Levofloxacin versus clarithromycin in a 10 day triple therapy regimen for first-line *Helicobacter pylori* eradication: a single-blind randomized clinical trial

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Received 1 February 2012; returned 1 March 2012; revised 20 April 2012; accepted 29 April 2012

Background: There is growing evidence that the standard triple therapy against *Helicobacter pylori* infection is losing clinical effectiveness. A triple therapy regimen with levofloxacin, amoxicillin and a proton pump inhibitor has been reported to be effective and well tolerated, and this regimen has been suggested as an alternative first-line treatment. The aim of this single-blind randomized clinical trial was to compare the eradication success of two first-line triple therapy regimens in the north of Spain: clarithromycin, amoxicillin and omeprazole (CAO) versus levofloxacin, amoxicillin and omeprazole (LAO).

Materials and methods: A total of 250 consecutive patients diagnosed by conventional methods with *H. pylori* infection were randomized into one of two 10 day therapeutic regimens: standard CAO (n = 128) or LAO (n = 122). Eradication was confirmed by the 13C-urea breath test. Adverse effects and compliance were also assessed. The clinical trial registration number was HPL08001HCLAD (EudraCT: 2008-001892-31).

Results: Intention-to-treat cure rates were: CAO, 75.0% (96/128; 95% CI: 66.6%–82.2%) and LAO, 82.8% (101/122; 95% CI: 74.9%–89.0%). Per-protocol cure rates were: CAO, 78.0% (96/123; 95% CI: 69.7%–85.0%) and LAO, 83.1% (98/118; 95% CI: 75.0%–89.3%). There were no statistically significant differences in effectiveness between the two regimens. In addition, no relevant differences in compliance or adverse effects were demonstrated.

Conclusions: Levofloxacin-based treatment for *H. pylori* infection did not improve upon the eradication rate of the standard clarithromycin-based triple therapy in this study. This may reflect the progressive increase in *in vitro* resistance rates to levofloxacin observed in our region.

Keywords: antibiotic resistance, clarithromycin, eradication, *Helicobacter pylori*, levofloxacin, omeprazole, randomized clinical trial, triple therapy

Introduction

*Helicobacter pylori* infects the gastric mucosa and represents the main cause of gastritis, gastroduodenal ulcer disease and gastric cancer. It has been demonstrated that eradication of *H. pylori* improves the clinical outcome of patients with duodenal ulcer, prevents its recurrence and decreases the risk of gastric cancer.1,2 However, the ideal regimen to treat this infection is still far from being achieved. Current guidelines on *H. pylori* eradication published in Europe and North America recommend
therapeutic regimens that attain *H. pylori* cure rates >80% in an intention-to-treat analysis, with combinations of a proton pump inhibitor (PPI) with two antibiotics (clarithromycin plus amoxicillin or metronidazole) as the preferred regimen.\(^{3,4}\) Although the initial eradication success rate for standard triple therapy was in >90% 10 years ago, treatment failures of up to 30%–40% using this regimen have been more recently reported.\(^{5–8}\) Antibiotic resistance has been identified as the leading factor responsible for eradication failure. This issue is of particular relevance in regard to clarithromycin, which can exhibit \(\sim 70\%\) loss of effectiveness when taken as part of an PPI/amoxicillin-based triple therapy, depending on the *in vitro* macrolide susceptibility.\(^{9}\) At present, clarithromycin-based triple therapies appear to achieve insufficient cure rates in some areas, and so more effective alternatives are being sought.

Regimens containing levofloxacin, a fluoroquinolone with a remarkable *in vitro* activity against *H. pylori*, have brought hope in the past decade. Although it has been mainly evaluated as a second-line therapy for use after one or more *H. pylori* eradication failures and has shown encouraging results (75%–86% eradication rate), several small studies have also evaluated the combination of levofloxacin and amoxicillin (together with a PPI) as a first-line regimen.\(^{10,11}\) Some of these studies have shown excellent results, with eradication rates between 85% and 92%.\(^{11–16}\) In addition, levofloxacin presents a good safety profile, thus facilitating its use in clinical practice. However, concerns have arisen regarding a progressive increase of *in vitro* resistance of *H. pylori* to this quinolone in recent years, which could jeopardize its use in the future.\(^{8,17}\)

The objective of this study was to assess the real clinical effectiveness of the ‘standard’ triple therapy (a clarithromycin-based regimen in combination with amoxicillin and omeprazole) in our area, and to compare it with that of an alternative regimen that substitutes clarithromycin with levofloxacin as a first-line therapy.

**Methods**

**Patients, treatments and follow-up**

This was a single-centre, single-blind, controlled, parallel-group study with balanced randomization (1:1), designed to examine the superiority of an alternative therapeutic regimen against *H. pylori*. It was conducted at the Hospital of Laredo, a community hospital in the north of Spain. From January 2009 to December 2010, 250 consecutive *H. pylori*-positive adult patients who had not been previously cleared of *H. pylori* were enrolled. These patients were referred to us for gastroscopy because of different upper digestive complaints, a familial history of gastric cancer and/or a personal history of gastroduodenal peptic ulcer disease. All of them underwent a diagnostic esophagogastroduodenoscopy including collection of biopsies of the gastric mucosa (from both the body and the antrum) for rapid urease testing; additionally, a sample of gastric mucosa was collected for histology according to medical judgement. A positive urease test was sufficient for a patient to be considered infected. Written informed consent was obtained from all patients, and the study was approved by our regional Ethics Committee. This study was registered in the European Union Clinical Trials Register Database (Clinicaltrialsregister.eu) with registration number ID HPL080011HCLA; the EudraCT number is 2008-001892-31. Previous *H. pylori* eradication therapy was an exclusion criterion for the study. Other exclusion criteria were: (i) age under 18 years, (ii) presence of serious concomitant illnesses (i.e. hepatic, cardiorespiratory or renal diseases, insulin-dependent diabetes mellitus, neoplastic diseases or coagulopathy), (iii) previous gastric surgery, (iv) allergy to any of the drugs used in the study, and (v) intake of antibiotics or PPIs within the previous month.

An investigator, who did not have clinical involvement in the trial, constructed a computer-generated numeric sequence for all patients. This sequence was used to completely randomize the patients and allocate them to receive one of the two first-line regimens for 10 days. After enrollment of patients by clinical investigators, a centralized assignment carried out by our hospital Pharmacy Service enabled appropriate allocation concealment. Then, patients were assigned to receive: (i) standard triple therapy (n = 128) consisting of clarithromycin 500 mg, amoxicillin 1 g and omeprazole 20 mg, all administered twice daily (CAO), or (ii) alternative triple therapy (n = 122) consisting of levofloxacin 500 mg, amoxicillin 1 g and omeprazole 20 mg, all administered twice daily (LAO). Omeprazole was given before meals, whereas the antibiotics were administered after meals. Although investigators were blind to the allotment, we could not completely mask the study drugs for all patients, so some participants could potentially have been aware of the allocated arm (thus it was a single-blind study, as previously stated). Patients were informed about the common side effects expected from the study medications. They were instructed to report any adverse events to their physician by a contact telephone number. Compliance and adverse events were assessed by personal interview after ending treatment. Patient compliance was also evaluated by a count of the pills remaining at the end of the treatment. Patients who used less than 80% of the study medication were considered non-compliant.

Even if a patient required a follow-up endoscopy, eradication of *H. pylori* infection (which was the primary endpoint in regard to efficacy) was defined as a negative \(^{13}\)C-urea breath test performed at least 4 weeks after completion of treatment, as recommended by the manufacturer. Neither antibiotics nor PPI were allowed during the 4 week or 2 week periods, respectively, prior to *H. pylori* reassessment. Relevant method changes after trial commencement were not performed.

**Statistical analysis**

*H. pylori* eradication rates were calculated by intention-to-treat (ITT) and per-protocol (PP) analyses. For ITT analysis, all randomized patients enrolled into the study were included; patients without an observed outcome were considered as treatment failures. For PP analysis, all protocol violators (non-compliant patients and patients lost to follow-up) were excluded. Categorical variables are described with percentages, and continuous variables are described with mean and standard deviation or median and range as appropriate. For univariate statistical analysis, a 95% CI, Student’s t-test and Fisher’s exact test were applied. Multivariate logistic regression analyses were also performed to evaluate independent predictive variables for eradication of *H. pylori*. The magnitude of the effect is described by OR and 95% CI. Variables chosen to be introduced in predictive models depended on statistical significance on univariate analysis or, at least, those known to have potential effects based on the literature. \(P\) values < 0.05 were considered statistically significant. No interim analyses for efficacy or futility were done.

The targeted sample size in each group, assuming an 80% power at a 5% significance level, was selected to detect a 15% difference in eradication rate between the groups. This target difference was established by taking into account an estimated 75% expected eradication rate for CAO (according to the alarmingly low figures previously reported) and a near 90% success rate expected for LAO (based on previous experience with regimens containing levofloxacin).\(^{11–16}\) The statistical software package STATA (Stata Corporation, College Station, TX, USA) was used for the analyses.
Results

The baseline demographic and clinical characteristics of the total cohort (250 patients) and of each therapeutic group are listed in Table 1. The two groups were similar in regard to age, gender, smoking habit, use of co-medications and indication for *H. pylori* eradication. Functional dyspepsia was the most common indication for *H. pylori* eradication (60%).

Figure 1 shows the study flow diagram for all enrolled patients. Five patients in the CAO group and one in the LAO group were lost to follow-up and were therefore not assessed. One patient initially assigned to take LAO received CAO because of a violation of the randomization schedule. Finally, two patients in the LAO group were withdrawn due to severe adverse events (see below). The CAO regimen achieved a 75.0% (96/128; 95% CI: 66.6%–82.2%) eradication rate in the ITT analysis and a 78.0% (96/123; 95% CI: 69.7%–85.0%) eradication rate in the PP analysis, while the LAO regimen obtained an 82.8% (101/122; 95% CI: 74.9%–89.0%) eradication rate in the ITT analysis and an 83.1% (98/118; 95% CI: 75.0%–89.3%) eradication rate in the PP analysis. Neither the ITT nor PP analysis showed a statistically significant difference in eradication success rates between the two treatment arms [OR 1.5 (95% CI: 0.85%–2.95%) in the ITT analysis; OR 1.38 (95% CI: 0.85%–2.95%) in the PP analysis]. Analysis of treatment (either CAO or LAO) by age, gender, use of co-medication for concomitant illnesses, cigarette smoking and indication for *H. pylori* eradication showed no significant difference between *H. pylori*-eradicated and -non-eradicated patients, either in the univariate or in the multivariate analysis.

The mean adherence to the treatment was 99% (95% CI: 98.4%–99.8%) throughout the study, without differences between the treatment groups. Table 2 summarizes the type and relevance of side effects in the study population. Overall, 165 adverse events were reported by 127 (50.8%) patients in the total cohort [59 (46.1%) patients in the CAO group; 68 (55.7%) in the LAO group]. Most adverse events were rated as ‘mild’ in the whole cohort (112/165; 67.9%) [54/75 (72%) in the CAO group; 58/90 (64.4%) in the LAO group]. Only two patients (both in the LAO group) needed to stop the assigned treatment because of the severity of their adverse events: one had an episode of severe insomnia and irritability that resolved after stopping the treatment, and one with an episode of cholecystitis during treatment required a cholecystectomy. No other patients dropped out of the study due to side effects of the treatments. Patients in the CAO group experienced fewer side effects (75 events in 59 patients) when compared with the LAO group (90 events in 68 patients). Except for the two patients in the LAO group who discontinued the treatment, there were no differences between both regimens with regard to the severity of side effects. However, a higher number of patients experienced mild/moderate myalgia or mucosal complaints (i.e. aphthous stomatitis, vulvar pruritus and local candidiasis) in the LAO group, while more patients in the CAO group suffered from mild or moderate headache.

Discussion

The present study demonstrates that the eradication rate of the alternative levofloxacin-based regimen was slightly better than that of the standard clarithromycin-based triple therapy, but not enough to reach statistical significance. Both regimens were, nevertheless, virtually within the current recommendations for eradication regimens stated in the most recent consensus conferences, which encourage the use of regimens that achieve *H. pylori* cure rates >80% in an ITT analysis.\(^1,4\)

When planning to treat this infection, clinicians should ideally be aware of the prevalence of antimicrobial resistance locally or regionally, as well as the efficacy of treatments in their practice. Unfortunately, most clinical studies lack antimicrobial susceptibility testing of *H. pylori*, preventing clinicians from correlating their clinical results with microbiological data. Thus, to determine *H. pylori* susceptibility to antibiotics in our area, we designed another parallel, specific in vitro study, which has been recently published.\(^1,7\) The main combined contribution of this and the present trial is that we have been able to correlate in vitro susceptibility trends with data on clinical effectiveness over a period of time in a particular area. In this setting, a lower than expected eradication rate of the levofloxacin-based regimen can be explained by the progressive rise of *H. pylori* resistance to this quinolone in our region (from 6% in 2006 to 14.5% in 2011).\(^1,7,18\) Similarly, the acceptable and encouraging clinical results with the standard clarithromycin-based triple therapy appear to reflect a ‘stabilization’ of *in vitro* *H. pylori* resistance to clarithromycin over the last decade in Spain (15.2% in 2001 and 14.7% in 2011).\(^1,7,19\)

The main shortcoming of the present study is the quite small area of inclusion of a single clinical centre, which could limit the applicability of this trial to larger populations. However, the representative population coverage of our centre (~200000 inhabitants of a ~500000 inhabitant region) and the consistency of our results with what is presently known support the broader validity of the study.

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### Table 1. Demographic and clinical characteristic of patients from the total cohort and therapeutic subgroups after randomization

<table>
<thead>
<tr>
<th>Value</th>
<th>Total cohort</th>
<th>CAO</th>
<th>LAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>250</td>
<td>128</td>
<td>122</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>120/130</td>
<td>66/62</td>
<td>54/68</td>
</tr>
<tr>
<td>Age [median (range)]</td>
<td>43 (18–75)</td>
<td>42 (19–73)</td>
<td>44 (18–75)</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>33</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Co-medication, n (%)</td>
<td>115 (46)</td>
<td>56 (43.8)</td>
<td>59 (48.4)</td>
</tr>
<tr>
<td>Indication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>functional dyspepsia</td>
<td>151 (60)</td>
<td>76 (59)</td>
<td>75 (62)</td>
</tr>
<tr>
<td>gastric or duodenal ulcer</td>
<td>73 (29)</td>
<td>39 (31)</td>
<td>34 (28)</td>
</tr>
<tr>
<td>familial gastric cancer</td>
<td>26 (10)</td>
<td>13 (10)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Diagnostic method, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rapid urease test</td>
<td>219 (88)</td>
<td>109 (85)</td>
<td>110 (90)</td>
</tr>
<tr>
<td>combined(^a)</td>
<td>31 (12)</td>
<td>19 (15)</td>
<td>12 (10)</td>
</tr>
</tbody>
</table>

CAO, clarithromycin/amoxicillin/omeprazole (standard triple therapy); LAO, levofloxacin/amoxicillin/omeprazole (alternative triple therapy).

\(^a\)Combined refers to a positive test obtained by two methods: a rapid urease test and histological study.
LAO versus CAO in Helicobacter pylori infection

The use of levofloxacin as a salvage therapy has been supported by many previous studies. However, its role as part of an alternative first-line therapy is more controversial. In a recent randomized trial performed in Spain, clarithromycin and levofloxacin were compared as first-line therapies for H. pylori eradication in triple as well as sequential regimens. Two of the four arms of the study were equivalent to the CAO and LAO branches of our study. The authors found an eradication rate of 80% for LAO, similar to that achieved with a levofloxacin-based sequential therapy (82%). Recently, another report from Taiwan comparing the two regimens (CAO and LAO) as first-line treatments showed an advantage of the standard triple therapy (84%) over the levofloxacin counterpart (74%), although the regimen schedule of levofloxacin was inferior. Such figures are, however, worse than the encouraging rates of eradication (>90%) obtained with levofloxacin-based regimens used in

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**Figure 1.** Flow diagram for the subjects enrolled in the study. AE, adverse event; CAO, clarithromycin/amoxicillin/omeprazole (standard triple therapy); LAO, levofloxacin/amoxicillin/omeprazole (alternative triple therapy); ER, eradication rate. *Patient number 150 received CAO instead of LAO. *Two patients were withdrawn because of severe adverse events, although a 13C-urea breath test was done in both of them during follow-up.
first-line schemes in some countries (mainly Italy and The Netherlands) in the middle of the last decade. This decrease in the eradication rate of levofloxacin could be attributed to a rapidly increasing rate of quinolone resistance reported in several countries (e.g. 16.8% in Belgium, 23.1% in Italy and from 3% in 1999 to 15% in 2004 in France, among others) and now in Spain (see above). A comprehensive review of the role of quinolones used as first-line therapy for H. pylori eradication has recently been carried out. The authors of this review conclude that a quinolone-based triple therapy cannot be generally recommended in such clinical setting. However, it might be considered as an individual first-treatment option under some specific circumstances (mainly depending on local primary resistances to quinolones and macrolides). In any case, the authors suggest new randomized clinical trials to explore further the role of quinolones in first-line treatments.

The eradication rate of the standard clarithromycin-based triple therapy observed in our trial remains close to the ‘80% recommendation rule’. Taking into account recent reports using the standard triple therapy, where up to 60% of studies failed to reach 80% eradication as determined by ITT analysis, the rate of eradication found in the present study is better than expected. For instance, in the recent aforementioned trial performed in Spain, a poor eradication rate of 64% was found. Nevertheless, the study lacked pre-treatment susceptibility testing for clarithromycin, as the authors acknowledged. Our encouraging clinical results are supported by in vitro data, as was previously stated. Additionally, the recently published revised European survey shows clarithromycin resistance rates of 17% overall; however, while countries from the centre, west and south of Europe have experienced great increases in the rates of resistance to clarithromycin (20%), northern countries (e.g. Germany), as well as certain non-northern countries, (e.g. Spain) maintain low to intermediate rates of resistance. Of note, the Maastricht IV consensus conference on H. pylori infection management that was held during the last United European Gastroenterology Week in Stockholm (October 2011) retained the recommendation of using the standard triple therapy as first-line treatment in regions where clarithromycin resistance is lower than 15%.

Although the safety differences between CAO and LAO regimens observed in our study are not significant, the levofloxacin-containing regimen seems to be more poorly tolerated, mainly due to mucosal complaints and myalgias. This may be due in part to the high doses of the drug used here. The present trial shows acceptable and stable eradication rates for the standard clarithromycin-based triple therapy in our region, which correlate well with a low to moderate in vitro resistance of H. pylori to clarithromycin (<15%). Thus, it still supports the inclusion of this macrolide in H. pylori eradication regimens in our area, on the basis of current consensus. Furthermore, an alternative levofloxacin-based regimen appears not to improve upon the standard therapy in terms of clinical efficacy, which can be explained by a progressive increase in the in vitro resistance rates of H. pylori to this quinolone. Finally, a poorer tolerance profile and the higher cost of levofloxacin leave levofloxacin-based regimens confined to second-line treatment, with some exceptions. All efforts should be made to find new regimens that will result in >90% eradication in first-line treatment. Following expert recommendations, quadruple regimens (mainly sequential and concomitant therapies) appear to be valuable alternatives as first-line options on the basis of their high eradication rates and their capabilities to overcome the increasing H. pylori resistance to clarithromycin.

Acknowledgements

We gratefully acknowledge Mrs Marien Cacho and Emna Fernández (members of the nursing team) for their invaluable collaboration in this study.

Funding

This work was funded by a grant from the Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (grant number, EC08/00045). The Instituto de Formación e Investigación Marqués de Valdecilla (IFIMAV) hired Dra. González-Colominas in order to perform a part of this project.

Transparency declarations

None to declare.

Contributions

The involvement of each author was as follows:

A. C.-L. (1–8), J. R. S.-C. (1, 3, 5, 7, 8), M.F.C. (2, 3, 4, 5, 7, 8), T. D.-S. (2, 3, 5, 6), M. C. (2, 3, 5, 7), M. R. C. (2, 3, 5, 7), B. A. (2, 3, 5, 7), A. F.-P (2, 3, 5, 7), E. G.-C. (2, 3, 5, 7), S. A-Z. (2, 3, 5, 7), M. H. (5, 7, 8), E. L. P. (2, 5, 7). [Key: (1) Study concept and design; (2) Acquisition of data; (3) Analysis and interpretation of data; (4) Drafting of the manuscript; (5) Critical revision of the manuscript for important intellectual content; (6) Statistical analysis; (7) Administrative, technical, or material support; (8) Study supervision.]

Table 2. Side effects in the study population

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Total cohort, n (%)</th>
<th>CAO, n (%)</th>
<th>LAO, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>165 (66)</td>
<td>75 (58.6)</td>
<td>90 (73.8)</td>
<td></td>
</tr>
<tr>
<td>Metallic taste</td>
<td>29 (11.6)</td>
<td>19 (14.8)</td>
<td>10 (8.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>29 (11.6)</td>
<td>12 (9.4)</td>
<td>17 (13.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Nausea, dyspepsia</td>
<td>25 (10.0)</td>
<td>13 (10.2)</td>
<td>12 (9.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (10.0)</td>
<td>18 (14.1)</td>
<td>7 (5.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14 (5.6)</td>
<td>3 (2.3)</td>
<td>11 (9.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mucosal complaintsab</td>
<td>13 (5.2)</td>
<td>2 (1.6)</td>
<td>11 (9.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
<td>4 (3.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (1.2)</td>
<td>1 (0.8)</td>
<td>2 (1.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Others</td>
<td>22 (8.8)</td>
<td>7 (5.5)</td>
<td>15 (12.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
References