Helicobacter Pylori First-Line and Rescue Treatments in the Presence of Penicillin Allergy

Javier P. Gisbert · Jesús Barrio · Inés Modolell · Javier Molina-Infante · Angeles Perez Aisa · Manuel Castro-Fernández · Luis Rodrigo · Angel Cosme · Jose Luis Gisbert · Miguel Fernández-Bermejo · Santiago Marcos · Alicia C. Marín · Adrián G. McNicholl

Gastroenterology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Playa de Mojacar 29, Urb. Bonanza, 28669 Boadilla del Monte, Madrid, Spain

Received: 4 August 2014 / Accepted: 9 September 2014 © Springer Science+Business Media New York 2014

Abstract

Background Helicobacter pylori eradication is a challenge in penicillin allergy.

Aim To assess the efficacy and safety of first-line and rescue treatments in patients allergic to penicillin.

Methods Prospective multicenter study. Patients allergic to penicillin were given a first-line treatment comprising (a) 7-day omeprazole–clarithromycin–metronidazole and (b) 10-day omeprazole–bismuth–tetracycline–metronidazole. Rescue treatments were as follows: (a) bismuth quadruple therapy; (b) 10-day PPI–clarithromycin–levofloxacin; and (c) 10-day PPI–clarithromycin–rifabutin. Eradication was confirmed by $^{13}$C-urea breath test. Compliance was determined through questioning and recovery of empty medication envelopes. Adverse effects were evaluated by questionnaires.

Results In total, 267 consecutive treatments were included. (1) First-line treatment: Per-protocol and intention-to-treat eradication rates with omeprazole–clarithromycin–metronidazole were 59 % (62/105; 95 % CI 49–62 %) and 57 % (64/112; 95 % CI 47–67 %). Respective figures for PPI–bismuth–tetracycline–metronidazole were 75 % (37/49; 95 % CI 62–89 %) and 74 % (37/50; 95 % CI 61–87 %) ($p < 0.05$). Compliance with treatment was 94 and 98 %, respectively. Adverse events were reported in 14 % with both regimens (all mild). (2) Second-line treatment: Intention-to-treat eradication rate with omeprazole–clarithromycin–levofloxacin was 64 % both after triple and quadruple failure; compliance was 88–100 %, with 23–29 % adverse effects (all mild). (3) Third-/fourth-line treatment: Intention-to-treat eradication rate with PPI–clarithromycin–rifabutin was 22 %.
**Conclusion** In allergic to penicillin patients, a first-line treatment with a bismuth-containing quadruple therapy (PPI–bismuth–tetracycline–metronidazole) seems to be a better option than the triple PPI–clarithromycin–metronidazole regimen. A levofloxacin-based regimen (together with a PPI and clarithromycin) represents a second-line rescue option in the presence of penicillin allergy.

**Keywords** Eradication · *Helicobacter pylori* · Bismuth · Levofloxacin · Quinolone · Allergic · Allergy · Penicillin

**Abbreviations**

*H. pylori* · *Helicobacter pylori*  
PPI · Proton pump inhibitor

**Introduction**

*Helicobacter pylori* (*H. pylori*) infection is the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. Amoxicillin is one of the most effective antimicrobial agents against *H. pylori*, and therefore, most eradication regimens include this antibiotic. Triple therapy including a proton pump inhibitor (PPI) and two antibiotics, mainly amoxicillin and clarithromycin, constitutes the standard care for *H. pylori* infection treatment in many countries [1, 2]. However, when penicillin allergy is present—a relatively frequent scenario [3]—replacing amoxicillin with metronidazole has been recommended in PPI-based triple combinations [1, 4]. On the other hand, *H. pylori* eradication constitutes a particular challenge in patients allergic to penicillin who have failed a first eradication trial with key antibiotics such as clarithromycin and metronidazole.

To date, only few studies have evaluated the efficacy of *H. pylori* eradication treatment, specifically in those patients allergic to penicillin. Furthermore, the appropriate rescue therapy when eradication therapy fails in this particular situation has not been properly evaluated. In our previous studies [5, 6], PPI–clarithromycin–metronidazole therapy achieved discouraging results as first-line therapy, although the sample size of these studies was small. A bismuth-containing quadruple therapy may, perhaps, be preferred in this situation, but this regimen has not been previously evaluated in patients allergic to penicillin. On the other hand, *H. pylori*-infected patients allergic to penicillin failing first-line treatment in a previously mentioned study received a second-line treatment with a PPI, clarithromycin, and levofloxacin, with which infection was cured in approximately 70% of the patients [6]; again, however, the number of patients treated with this regimen (15) was small.

The aim of the present study was to assess, in patients allergic to penicillin, the efficacy and safety of *H. pylori* first-line treatment with either a PPI–clarithromycin–metronidazole triple therapy or a bismuth-containing quadruple therapy and also to evaluate several rescue regimens, mainly a levofloxacin-containing treatment, in the presence of penicillin allergy.

**Methods**

**Patients**

This was a prospective multicenter study including consecutive treatments in patients infected by *H. pylori* with documented allergy to penicillin. Diagnosis of *H. pylori* infection was initially established either by histology, rapid urease test, or 13C-urea breath test. Exclusion criteria were as follows: (1) age under 18, (2) presence of clinically significant associated conditions (hepatic, cardiorespiratory or renal diseases, neoplastic diseases, or coagulopathy), (3) previous gastric surgery, and (4) allergy to any of the drugs used in the study. Some patients included in the present study had already been included in two previous small pilot studies [5, 6]. The protocol was approved by the ethics committee of our institution, and informed consent was obtained from all the patients.

**Therapy**

Dose and administration scheme of the drugs prescribed in the eradication regimens are summarized in Table 1. Regarding first-line treatments, a combination of omeprazole, clarithromycin, and metronidazole was prescribed in

<table>
<thead>
<tr>
<th>Therapy combination</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg b.i.d.</td>
<td>7 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg b.i.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>Bismuth subcitrate</td>
<td>120 mg q.i.d.</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Oxytetracycline 500 mg q.i.d or doxycycline 100 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg t.i.d.</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg b.i.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg b.i.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>150 mg b.i.d.</td>
<td></td>
</tr>
</tbody>
</table>
Table 2  Results with the first-line eradication treatment

<table>
<thead>
<tr>
<th>First eradication therapy</th>
<th>Second eradication therapy</th>
<th>Efficacy PP (%) (95 % CI)</th>
<th>Efficacy ITT (%) (95 % CI)</th>
<th>Compliance (%)</th>
<th>Adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>62/105 (59) (49–69 %)*</td>
<td>64/112 (57) (47–67 %)$</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>O + B + T + M</td>
<td></td>
<td>37/49 (75) (62–89 %)*</td>
<td>37/50 (74) (61–87 %)$</td>
<td>98</td>
<td>14</td>
</tr>
</tbody>
</table>

95 % CI 95 % confidence interval, PP per-protocol, ITT intention to treat, O omeprazole, C clarithromycin, M metronidazole, B bismuth, T tetracycline

$ p < 0.05; * p < 0.05$

Table 3  Results with the second-line eradication treatment

<table>
<thead>
<tr>
<th>First eradication therapy (failed)</th>
<th>Second eradication therapy</th>
<th>Efficacy PP (%) (95 % CI)</th>
<th>Efficacy ITT (%) (95 % CI)</th>
<th>Compliance (%)</th>
<th>Adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>8/21 (38) (18–63 %)*</td>
<td>9/24 (37) (16–59 %)$</td>
<td>87</td>
<td>58*</td>
</tr>
<tr>
<td>O + C + M</td>
<td>O + C + L</td>
<td>32/44 (73) (58–87 %)*</td>
<td>32/50 (64) (50–78 %)$</td>
<td>88</td>
<td>23*</td>
</tr>
<tr>
<td>O + B + T + M</td>
<td>O + C + L</td>
<td>9/14 (64) (35–87 %)</td>
<td>9/14 (64) (35–87 %)</td>
<td>100</td>
<td>29</td>
</tr>
</tbody>
</table>

95 % CI 95 % confidence interval, PP per-protocol, ITT intention to treat, O omeprazole, C clarithromycin, M metronidazole, B bismuth, T tetracycline, L levofloxacin

$ p < 0.01; * p < 0.05$

Table 4  Results with the third-line eradication treatment

<table>
<thead>
<tr>
<th>First eradication therapy (failed)</th>
<th>Second eradication therapy (failed)</th>
<th>Third eradication therapy</th>
<th>Efficacy PP (%)</th>
<th>Efficacy ITT (%)</th>
<th>Compliance (%)</th>
<th>Adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>O + C + L</td>
<td>1/2 (50)</td>
<td>1/3 (33)</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>O + C + R</td>
<td>1/5 (20)</td>
<td>1/7 (14)</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>O + C + M</td>
<td>O + C + L</td>
<td>O + B + T + M</td>
<td>3/3 (100)</td>
<td>3/3 (100)</td>
<td>100</td>
<td>67</td>
</tr>
</tbody>
</table>

PP per-protocol, ITT intention to treat, O omeprazole, C clarithromycin, M metronidazole, B bismuth, T tetracycline, L levofloxacin, R rifabutin

Table 5  Results with the fourth-line eradication treatment

<table>
<thead>
<tr>
<th>First eradication therapy (failed)</th>
<th>Second eradication therapy (failed)</th>
<th>Third eradication therapy (failed)</th>
<th>Fourth eradication therapy</th>
<th>Efficacy PP (%)</th>
<th>Efficacy ITT (%)</th>
<th>Compliance (%)</th>
<th>Adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>O + C + L</td>
<td>O + C + R</td>
<td>0/1 (0)</td>
<td>1/2 (50)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>O + C + M</td>
<td>O + B + T + M</td>
<td>O + C + L</td>
<td>O + C + L</td>
<td>1/1 (100)</td>
<td>2/2 (100)</td>
<td>100</td>
<td>67</td>
</tr>
</tbody>
</table>

O omeprazole, C clarithromycin, M metronidazole, B bismuth, T tetracycline, L levofloxacin, R rifabutin

the first 112 patients, while a quadruple regimen containing omeprazole, bismuth subcitrate, tetracycline, and metronidazole was administered to the following 50 patients. The number of patients treated with each rescue regimen is summarized in Tables 2, 3, 4, and 5, and a flow diagram of subject progress through the phases of the study is shown in Fig. 1.

Compliance with therapy was determined with a questionnaire, and the recovery of medication’s empty envelopes at the time *H. pylori* eradication success was confirmed. Compliance with therapy was defined as the intake of 100 % of the prescribed drugs. Incidence of adverse effects was evaluated by means of a specific questionnaire (subjects were asked to recall side effects of therapy at the time *H. pylori* eradication success was confirmed with $^{13}$C-urea breath, see later); the questionnaire included both the spontaneous report of adverse effects by the patient and a list of the most commonly described adverse effects with the antibiotics prescribed (including metallic taste, nausea, vomiting, abdominal pain, diarrhea, and myalgias).

Diagnostic Methods to Confirm *H. Pylori* Eradication

*Helicobacter pylori* eradication was defined as a negative result in $^{13}$C-urea breath test (with citric acid and 100 mg of urea, as previously reported [7]) performed 8 weeks after the completion of eradication treatment. $^{13}$C-urea
breath test was carried out by operators unaware of therapy and patients’ H. pylori status and the treatment received. As endoscopy—and consequently culture—was not performed after therapy, H. pylori antibiotic susceptibility was unknown, and therefore, the rescue H. pylori eradication regimen was chosen empirically.

Statistical Analysis

For continuous variables, mean and standard deviation were calculated. For categorical variables, percentages (and 95% confidence intervals) were provided. Analysis of H. pylori eradication efficacy was performed on an “intention-to-treat” basis (included all eligible patients enrolled into the study regardless of compliance with the study protocol; patients with uneventful data were assumed to have been unsuccessfully treated) and on a “per-protocol” basis (excluded patients with poor compliance of therapy and patients with uneventful data after therapy). Comparisons between independent proportions were made by chi-square (χ²) test.

Results

Two hundred and sixty-seven prescribed treatments were evaluated in the present study. Mean age was 52 years, 66% were females, and 24% were smokers. Twenty-four percent had peptic ulcer disease, while 76% had non-investigated or functional dyspepsia.

Data on efficacy, compliance with the protocol, and tolerance with H. pylori first-line treatment are summarized in Table 2. Intention-to-treat eradication rate with omeprazole–clarithromycin–metronidazole was 64% both after triple and quadruple treatments failure. In particular, after omeprazole–clarithromycin–metronidazole failure, the levofloxacin triple regimen achieved a higher cure rate than the bismuth quadruple regimen (64 vs. 37%; p < 0.05). Compliance with treatment was good (88–100%) with both triple and quadruple regimens. However, adverse effects were more common with the quadruple treatment (p < 0.01). The most frequent adverse effects with the omeprazole–clarithromycin–levofloxacin regimen were as follows: nausea/vomiting (seven patients), metallic taste (six patients), myalgias (four patients, being intense in two), asthenia (three patients), abdominal pain (two patients, being intense in one), and diarrhea (one patient).

Results with the third- and fourth-line eradication treatment, regarding both efficacy and tolerance, are summarized in Tables 4 and 5.

Discussion

To the best of our knowledge, our study, with 267 prescribed eradication treatments, is the largest one assessing H. pylori management in the presence of penicillin allergy. In these patients, a triple therapy including a PPI, clarithromycin, and a nitroimidazole constitutes one of the most frequently recommended regimens [1, 4]. Although this regimen is considered relatively effective to treat H. pylori infection, with mean eradication rates of approximately 80% [8], our cure rate in penicillin allergic patients was lower than 60%. These discouraging results had been previously reported in our geographical area (also in patients allergic to penicillin) [5] and may be due, at least in part, to the relatively high rate of metronidazole and clarithromycin resistance in our country [9–11]. It may be speculated that the rate of resistance to other antibiotics

Fig. 1 Flow diagram of subject progress through the phases of the study. O omeprazole, C clarithromycin, M metronidazole, B bismuth, T tetracycline, L levofloxacin, R rifabutin

( p < 0.05). Compliance was similar for both regimens. Adverse events were reported by 14% of patients in both groups, mostly mild. For omeprazole–clarithromycin–metronidazole treatments, the most frequent adverse effects were as follows: metallic taste (eight patients), nausea/vomiting (seven patients, in one of them it forced to treatment discontinuation), abdominal pain (three patients), diarrhea (one patient), and asthenia (one patient). Corresponding adverse effects for the bismuth-containing quadruple regimen were as follows: metallic taste (five patients), nausea/vomiting (five patients), asthenia (two patients), and diarrhea (1 patient).

Data on efficacy, compliance with the protocol, and tolerance with H. pylori second-line treatment are summarized in Table 3. Intention-to-treat eradication rate with omeprazole–clarithromycin–levofloxacin was 64% both after triple and quadruple treatments failure. In particular, after omeprazole–clarithromycin–metronidazole failure, the levofloxacin triple regimen achieved a higher cure rate than the bismuth quadruple regimen (64 vs. 37%; p < 0.05). Compliance with treatment was good (88–100%) with both triple and quadruple regimens. However, adverse effects were more common with the quadruple treatment (p < 0.01). The most frequent adverse effects with the omeprazole–clarithromycin–levofloxacin regimen were as follows: nausea/vomiting (seven patients), metallic taste (six patients), myalgias (four patients, being intense in two), asthenia (three patients), abdominal pain (two patients, being intense in one), and diarrhea (one patient).

Results with the third- and fourth-line eradication treatment, regarding both efficacy and tolerance, are summarized in Tables 4 and 5.
different to beta-lactamic antibiotics could be even higher in patients allergic to penicillin; this may be due to the fact that these patients have probably been previously treated with other non-beta-lactamic antibiotics.

On the other hand, two other research groups prescribed a 10-day regimen of PPI, tetracycline, and metronidazole to five patients and 17 patients, respectively, with documented allergy to penicillin and reported an 80–85% eradication rate by intention to treat [12, 13]. These results suggest that this triple combination (or even better, with the addition of bismuth, resulting in a quadruple regimen) may be a better alternative for first-line treatment in the presence of penicillin allergy, probably because the negative effect of metronidazole resistance is mostly overcome by the co-administration of bismuth [14] and because the efficacy of this regimen is not influenced by clarithromycin resistance [15]. In our study, the cure rate achieved with PPI–bismuth–tetracycline–metronidazole therapy (75%) was significantly higher than that obtained with the PPI–clarithromycin–metronidazole one. Compliance was excellent, and similar for both regimens. Adverse events were reported by only 14% of patients and were generally mild, mainly including metallic taste and nausea.

*Helicobacter pylori* eradication is a challenge in patients allergic to penicillin in general, and especially in those who have failed a first eradication attempt with key antibiotics such as clarithromycin and metronidazole [16]. After standard PPI-based triple regimen failure, the use of the quadruple therapy (that is, PPI, bismuth, tetracycline, and metronidazole) has been generally recommended as the optimal second-line therapy [1, 4, 17]. However, this quadruple regimen requires the administration of four drugs with a complex scheme, and bismuth salts are not widely available worldwide. Levofloxacin is a fluoroquinolone antibiotic agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens [18]. Some studies have demonstrated that this antibiotic has remarkable in vitro activity against *H. pylori* [19]. Furthermore, it has been shown in vitro that levofloxacin retains its activity when *H. pylori* strains are resistant to clarithromycin and metronidazole [20–22]. These favorable results have been confirmed in vivo, indicating that most (from 63 to 92%) of the patients with both metronidazole resistance and clarithromycin resistance are cured with the levofloxacin-containing regimen [23–25]. Thus, levofloxacin-based therapies are an encouraging strategy for *H. pylori* infection, mainly after eradication failures. In fact, four meta-analyses have demonstrated that levofloxacin-based rescue regimen is at least similar to, and probably more effective than, the generally recommended quadruple therapy after *H. pylori* eradication failure [26–29].

In the present study, intention-to-treat eradication rate with omeprazole–clarithromycin–levofloxacin was 64% both after triple and quadruple treatments failure. In particular, after omeprazole–clarithromycin–metronidazole failure, the levofloxacin triple regimen achieved a higher cure rate than the bismuth quadruple regimen. Recently, Furuta et al. [30] treated 28 patients allergic to penicillin with a PPI, metronidazole, and sitafloxacin for 1 or 2 weeks and achieved *H. pylori* eradication in 100% of the patients. Seventeen of these patients had experienced an allergic reaction either during or just after the end of first- or second-line therapy with a PPI, amoxicillin and clarithromycin, or metronidazole and thus exhibited a failure of eradication therapy. It should be noted that culture (and therefore susceptibility testing) was performed in most of the cases and that the CYP2C19 genotype was also measured, which may explain the excellent results obtained in this present study. Furthermore, sitafloxacin is reported to have a lower MIC than levofloxacin and to be effective in patients infected with strains with mutations in *gyrA*, a genetic marker for resistance to levofloxacin [31].

As previously mentioned, the quadruple regimen requires the administration of a complex scheme. On the contrary, levofloxacin-containing regimens (with PPI plus either amoxicillin or clarithromycin administered twice daily, and levofloxacin every 12 or 24 h) are an encouraging simple alternative to quadruple therapy. Furthermore, the quadruple regimen is associated with a relatively high incidence of adverse effects [17]. In contrast, levofloxacin is generally well tolerated and most adverse events associated with its use are transient and mild in severity [32]. Furthermore, several meta-analyses have demonstrated a lower incidence of adverse effects with levofloxacin-based treatments than with the bismuth quadruple combination [26, 27]. Accordingly, compliance with treatment was excellent in our study, and adverse effects were less common with the levofloxacin triple than with the bismuth quadruple regimen, the most frequent being nausea, metallic taste, and myalgias.

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 [2, 10, 33]. 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 [34]. In this respect, the major drawback of our study is that culture was not performed, and therefore, information on the prevalence of levofloxacin resistance is lacking. Additionally, the impact of antibiotic resistance to levofloxacin in the rescue therapy could not be evaluated by this study.
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 14% in Spain [10, 35].

Finally, rifabutin-containing rescue therapy represents an option after multiple (usually three) previous eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin. In a recent systematic review, mean *H. pylori* eradication rate with rifabutin-containing regimens was 73% [36]. In particular, cure rates for third- or fourth-line rifabutin rescue therapies were 66–79% [36]. However, in the present study, third-/fourth-line treatment with PPI–clarithromycin–rifabutin achieved *H. pylori* eradication in only 22% of the cases, although it should be stressed that this regimen was evaluated in only nine patients. Recently, Tay et al. prescribed a quadruple therapy including a PPI, bismuth, rifabutin, and ciprofloxacin to 69 patients allergic to penicillin (for whom PPI–clarithromycin–metronidazole had failed in most of the cases) and reported a cure rate as high as 94%. It should be taken into account that antibiotics were prescribed based on susceptibility testing by culture and that high doses of both PPI and bismuth were used [37].

In summary, in allergic to penicillin *H. pylori* infected patients, a first-line treatment with a bismuth-containing quadruple therapy (PPI–bismuth–tetracycline–metronidazole) seems to be a better option than PPI–clarithromycin–metronidazole. A levofloxacin-based regimen (together with a PPI and clarithromycin) represents a second-line rescue option in the presence of penicillin allergy.

**Conflict of interest** None.

**References**


