

Second-line treatment for *Helicobacter pylori* eradication after sequential therapy failure: a pilot study

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Background: *Helicobacter pylori* plays a role in peptic ulcer and gastric carcinogenesis. It has been found that the success rate following standard 7-day triple therapies is decreasing. We have recently proposed a more successful 10-day sequential regimen as first-line therapy. However, no data are currently available for a rescue treatment in the event of eradication failure. **Objective:** We designed the present study in order to evaluate the efficacy of a levofloxacin–amoxicillin-based regimen as second-line therapy in sequential therapy-failure patients. **Methods:** This was a prospective, open-label, pilot study enrolling patients who failed *H. pylori* eradication after sequential therapy. Patients received a 10-day triple therapy comprising rabeprazole 20 mg twice a day, levofloxacin 250 mg twice a day and amoxicillin 1 g twice a day. Bacterial eradication was examined 4–6 weeks after treatment by using a ¹³C urea breath test. **Results:** Overall, 35 patients were enrolled (Males: 20; mean age: 49 ± 12 years), 29 with nonulcer dyspepsia and six with peptic ulcer. *H. pylori* infection was successfully cured in 30 patients, accounting for a 85.7% (95% confidence interval [CI]: 74–97) and 88.2% (95% CI: 77–99) eradication rates at intention-to-treat and per protocol analyses, respectively. One patient stopped the treatment earlier due to side effects. **Conclusions:** Data showed that levofloxacin–amoxicillin triple therapy is a successful second-line treatment for sequential therapy-failure patients. Therefore, the 10-day sequential regimen plus the 10-day levofloxacin-based triple therapy may represent a valid therapeutic package for *H. pylori* management in clinical practice.

Helicobacter pylori plays a pivotal role in the pathogenesis of chronic, active gastritis, peptic ulcer and gastric mucosa-associated lymphoid tissue (MALT)-lymphoma, and it is involved in carcinogenesis of the stomach [1]. Triple therapies over 7 days, comprising proton-pump inhibitors (PPIs), clarithromycin and amoxicillin or metronidazole are advised as first-line treatments for *H. pylori* infection according to current European guidelines [2]. However, several recent studies have found that the success rate following such regimens is decreasing. Indeed, two very large meta-analyses showed that these therapies fail to eradicate *H. pylori* infection in up to 20% of patients [3,4]. During the last few years we have proposed a novel 10-day sequential regimen, consisting of a simple dual therapy (PPI plus amoxicillin) given for the first 5 days followed by a triple therapy (PPI, clarithromycin and tinidazole) for the remaining 5 days [5]. In several studies, such a sequential regimen was proven highly successful as first-line therapy for *H. pylori* eradication as compared with both 7- and 10-day triple therapies in children, adults and elderly patients [6–8]. Moreover, this therapeutic regimen does not appear to be affected by those factors which have been shown

to drastically influence triple-therapy success, such as presence of CagA-negative strains, antibiotic bacterial resistance, smoking and nonulcer dyspepsia [9]. Despite the high eradication rate constantly achieved following this sequential regimen (>90%), some patients still remain infected, and no data are currently available for a rescue treatment in these cases. In our previous studies, an acceptably high eradication rate was achieved using a 10-day levofloxacin–amoxicillin therapy in those patients who have failed two or more standard treatments for *H. pylori* eradication [10–12], and other studies have confirmed these results [13].

Therefore we designed the present, prospective study in order to evaluate the efficacy of this levofloxacin–amoxicillin-based regimen as second-line therapy in sequential therapy-failure patients.

Materials & methods

Trial organization

This was a prospective, open-label, pilot study conducted in two Italian centers, enrolling patients aged over 18 years. Written informed consent was obtained from each patient prior to study enrollment.

Keywords: amoxicillin,
Helicobacter pylori,
levofloxacin, peptic ulcer,
sequential therapy



Table 1. Patients enrolled and *Helicobacter pylori* eradication rates achieved in the two centers.

	Foggia*	Rome*
Number of patients	15	20
Age (mean \pm standard deviation)	48 \pm 9	49 \pm 13
Gender (male/female)	9/6	11/9
Nonulcer dyspepsia	13	16
Peptic ulcer	2	4
Eradication rate	13/15 (87%)	17/20 (85%)

**p* values were not significant

Participants

Consecutive patients with persistent *H. pylori* infection after a 10-day, sequential regimen were invited to participate in the present study. The majority of these patients were enrolled in previous studies aimed at assessing the efficacy of sequential therapy [7–9]. Exclusion criteria included allergies towards penicillin and/or quinolones, pregnancy and hepatic impairment or kidney failure. Infection at entry was determined by a rapid urease test and histological examination and/or a ^{13}C urea breath test. The rapid urease test was performed using biopsy specimens, one each from the antrum and corpus. The histological assessment of *H. pylori* status was performed using a further four biopsy specimens stained with Giemsa, two from the antrum and two from the gastric body.

Intervention

Patients were assigned to receive a 10-day triple therapy comprising rabeprazole 20 mg twice a day, levofloxacin 250 mg twice a day, and amoxicillin 1 g twice a day. Rabeprazole was administered half an hour before breakfast and dinner, and the antibiotics were taken after these meals. Patients were thoroughly instructed and motivated to the therapy. Each patient was asked to return at the end of treatment for a clinical check-up, and assessment of therapy compliance and side effects. Compliance was defined as consumption of over 90% of the prescribed drugs and was determined by pill counts. Side effects were evaluated using a structured questionnaire by personal interview.

Outcome

The primary outcome was to assess the *H. pylori* eradication rate following this second-line triple therapy. Compliance and side-effect incidence were the secondary outcomes of the study. Bacterial eradication was examined 4–6 weeks after

treatment using a ^{13}C urea breath test. Citric acid (1.5 g) as test meal and 75 mg of ^{13}C urea as water solution was given to the patients after collection of a baseline sample, obtained by blowing through a disposable plastic straw into a 20 ml container, and a further breath sample was collected 30 min later. The breath samples were considered positive if there was a greater than 3.5/1000 of CO_2 difference over baseline, according to the manufacturer's recommendations.

Statistical analysis

The eradication rates and their 95% confidence intervals (CIs) at both intention-to-treat (ITT) and per protocol (PP) analyses were calculated. All patients were included in the ITT analysis but were not incorporated in the PP analysis when consumption of the prescribed drugs was less than 50% or if they did not complete the follow-up. These criteria were determined before commencing the study. The difference between the eradication rates achieved in the two participating centers was estimated. Before pooling that estimate, a Fisher's exact test was applied to investigate heterogeneity between the differences.

Results

Eradication rates

A total of 35 patients were enrolled in the study – 20 (57%) males and 15 (43%) females, with a mean age of 49 \pm 12 years. Before first-line therapy, 29 (83%) patients complained of nonulcer dyspepsia, while the remaining six (17%) had peptic ulcer (four duodenal and two gastric). One patient with nonulcer dyspepsia stopped the treatment earlier due to side effects, and he did not undergo urea breath test control. Thus, the final PP population consisted of 34 patients. As shown in Table 1, no significant difference emerged in eradication rates between the two participating centers. Overall, *H. pylori* infection was successfully cured in 30 patients, accounting for 85.7% (95% CI: 74–97) and 88.2% (95% CI: 77–99) eradication rates at ITT and PP analyses, respectively. According to the gastroduodenal pathology, eradication at PP analysis was achieved in all six (100%) patients with peptic ulcer and in 24 of 28 (85.7%) of those with nonulcer dyspepsia (*p* = NS).

Compliance & side effects

Compliance to the therapy was good (>95% of prescribed drugs) in all but one patient who stopped the treatment within 3 days for oral candidiasis. Overall, eight (22.8%) patients

complained of side effects consisting of four patients with glossitis, one with oral candidiasis, one vaginal candidiasis, one diarrhea and one patient with abdominal pain.

Discussion

There is mounting evidence that the *H. pylori* eradication rate following triple therapies is substantially decreasing in several countries [3], with an eradication rate as low as 25–45% in some recent studies [14,15]. Moreover, bacterial eradication following a failed initial standard triple therapy is notoriously difficult to achieve. Based on these observations, in the last 5 years we have proposed a novel 10-day sequential regimen as first-line therapy, and high performance of such a therapy has been successfully proved in different, multicenter studies [6–9]. In detail, the sequential regimen has been shown to be highly effective (93.5% eradication rate in 1.208 patients; 95% CI: 92–95), safe, relatively short, and cost-effective when compared with other strategies [16]. Unfortunately, some patients still remain infected even after the sequential regimen, hence warranting further therapy.

The current European guidelines suggest the use of a quadruple regimen as a second-line treatment after standard triple-therapy failure [2]. However, the cure rates achieved by this regimen are controversial, with an eradication rate as low as 37% in recent studies [13]. Moreover, a large number of tablets need to be taken with such a quadruple regimen, reducing patient compliance [17]. In addition, both side effects [18] and bismuth toxicity may also be a cause for concern, since a recent study found that 9% of patients receiving the quadruple regimen had very high blood bismuth concentrations within alarm levels [19]. Recent studies have found that an acceptably high eradication rate was achieved by using a levofloxacin–amoxicillin combination as a rescue therapy in patients who have failed two or more standard treatments for *H. pylori* eradication [10–13]. Such a therapy regimen has been administered for 7 or 10 days, with some observations suggesting that the eradication rate tends to be higher during prolonged treatment [13].

For the first time, the present study assessed the efficacy of a 10-day levofloxacin–amoxicillin combination as second-line therapy in patients who have failed sequential therapy. Our data demonstrated a very high efficacy for this therapeutic regimen, being successful at ITT analysis in over 85% of patients. Since it has been calculated that a sample of 30–40 patients is sufficient to identify a potentially effective regimen for *H. pylori* eradication, the population of the present pilot study may be regarded as adequate [20]. Regarding compliance to therapy, it resulted in being very high in the present study, in agreement with previous reports. However, this could be due, at least in part, to the fact the most of the enrolled patients were motivated by their previous participation in controlled trials. In addition, the levofloxacin–amoxicillin combination was well tolerated and no major side effects were observed, with an overall side-effect incidence no higher than 20%, confirming the results observed in other studies [13]. In detail, only one (3%) patient discontinued the treatment due to side effects. The results of the present study suggest that the combination of levofloxacin, an antibiotic not included in previous treatments, and amoxicillin, a compound towards which bacterial resistance has been only seldom reported, appears to be an effective strategy in the retreatment of *H. pylori* infection, even after sequential therapy failure. Therefore, the use of this rescue therapy could be suggested in the event of sequential regimen failure, without having to resort to the notoriously difficult bacterial culture [21], and before turning to an alternative, more costly and potentially unsafe regimen [22].

Expert commentary

In conclusion, this pilot study showed that levofloxacin–amoxicillin triple therapy is a suitable therapeutic approach for second-line treatment in sequential therapy–failure patients. Therefore, the 10-day sequential regimen plus the 10-day levofloxacin-based triple therapy appears to be a convincing ‘therapeutic package’ for *H. pylori* management in clinical practice.

Highlights

- A 10-day levofloxacin–amoxicillin triple therapy is an effective treatment to cure *Helicobacter pylori* infection in sequential therapy eradication-failure patients.
- This triple therapy is safe and well tolerated.
- Sequential therapy followed by the 10-day levofloxacin-based triple therapy appears to be a tempting therapeutic package for *H. pylori* management in clinical practice.

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