy could have an impact on some public health issues such as tuberculosis management. Indeed, a long exposure to fluoroquinolones may delay the diagnosis of the infection, as well as raising drug resistances[69].

In summary, *H. pylori* eradication guidelines recommend the prescription of levofloxacin as first-line therapy only in areas with high clarithromycin resistances. In second-line regimens, levofloxacin-based protocols are a promising strategy as an alternative to quadruple therapy, when the PPI-clarithromycin-amoxicillin association fails. These protocols, moreover, offer the advantages of efficacy, simplicity, and safety. Finally, as regards third-line and "rescue" protocols, the antibiotic choice should be guided by antimicrobial susceptibility testing. This can be achieved by culture-based (E-test) and/or molecular-based methods (real-time PCR to detect the presence of a *gyrA* mutation).

On the bases of what has been reported above, fluoroquinolones appear to be a very useful and effective treatment option for *H. pylori* eradication. However, they need to be adopted with some caution, and the criteria for their proper use defined, so as to avoid the risk that abuse could lead to a rapid ineffectiveness.

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