

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 ¹³C-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)

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Conflict of Interest: None

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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

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 ¹³C 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 $\geq 80\%$ of prescribed drugs, and underwent UBT control were considered.

Results

A total of 56 (male/female = 32/24; mean age: 51.3 \pm 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.

References

1. McColl KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med* 2010; **362**:1597-1604.
2. Zullo A, Hassan C, Ridola L, et al. Gastric MALT lymphoma: old and new insights. *Ann Gastroenterol* 2014;**27**:27-33.
3. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection - the Maastricht IV/Florence Consensus Report. *Gut* 2012;**61**:646-664.
4. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;**102**:1808-1825.
5. Hunt RH, Xiao SD, Megraud F, et al. *Helicobacter pylori* in developing countries. World Gastroenterology Organisation Global Guideline. *J Gastrointest Liver Dis* 2011;**20**:299-304.
6. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter* 2010;**15**:1-20.
7. De Francesco V, Giorgio F, Hassan C, et al. Worldwide *H. pylori* antibiotic resistance: a systematic review. *J Gastrointest Liver Dis* 2010;**19**:409-414.
8. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;**62**:34-42.
9. De Francesco V, Ierardi E, Hassan C, et al. *Helicobacter pylori* therapy: present and future. *World J Gastrointest Pharmacol Ther* 2012;**3**:68-73.
10. Fiorini G, Zullo A, Gatta L, et al. Newer agents for *Helicobacter pylori* eradication. *Clin Exp Gastroenterol* 2012;**5**:109-112.
11. De Francesco V, Zullo A, Hassan C, et al. Mechanisms of *Helicobacter pylori* antibiotic resistance: an updated appraisal. *World J Gastrointest Pathophysiol* 2011;**2**:35-41.
12. van Zwet AA, Vandenbroucke-Grauls CM, Thijs JC, et al. Stable amoxicillin resistance in *Helicobacter pylori*. *Lancet* 1998;**352**:1595.
13. Dore MP, Osato MS, Realdi G, et al. Amoxicillin tolerance in *Helicobacter pylori*. *J Antimicrob Chemother* 1999;**43**:47-54.
14. Grayson ML, Eliopoulos GM, Ferraro MJ, et al. Effect of varying pH on the susceptibility of *Campylobacter pylori* to antimicrobial agents. *Eur J Clin Microbiol Infect Dis* 1989;**8**:888-889.
15. Lambert JR. Pharmacology of the gastric mucosa: a rational approach to *Helicobacter* polytherapy. *Gastroenterology* 1996;**111**:521-523.
16. Goddard AF, Jessa MJ, Barrett DA, et al. Effect of omeprazole on the distribution of metronidazole, amoxicillin, and clarithromycin in human gastric juice. *Gastroenterology* 1996;**111**:358-367.
17. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol* 2008;**64**:935-951.

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

18. Gatta L, Perna F, Figura N, et al. Antimicrobial activity of esomeprazole versus omeprazole against *Helicobacter pylori*. *J Antimicrob Chemother* 2003;**51**:439-442.
19. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013;**347**:f4587.
20. Bayerdorffer E, Miehke S, Mannes GA, et al. Double-blind trial of omeprazole and amoxicillin to cure *Helicobacter pylori* infection in patients with duodenal ulcers. *Gastroenterology* 1995;**108**:1412-1417.
21. Zullo A, Hassan C, Andriani A, et al. Eradication therapy for *Helicobacter pylori* in patients with gastric MALT-lymphoma: a pooled data analysis. *Am J Gastroenterol* 2009;**104**:1932-1937.
22. Furuta T, Shirai N, Kodaira M, et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of *H. pylori*. *Clin Pharmacol Ther* 2007;**81**:521-528.
23. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* Infection. *Clin Gastroenterol Hepatol* 2015;**13**:895-905.
24. Ince AT, Tozlu M, Baysal B, Şentürk H, Arıcı S, Özden A. Yields of dual therapy containing high-dose proton pump inhibitor in eradication of *H. pylori* positive dyspeptic patients. *Hepatogastroenterology* 2014;**61**:1454-1458.
25. Zullo A, De Francesco V, Hassan C, et al. Modified sequential therapy regimens for *Helicobacter pylori* eradication: a systematic review. *Dig Liver Dis* 2013;**45**:18-22.
26. Attumi TA, Graham DY. High-dose extended-release lansoprazole (dexlansoprazole) and amoxicillin dual therapy for *Helicobacter pylori* infections. *Helicobacter* 2014;**19**:319-322.
27. Sánchez-Delgado J, García-Iglesias P, Castro-Fernández M, et al. High-dose, ten-day esomeprazole, amoxicillin and metronidazole triple therapy achieves high *Helicobacter pylori* eradication rates. *Aliment Pharmacol Ther* 2012;**36**:190-196.
28. Shirai N, Sugimoto M, Kodaira C, et al. Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for *Helicobacter pylori* infection after the standard triple therapy. *Eur J Clin Pharmacol* 2007;**63**:743-749.