Levofloxacin-based triple therapy vs. quadruple therapy in second-line Helicobacter pylori treatment: a randomized trial


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SUMMARY

Background: Levofloxacin has been shown to be effective in Helicobacter pylori eradication. Two 10-day levofloxacin-based triple therapies were compared with standard 7- and 14-day quadruple regimens in second-line treatment.

Methods: Two hundred and eighty consecutive patients who failed to respond to standard triple therapy (clarithromycin, amoxicillin, rabeprazole) were randomly assigned to four groups: (1) levofloxacin 500 mg o.d., amoxicillin 1 g b.d., rabeprazole 20 mg b.d. for 10 days (LAR, n = 70); (2) levofloxacin 500 mg o.d., tinidazole 500 mg b.d., rabeprazole 20 mg b.d. for 10 days (LTR, n = 70); (3) tetracycline 500 mg q.d.s., metronidazole 500 mg t.d.s., bismuth salt 120 mg q.d.s., rabeprazole 20 mg b.d. for 7 days (7TMBR, n = 70); and (4) for 14 days (14TMBR, n = 70). Helicobacter pylori status and side-effects were assessed 6 weeks after treatment.

Results: The eradication rate was 94% in the LAR group and 90% in the LTR group in both intention-to-treat and per protocol analyses. Helicobacter pylori eradication was achieved in 63 and 69% of the 7TMBR group and in 69 and 80% of the 14TMBR group in intention-to-treat and per protocol analysis, respectively. Side-effects were significantly lower in the LAR and LTR groups than in the 14TMBR group.

Conclusion: Ten-day levofloxacin-based therapies are better than standard quadruple regimens as second-line option for H. pylori eradication.

INTRODUCTION

The Maastricht 2000 Consensus Report recommends the eradication of Helicobacter pylori in all patients with gastric and duodenal ulcers, low-grade gastric mucosa-associated lymphoid tissue lymphoma, atrophic gastritis, after stomach resection for gastric cancer, in first-degree relatives of gastric cancer patients and in symptom-free subjects who wish to be treated.1, 2

At present, triple therapy schemes are recommended by national and international consensus conferences and guidelines and are widely used in Europe. In these schemes, a proton pump inhibitor or ranitidine bismuth citrate are administered with a combination of two antibiotics (such as clarithromycin, amoxicillin or metronidazole) for a minimum of 7 days.3

Antibiotic resistance, however, is a major issue and triple therapies fail to eradicate the infection in approximately 20% of patients.4 The development of new treatment solutions to be deployed after failure of the first-line treatment is an area of current investigation. Second-line regimens that may elude bacterial resistance should include the lowest number of drugs, in order to minimize side-effects and to optimize compliance.

According to the Maastricht 2-2000 Consensus Report, the recommended second-line treatment should include a proton pump inhibitor, bismuth salt, metronidazole and tetracycline for a minimum of 7 days.
Such a second-line approach, however, has led to success rates ranging from less than 60% to more than 95% in per protocol analysis, with the most relevant determinants of success being microbial sensitivity and patient compliance. In the search for an ideal antibiotic scheme for second-line regimens, macrolides, furazolidone, rifafurin and new fluoroquinolones have been used with variable eradication rates. 

Levofloxacin is a levorotatory isomer of ofloxacin with known activity against many Gram-negative and Gram-positive bacteria. The mode of action of levofloxacin is based on the inhibition of bacterial DNA topoisomerase II (the enzyme responsible for DNA hyperspiralized rolling up and unrolling). Recent reports have shown a H. pylori eradication rate higher than 90% and a low side-effects incidence using a 7-day rabeprazole/levofloxacin-based triple therapy, associated with amoxicillin or tinidazole, in first-line or with rifabutin in second-line treatment.

The present study was carried out in patients in whom H. pylori was not eradicated after an initial triple therapy. Using two triple therapies that included levofloxacin vs. two quadruple therapy schemes recommended by the Consensus statement as second-line treatments, the eradication rate achieved and the incidence of side-effects observed were compared.

PATIENTS AND METHODS

This prospective, parallel-group, randomized trial was conducted between October 2001 and December 2002 in consecutive out-patients from the Gastroenterology and Internal Medicine Departments of the Gemelli Hospital, Catholic University of Rome. This trial is reported according to the recommendations of the CONSORT statement for the quality of reports of parallel-group, randomized trials.

Eligibility criteria

Consecutive patients affected by non-ulcer dyspepsia, as shown by upper endoscopy, H. pylori positive, with one previous failed eradication attempt in whom a standard triple therapy (clarithromycin 500 mg b.d., amoxicillin 1 g b.d., rabeprazole 20 mg b.d.) was used, were included in the study after giving written informed consent. Dyspepsia was classified in the following subcategories: ulcer-like, dysmotility-like and reflux-like, according to the Rome I criteria.

The exclusion criteria were: recent (within the previous 30 days) use of antimicrobial agents, bismuth compounds, proton pump inhibitors and H2 receptor antagonists, hypersensitivity to one of the studied drugs, previous treatment with one of the studied combinations. Pregnant or lactating women, patients with major concomitant diseases or who had undergone gastric surgery were excluded from the study.

Interventions

The original diagnosis and post-therapy determination of H. pylori positivity were assessed through the 13C urea breath test and histology (two biopsy samples were obtained from the antral mucosa and two from the gastric corpus).

Outcomes

The primary outcomes of the study were the H. pylori eradication rates using the four different antibiotic schemes. The H. pylori status post-therapy was determined using the 13C urea breath test, performed with citric acid and 75 mg of 13C urea, 6 weeks after the end of the therapy. The cut-off for positivity was delta > 3.5 units. Secondary outcomes were patient compliance and incidence of side-effects in the four therapeutic schemes. Compliance was assessed both by an interview (administered by a trained physician) conducted the day after the last day of therapy administration, and by a pill count of the drugs boxes returned at the same interview. Low compliance was defined as more than 20% of pills returned at the time of the interview. At enrolment, the patients were informed of the common side-effects expected from the studied antibiotics. A validated questionnaire was administered to each patient to evaluate the presence and intensity (0–3) of side-effects (dysgeusia, nausea, vomiting, bloating, abdominal pain, constipation, diarrhoea, loss of appetite, taste disturbances, headache). The questionnaire was administered at enrolment and diary cards in the same format (Likert scales) were completed by the patients during the treatment period and then returned at the post-therapy interview.

Randomization

Using a computer-generated number sequence, the patients were randomly assigned to one of four
The sequence was generated by a statistician. The treatment groups were:
(1) levofloxacin 500 mg o.d., amoxicillin 1 g b.d. and rabeprazole 20 mg b.d. (LAR, n = 70) for 10 days; (2) levofloxacin 500 mg o.d., tinidazole 500 mg b.d. and rabeprazole 20 mg b.d. (LTR, n = 70) for 10 days; (3) tetracycline 500 mg q.d.s., metronidazole 500 mg t.d.s., bismuth salt 120 mg q.d.s and rabeprazole 20 mg b.d. for 7 days (7TMBR, n = 70); and (4) for 14 days (14TMBR, n = 70).

**Sample size**

The estimated sample size was 60 subjects per group, with a power of 0.90 and a significance level of 0.05 (alpha = 0.05, two-sided). The sample size was estimated in order to detect a difference of 5% in the eradication rate between the levofloxacin and amoxicillin-based therapies (assumed to have an eradication rate of 80%) and the 7- and 14-day tetracycline and metronidazole-based therapies (assumed to have an eradication rate of 70%).

**Data analysis**

Both per protocol and intention-to-treat analyses were performed. For the purpose of the analysis, the incidence of side-effects was considered as a binomial variable (present/absent). Any ‘side-effect’ was considered absent if the subject reported the same complaint at the baseline visit, as assessed by the questionnaire. To detect differences in *H. pylori* eradication rates and the incidence of side-effects, the χ² or Fisher exact tests were used. Odds ratio (OR) for achieving *H. pylori* eradication with 95% confidence intervals (95%CI) were calculated. The statistical analysis was performed using Stata 6.0.

**RESULTS**

**Study flow and overall compliance**

The trial flow is summarized in Figure 1. Two hundred and eighty (134 males, aged 18–65 years) patients with non-ulcer dyspepsia were enrolled. Demographic and clinical characteristics of the study groups are summarized in Table 1. Overall, 264 patients (94%) completed the studied therapeutic regimens. Six drop-outs occurred in the 7TMBR group (one for low compliance and five due to side-effects self-rated as severe). Ten drop-outs occurred in the 14TMBR group (three for low compliance and seven due to side-effects self-rated as severe).

**H. pylori eradication rates**

The eradication rate was 94% (66/70 patients) in the LAR group and 90% in the LTR group (63/70 patients) in both intention-to-treat and per protocol analysis. *Helicobacter pylori* eradication was achieved in 63%
(44/70 patients) and 69% (44/64 patients) in the 7TMBR group and in 69% (48/70 patients) and 80% (48/60 patients) in the 14TMBR group in intention-to-treat and per protocol analysis, respectively (Figure 2).

In particular, the eradication rates of levofloxacin-based therapies were significantly higher than those observed using quadruple therapy for 7 days in both intention-to-treat (94 vs. 63%; OR, 4.50; 95%CI, 3.18–29.87 and 90 vs. 63%; OR, 2.78; 95%CI, 2.12–13.3) and per protocol (94 vs. 69%; OR, 3.76; 95%CI, 2.45–23.37 and 90 vs. 69%; OR, 2.27; 95%CI, 1.59–10.50; Table 2) analysis. Both levofloxacin-based treatments showed a higher eradication rate than the 14-day quadruple therapy in intention-to-treat analysis (94 vs. 69%; OR, 3.76; 95%CI, 2.45–23.37 and 90 vs. 69%; OR, 2.27; 95%CI, 1.59–10.50; Table 2). No significant differences were found between LTR and 14TMBR in per protocol analysis (90 vs. 80%; OR, 1.54; 95%CI, 0.82–6.15; Table 2).

Side-effects profile

Details of the incidence and severity of side-effects during the study period are reported in Tables 3 and 4 and Figure 3. The overall prevalence of side-effects was significantly lower in the LAR and LTR groups than in the 14TMBR group (10 vs. 33%; OR, 0.41; 95%CI, 0.09–0.57 and 11 vs. 33%; OR, 0.45; 95%CI, 0.11–0.64, respectively). No significant differences were found among the LAR, LTR and 7TMBR groups in the prevalence of overall side-effects (10 vs. 21%; OR, 0.6; 95%CI, 0.15–1.07 and 11 vs. 21%; OR, 0.66; 95%CI, 0.19–1.3, respectively; Table 3). The incidence of taste impairment was significantly higher in the 14TMBR group than in the LAR group. Bloating was experienced in a significantly higher number of patients in...

**Table 1. Demographic and clinical characteristics of patients randomized according to Rome I criteria**

<table>
<thead>
<tr>
<th>Gender (male/female)</th>
<th>Age (mean ± s.d.)</th>
<th>Ulcer-like dyspepsia (%)</th>
<th>Dismotility-like dyspepsia (%)</th>
<th>Reflux-like dyspepsia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAR</td>
<td>33/37</td>
<td>47 ± 10.4</td>
<td>37 (26/70)</td>
<td>33 (23/70)</td>
</tr>
<tr>
<td>LTR</td>
<td>34/36</td>
<td>48 ± 9.4</td>
<td>41 (29/70)</td>
<td>30 (21/70)</td>
</tr>
<tr>
<td>7TMBR</td>
<td>34/36</td>
<td>48 ± 9.9</td>
<td>40 (28/70)</td>
<td>34 (24/70)</td>
</tr>
<tr>
<td>14TMBR</td>
<td>33/37</td>
<td>49 ± 11.1</td>
<td>43 (30/70)</td>
<td>33 (23/70)</td>
</tr>
</tbody>
</table>

LAR, levofloxacin, amoxicillin, rabeprazole; LTR, levofloxacin, tinidazole, rabeprazole; TMBR, tetracycline, metronidazole, bismuth salt, rabeprazole for 7 or 14 days; s.d., standard deviation.

**Table 2. Comparison between the eradication rates of levofloxacin-based triple therapies and quadruple therapies**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Therapies</th>
<th>%</th>
<th>OR [%95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td>LAR vs. 7TMBR</td>
<td>94 vs. 63</td>
<td>4.50 [3.18–29.87]</td>
</tr>
<tr>
<td></td>
<td>LTR vs. 7TMBR</td>
<td>90 vs. 63</td>
<td>2.78 [2.12–13.3]</td>
</tr>
<tr>
<td></td>
<td>LAR vs. 14TMBR</td>
<td>94 vs. 69</td>
<td>3.76 [2.45–23.37]</td>
</tr>
<tr>
<td></td>
<td>LTR vs. 14TMBR</td>
<td>90 vs. 69</td>
<td>2.35 [1.63–10.45]</td>
</tr>
<tr>
<td>Per protocol</td>
<td>LAR vs. 7TMBR</td>
<td>94 vs. 69</td>
<td>3.60 [2.40–23.43]</td>
</tr>
<tr>
<td></td>
<td>LTR vs. 7TMBR</td>
<td>90 vs. 69</td>
<td>2.27 [1.59–10.50]</td>
</tr>
<tr>
<td></td>
<td>LAR vs. 14TMBR</td>
<td>94 vs. 80</td>
<td>3.32 [1.25–13.57]</td>
</tr>
<tr>
<td></td>
<td>LTR vs. 14TMBR</td>
<td>90 vs. 80</td>
<td>1.54 [0.82–6.15]</td>
</tr>
</tbody>
</table>

LAR, levofloxacin, amoxicillin, rabeprazole; LTR, levofloxacin, tinidazole, rabeprazole; TMBR, tetracycline, metronidazole, bismuth salt, rabeprazole; OR, odds ratio for *Helicobacter pylori* eradication; 95%CI, 95% confidence interval.

Figure 2. *Helicobacter pylori* eradication. P-values according to χ² tests.
DISCUSSION

The present study suggests that 10-day triple proton pump inhibitor-based therapies using levofloxacin against *H. pylori* infection can be more effective and better tolerated than the recommended proton pump inhibitor- and ranitidine bismuth citrate-based quadruple therapies. Notably, the compliance for dual and triple proton pump inhibitor-based rescue therapies using levofloxacin was optimal. Many authors have investigated the role of alternative antibiotics to those used in standard regimens, such as rifabutin, ketolides, quinolones and nitazoxanide, in second-line treatment trials. Among these attempts, two studies from our group have shown an eradication rate of two different levofloxacin-based triple therapies (associated with rabeprazole and amoxicillin or metronidazole) of at least 90% in first-line treatment. In the study conducted by Wong et al., levofloxacin was tested in second-line treatment in association with rabeprazole and rifabutin for 7 days. The eradication rate achieved was 91%, even if patients who had failed to respond to more than one course of anti-*H. pylori* therapy were included. However, rifabutin is very expensive and is used against multiresistant *Mycobacterium tuberculosis*, suggesting a restricted use in order to avoid increasing resistance. Our data are relevant to the clinical question on the safest and most effective therapeutic regimen for subjects who fail to achieve eradication of *H. pylori* infection at the first attempt. In fact, it is estimated that *H. pylori* eradication fails in at least 10–20% of patients after standard triple therapy based on amoxicillin and clarithromycin. In these cases, an alternative regimen is required.

In the majority of cases, the failure of first-line schemes is attributable to clarithromycin or metronidazole resistance. It is advisable not to use these agents together in first-line eradication schemes, in order to avoid inducing combined strain resistance and to ‘save’ either clarithromycin or metronidazole for a subsequent attempt. Indeed, the Maastricht 2-2000 Consensus Report suggests using nitroimidazoles in second-line therapies, and combining metronidazole with amoxicillin and a proton pump inhibitor in a triple therapy or with bismuth salt, tetracycline and a proton pump inhibitor (or ranitidine) in a quadruple regimen.

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Table 3. Details of the incidence and severity of side-effects during the study. The data are reported as percentages in intention-to-treat analysis.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>LAR</th>
<th>LTR</th>
<th>7TMBR</th>
<th>14TMBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>13*</td>
</tr>
<tr>
<td>Bloating</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>11‡</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>11</td>
<td>21</td>
<td>33†</td>
</tr>
</tbody>
</table>

LAR, levofloxacin, amoxicillin, rabeprazole; LTR, levofloxacin, tinidazole, rabeprazole; TMBR, tetracycline, metronidazole, bismuth salt, rabeprazole; OR, odds ratio; 95%CI, 95% confidence interval.

* vs. LAR (OR, 1.73; 95%CI, 1.04–24.13).
‡ vs. LTR (OR, 1.88; 95%CI, 1.08–73.22).
† vs. LAR (OR, 0.41; 95%CI, 0.09–0.57) and vs. LTR (OR, 0.45; 95%CI, 0.11–0.64).

Table 4. Intensity of side-effects between therapies (intention-to-treat analysis). Percentages are presented in parentheses.

<table>
<thead>
<tr>
<th>Intensity</th>
<th>LAR</th>
<th>LTR</th>
<th>7TMBR</th>
<th>14TMBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>7/70 (10)</td>
<td>8/70 (11)</td>
<td>5/70 (7)</td>
<td>12/70 (17)</td>
</tr>
<tr>
<td>Moderate</td>
<td>–</td>
<td>–</td>
<td>4/70 (6)</td>
<td>3/70 (4)</td>
</tr>
<tr>
<td>Severe</td>
<td>–</td>
<td>–</td>
<td>6/70 (9)</td>
<td>8/70 (8)</td>
</tr>
<tr>
<td>Caused drop-out</td>
<td>–</td>
<td>–</td>
<td>5/70 (5)</td>
<td>7/70 (10)</td>
</tr>
</tbody>
</table>

LAR, levofloxacin, amoxicillin, rabeprazole; LTR, levofloxacin, tinidazole, rabeprazole; TMBR, tetracycline, metronidazole, bismuth salt, rabeprazole.

Figure 3. Incidence of side-effects during *Helicobacter pylori* treatment with levofloxacin-based triple therapies and 7- and 14-day quadruple therapies. P-values according to χ² tests.

** 7TMBR and LAR vs. LTR P<0.01
** 14TMBR vs. LAR and LTR P<0.0001
The strengths of the current study were the number of patients included, the homogeneity of the first-line therapy used (the same for all patients enrolled) and the use of quadruple therapies for control groups in accordance with the Maastricht criteria. We used two quadruple therapy schemes lasting 7 and 14 days in order to determine the differences in side-effects incidence that could only be attributable to the 2-weeks duration of treatment vs. the 10 days of the schemes using levofloxacin. As expected, the 14-day quadruple therapy achieved a higher success rate than its 7-day counterpart, but compliance and the side-effect burden were worse. Longer quadruple regimens may be associated with higher exposure and a greater eradication rate, but also with lower compliance. Our results concerning the control groups (quadruple schemes) are different from those obtained by Rinaldi et al. and Zullo et al. who observed eradication rates of 82 and 96%, respectively, for triple therapies using ranitidine bismuth citrate, tinidazole and tetracycline, without any proton pump inhibitor. Our results suggest that including a proton pump inhibitor in the regimen with bismuth salt does not improve the eradication rate. This difference might be attributable to differences in baseline resistance to tinidazole, although characterization of antibiotic resistance using an antibiogram was not performed in our study or the previous studies. However, the number of patients included in most of the trials with quadruple schemes was low and the results often discordant. The eradication rate ranged between 60 and 95%. These differences may be due, at least in part, to heterogeneity in drug dosages and treatment durations. Our eradication rate for the same combination of antibiotics and bismuth was within the range described above. According to a recent meta-analysis, there seems to be no difference between proton pump inhibitor-based and ranitidine bismuth citrate-based triple therapy.

Nitroimidazole resistance could have determined the low efficacy of the quadruple therapy schemes. Nitroimidazole primary resistance has been investigated in two studies, which found a prevalence of 12–15% in Italy, but has never been studied after a standard triple therapy. However, it has been shown that metronidazole resistance is not a major determinant of the failure rate of quadruple therapy. Hence, the reasons for quadruple therapy failure cannot only be ascribed to the use of metronidazole.

We perceive that the present study had some limitations. First, we were not aware of any baseline differences in resistance to nitroimidazole between groups. This may have inflated the differences in efficacy between the schemes with levofloxacin and the other groups. However, this would have required an antibiogram of all patients enrolled in the study, which would have been a demanding procedure given the number of subjects studied. Performing an antibiotic susceptibility test would not have increased the external validity of the study, as antibiograms are not performed routinely in clinical practice. Such an approach, however, will be useful in the future to address the question of resistance of H. pylori to levofloxacin.

Second, given the differences in the lengths of the therapy schemes, it was impossible to blind symptom assessment. Despite this, symptoms such as diarrhoea and vomiting are less subjective and the estimate of their incidence was probably unbiased.

In conclusion, in patients who failed to respond to eradication treatment based on amoxicillin, clarithromycin and rabeprazole, a 10-day course of levofloxacin with rabeprazole and amoxicillin or tinidazole was effective and well tolerated. These 10-day levofloxacin schemes were significantly superior to standard recommended 7- or 14-day quadruple therapies.

ACKNOWLEDGEMENTS

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