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High-dose esomeprazole and amoxicillin dual therapy for first-line *Helicobacter pylori* eradication: a proof of concept study

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Abstract

Background The prevalence of resistance to clarithromycin and metronidazole has considerably increased, with a corresponding decrease in the eradication rate for *Helicobacter pylori* (*H. pylori*) infection. Primary resistance to amoxicillin is extremely low, and esomeprazole was found to exert a noteworthy antimicrobial activity *in vitro* against *H. pylori*. A dual therapy with high-dose of esomeprazole coupled with high-dose amoxicillin might be therefore an ideal first-line treatment for *H. pylori* eradication. We aimed to assess the efficacy of a first-line 10-day, high-dose dual therapy consisting of amoxicillin and esomeprazole to eradicate *H. pylori* infection.

Methods Consecutive naïve *H. pylori*-infected patients, who underwent an upper endoscopy in 4 Italian hospitals due to dyspeptic symptoms and found to be infected at routine histological assessment, were invited to participate. Patients enrolled received a 10-day, high-dose dual therapy comprising esomeprazole (40 mg t.i.d) and amoxicillin (1 g t.i.d.). At least 4 weeks after the end of the treatment a ^{13}C-urea breath test was performed to evaluate the eradication.

Results A total of 56 patients agreed to participate in the study and were all followed-up. The overall eradication was 87.5% (95% CI=78.8•96.2), without a statistically significant difference among centres. Overall, 5 (8.9%; 1.5•16.4%) patients complained of side-effects.

Conclusions The 10-day, high-dose dual therapy with esomeprazole and amoxicillin might be an effective and safe first-line regimen. The efficacy of a longer 14-day regimen should be tested.

Keywords *Helicobacter pylori* infection, dual therapy, esomeprazole, amoxicillin

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Introduction

Helicobacter pylori (*H. pylori*) infection causes peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer [1,2]. Standard treatments for *H. pylori* infection endorsed by the U.S. as well as European scientific societies and by regulatory authorities rely on clarithromycin, metronidazole, or amoxicillin in conjunction with gastric acid inhibitors [3-6]. Disappointingly, the prevalence of clarithromycin and metronidazole resistance has increased substantially in recent years, and a corresponding decrease has occurred in the eradication rate for *H. pylori* infection [7,8]. Indeed, first-line therapy success rate has declined to unacceptable levels in most Western countries [9]. In addition, the primary resistance to levofloxacin – an antibiotic generally used for second-line therapy – is also increasing in several countries [7,8]. Consequently, to treat *H. pylori* eradication failure patients is progressively more difficult, suggesting that a highly successful first-line regimen is the key to contrast the phenomenon.

Considering that the availability of new antibiotics against *H. pylori* is uncertain in the next few years [10], the identification of new regimens, including the currently available molecules, able to achieve a >90% eradication rate is urgently needed. Such a regimen would need to overcome the increasing prevalence

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Conflict of Interest: None

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of strains of *H. pylori* resistant to clarithromycin and/or metronidazole. Amoxicillin is a β-lactam antibiotic included in all current therapeutic regimens for *H. pylori* eradication [11]. Indeed, minimum inhibitor concentration values against *H. pylori* strains are ranging from 0.06 to 0.25 mg/L [11]. Although amoxicillin resistance and tolerance have been reported in *H. pylori* isolates [12,13], the primary resistance to amoxicillin is extremely low in several countries, with a prevalence rate as low as <1% (95% CI: 0.06-1.06) and 3% in Europe and the U.S., respectively [7,8]. However, amoxicillin is largely inactivated by low pH values present in the stomach [14,15], so that a simultaneous proton pump inhibitor (PPI) therapy is mandatory [16]. In addition, a deep suppression of gastric acid secretion, allowing to achieve pH value >6, is expected to favor antibacterial activity of amoxicillin in the gastric juice [14]. However, such a condition is rarely achieved in Caucasian subjects with standard dose of PPIs, due to the genetic polymorphism of hepatic P450 cytochrome responsible of PPI metabolism. Indeed, as many as >95% of Caucasians are rapid or intermediate metabolizers of PPIs [17], suggesting that an increased dose is needed in the majority of Caucasian subjects. On the other hand, among PPIs, esomeprazole was found to exert a greater antimicrobial activity *in vitro* against *H. pylori* compared to omeprazole, which could help improve the success rate of eradication regimens [18]. Based on these considerations, a dual therapy with high-dose esomeprazole, which increases intragastric pH and exerts a direct anti-bacterial activity, coupled with high-dose amoxicillin, against which primary resistance is extremely low, would be an ideal first-line treatment for *H. pylori* eradication.

We therefore designed this proof of concept study to assess the efficacy of such a high-dose dual therapy as first-line treatment in *H. pylori*-infected patients.

Patients and methods

Patients

This was an open-label, study performed in 4 Italian Hospitals (1 Northern; 2 Central, and 1 Southern Italy). In each participating center, consecutive adult (>18 years) patients, who underwent upper endoscopy due to dyspeptic symptoms and found to be infected with *H. pylori* at routine histological assessment, were invited to participate. Exclusion criteria were: 1) previous *H. pylori* eradication therapy; 2) known or suspected allergy to penicillin; 3) use of PPI or antibiotics in the previous 4 weeks; 4) previous surgery of upper gastrointestinal tract; 5) severe diseases (cardiovascular, pulmonary, renal or hepatic); 6) malignant disease during the previous 5 years; 7) alcohol abuse or severe psychiatric or neurologic disorders; 8) pregnancy or lactation; and 9) refusal to consent.

Therapy regimen

All patients received a 10-day, high-dose dual therapy comprising esomeprazole (40 mg t.i.d) and amoxicillin (1 g t.i.d.). The PPI was given half an hour before breakfast, lunch and dinner, whilst amoxicillin just after these meals. At the end of the treatment, compliance to therapy and reported side-effects were assessed by a personal interview. At least 4 weeks after the end of the treatment a ^{13}C urea breath test (UBT) was performed to evaluate *H. pylori* eradication rate.

Statistical analysis

The eradication rate with 95% confidence intervals was calculated. Before pooling the estimates, a Fisher's exact test was performed to exclude a significant heterogeneity among the different centers. Based on the study design (pilot study), data of only those patients who took ≥80% of prescribed drugs, and underwent UBT control were considered.

Results

A total of 56 (male/female = 32/24; mean age: 51.3±13.7 years) patients agreed to participate in the study. All patients confirmed having taken all the prescribed drugs, but two patients who performed the therapy for 9 and 8 days, respectively. All these patients underwent the scheduled UBT control. As shown in Table 1, *H. pylori* infection was successfully cured in 87.5% (95% CI=78.8•96.2), without a statistically significant difference among the participating centers. Overall, 5 (8.9%; 1.5•16.4%) patients complained of side-effects (2 vomiting, 2 nausea, and 1 mild diarrhea), but only the 2 patients with vomiting early interrupted the treatment (at 9 and 8 days). All side-effects were self-limited.

Discussion

The success rate of standard triple therapies for *H. pylori* eradication is decreasing worldwide [19], suggesting the need of novel therapy regimens. Since newer agents with elevated activity against such an infection, including resistant strains, are still lacking [10], optimizing the use of available

Table 1 *Helicobacter pylori* eradication rate achieved in different centers

Centre	Patients enrolled	Patients cured	Eradication rate, % (95% CI)
Rome	23	21	91.3
Latina	14	12	85.7
Foggia	10	8	80
Milan	9	8	88.9
Total	56	49	87.5 (78.8•96.2)

antibiotics would be advantageous. With this purpose, we tested the efficacy of a first-line, high-dose esomeprazole-amoxicillin dual therapy. The rationale of such a regimen consisted in coupling a deep suppression of acid secretion achieved with high-dose esomeprazole which would favor the efficacy of high-dose amoxicillin for which primary resistance in *H. pylori* isolates is very uncommon. Our study showed an interestingly high efficacy of this regimen, approaching a 90% success rate in our series. Of note, such a high cure rate was achieved using a regimen lasting only 10 days, suggesting that a longer 14-day therapy could perform better, particularly when considering the high tolerability we observed. Indeed, a 14-day high-dose dual therapy regimen with omeprazole 120 mg and amoxicillin 2.25 g achieved an 89% eradication rate in duodenal ulcer patients [20], and 96% in 126 MALT-lymphoma patients [21]. Likewise, a 95.5% eradication rate was achieved with a high-dose lansoprazole and amoxicillin 2 g first-line therapy in Japan [22]. In addition, a recent study performed in Taiwan showed that a high-dose dual therapy with rabeprazole 20 mg and amoxicillin 750 mg, all given q.i.d. for 14 days, achieved a 95.3% cure rate in naïve patients [23]. Interestingly, high-dose dual therapy with omeprazole 20 mg q.i.d and amoxicillin 1 g b.i.d achieved a significantly higher eradication rate than 14-day triple therapy in Turkey [24], where achieving *H. pylori* eradication is notoriously difficult [25]. On the contrary, a disappointing 53.8% success rate was achieved in 13 patients using dexlansoprazole 120 mg and amoxicillin 1 g, both b.i.d. for 14 days [26]. Moreover, the attempt to improve a high-dose dual therapy with esomeprazole 40 mg b.i.d. and amoxicillin 1 g t.i.d for 10 days by adding metronidazole did not appear to be advantageous, the eradication rates being 82.4% and 88.2% at intention-to-treat and per protocol analysis, respectively [27]. Overall, all these observations would suggest that a study testing our proposed high-dose dual regimen with esomeprazole 40 mg and amoxicillin 1 g, both t.i.d., for 14 days is urged. The usefulness of a study is further supported by the high tolerability of such a regimen, for which the incidence of adverse events was reported to be not significantly superior to those observed in the comparison arms [20,22,28].

In conclusion, this is the first Italian study showing that a 10-day, high-dose dual therapy with esomeprazole and amoxicillin could achieve high eradication rates, suggesting that the efficacy of a longer 14-day regimen should be tested.

Summary Box

What is already known:

- The success rate of standard triple therapies for *Helicobacter pylori* (*H. pylori*) infection has declined to unacceptable levels
- The prevalence of primary resistance towards clarithromycin and metronidazole is high, whilst that towards amoxicillin remains extremely low

What the new findings are:

- A novel 10-day dual therapy with high-dose of esomeprazole coupled with high-dose amoxicillin was found to be acceptably effective and highly tolerated as a first-line therapy

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