Original Article

Clarithromycin-based triple therapy for *Helicobacter pylori* treatment in peptic ulcer patients

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Abstract

Introduction: The scheme proton pump inhibitor/amoxicillin/clarithromycin (PPI/AC) is still the first-line treatment for *Helicobacter pylori (H. pylori*) infections despite evidence suggesting its failure in up to 20% to 30% of patients.

Methodology: This study involved 493 patients who were prescribed omeprazole (20 mg twice a day) or another proton pump inhibitor in equivalent dosage, amoxicillin (1 g twice a day), and clarithromycin (500 mg twice a day) for seven days. Efficacy was determined by negative urease test and absence of *H. pylori* on gastric biopsy samples twelve weeks after the end of treatment. Safety was defined according to the adverse effects reported. Mean age of the patients was (± SD) 48.96 ± 13, and demographic and clinical data were recorded for correlation with treatment outcomes.

Results: Out of 493 patients, 316 (64.1%) presented duodenal ulcer, 111 (22.5%) gastric ulcer, and 66 (14.4%) simultaneous gastric and duodenal ulcers. Additionally, 267 (54.2%) patients had at least one risk factor for peptic ulcer disease, smoking being the most common (99 [36.5%]). Successful eradication was achieved in 408 patients. The eradication rates per protocol, and according to the intention to treat, were 88.8% and 82.7%, respectively. Of 164 (35.5%) patients who presented adverse effects, 100 (61%) reported them as mild and only six (3.7%) patients had to discontinue treatment. Previous use of tobacco and non-steroid anti-inflammatory drugs was the only risk factor for treatment failure (*P* 0.00).

Conclusion: PPI/AC is still a valuable and remarkably tolerable option for first-line *H. pylori* eradication in Brazil.

Key words: *Helicobacter pylori*, peptic ulcer disease, treatment

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Introduction

The description of the etiological role of *Helicobacter pylori* (*H.* pylori) in peptic ulcer disease (PUD) by Marshall and Warren [1] resulted in a remarkable change of the pathophysiological concepts of this common disorder. *H. pylori* eradication is paramount to improve mucosal healing and to reduce the rates of recurrence of peptic ulcer [2]. The eradication of this agent also seems to reduce the incidence of gastric cancer in high-risk patients [3]. Once treated with anti-acids and dietetic recommendations [4], PUD treatment evolved into complex combinations of anti-secretory drugs and antibiotics [5].

Currently, triple therapy with proton pump inhibitors (PPI), amoxicillin, and clarithromycin for seven days is considered the best initial therapeutic option [5]. However, concerns have been expressed regarding the progressive reduction of its efficiency over the past years [6], possibly due to the development of antimicrobial resistance, particularly in the United States and Europe [7,8]. Resistance is variable from country to country, and also within different regions of the same country [9,10]. This variability may have an influence on the efficiency of eradication schemes, and standardized therapy against *H. pylori* may not be applicable worldwide. In Brazil, for example, the resistance rates against clarithromycin are low, but metronidazole resistance is much more common [11,12]. Other factors such as age above 60 years, non-ulcer dyspeptic disease, the length of the treatment, and smoking status may also result in different eradication rates [13,14].

Triple therapy with PPI, amoxicillin, and clarithromycin has been evaluated in several clinical trials [15-20], but data regarding its efficiency and tolerability in Brazil are scarce [21,22, 28-30]. This study was designed to evaluate the rate of success and the safety profile of standard therapy in a large

cohort of Brazilian patients with PUD and well-documented *H. pylori* infection.

Methodology

Patients were selected from the Outpatient Gastroenterology Clinic of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo, between January 2003 and December 2007. The inclusion criteria were current or previous PUD and documented *H. pylori* infection, either through a positive urea breath test, serology, rapid urease test, or histological examination of gastric mucosa. Patients younger than 18 years of age were excluded, as were those who presented severe comorbidity, pregnant patients, infants, patients who had previously undergone gastrectomy, patients with a known history of allergy to the therapeutic regime drugs, and patients who had used nonsteroidal antiinflammatory drugs (NSAIDs), antibiotic therapy, or bismuth salts up to four weeks before study inclusion.

At the moment of inclusion, baseline demographic characteristics were recorded. Upper digestive endoscopy was performed in all patients for peptic ulcer identification and gradation according to the Sakita classification [26], and *H. pylori* status was determined through rapid urease test and histological examination through a modified Giemsa staining method performed on gastric mucosa samples obtained from the antrum and corpus.

In an open cohort study, the study subjects were invited to use a therapeutic regimen for seven days that consisted of 20 mg omeprazole or other PPI in equivalent dose, 1,000 mg amoxicillin, and 500 mg clarithromycin, all of which were prescribed twice a day. Participants were encouraged to take the full medication regularly and were informed about the importance of an adequate use of the medication for a successful treatment. No other medication was allowed until the end of the treatment, when patients were evaluated regarding compliance by counting the remaining tablets. Adverse effects were recorded in a questionnaire, and each adverse effect was specifically investigated. They were considered mild when modifications in the treatment regimen were not necessary, moderate when modifications were necessary, and severe when treatment suspension was necessary.

Treatment efficacy was determined by bacterial negativity at the rapid urease test and histological examination of gastric antrum and corpus mucosa samples taken during digestive endoscopy performed 12 weeks after the end of treatment.

Treatment success was evaluated per protocol (PP) and according to the intention to treat (ITT). A confidence interval of 95% was calculated for the eradication rate percentiles. The chi-square method with Pearson coefficient was used for the comparison among the variables (eradication rate for previous treatment, gender, and age), with a significance value of $P < 0.05$. Statistical analysis was performed with the statistics software, version 16.0 (SPSS Inc., USA).

The study was performed in accordance with the declaration of Helsinki, and was approved by the institutional Ethics Review Board for clinical research, and all patients signed an informed written consent form.

Results

A total of 518 patients were evaluated for inclusion in the protocol, but 25 were excluded (14 for absence of PUD, two for allergy to one of the components of the treatment scheme, three for current use of nonsteroidal anti-inflammatory drugs, and six for previous anti-*H. pylori* treatment without success). Ultimately, 493 patients were analyzed, and their characteristics are displayed in Table 1. Of the 493 participants, 226 (45.8%) had no risk factors for PUD, but among the remainder, tobacco smoking and use of NSAIDs were the most common risk factors observed, present in 99 (20.2%) and 74 (15.0%) patients, respectively (Table 2).

Table 1. Baseline characteristics of the study group (n = 493)

Age (years ± SD)	48.96 ± 13.96
Male sex (n (%))	209 (42.3)
Location of the ulcer	
Duodenal (n (%))	316 (64.1)
Gastric (n (%))	111 (22.5)
Gastric and duodenal (n (%))	66 (13,4)
Sakita classification	
A (n (%))	112 (24.7)
H (n (%))	85 (17.3)
S (n (%))	296 (60)

Note: Sakita classification for peptic ulcers – A (active), H (healing), and S (scar).

The eradication rates were 88.8% (95% CI 86%-92%) per protocol and 82.7% (95% CI 79%-86%) according to the intention to treat. Thirty-one patients were lost to follow-up after treatment. Among the 462 remaining patients, adverse effects were observed in 164 (35.5%), but only six (.,7%) of these patients presented with severe adverse effects demanding the suspension of the treatment. The severity and type of adverse effects are listed on Tables 3 and 4. When analyzing the baseline characteristics and adverse effects experienced by those who completed follow-up for evaluation of the success of eradication, none of the evaluated data was related to treatment failure, except for the combination of tobacco and NSAID (*P* value 0.00).

Table 2. Risk factors for peptic ulcer disease (n = 493)

Risk factor	Frequency	Percent
None	226	45.8
Tobacco	99	20.2
Alcohol consumption	15	3.0
Previous use of NSAID	74	15.0
Tobacco and alcohol consumption	12	2.4
Tobacco and NSAID use	33	6.7
Alcohol and NSAID use	20	4.1
Tobacco, alcohol consumption, and NSAID use	14	2.8

Table 3. Severity of the adverse effects observed among patients treated with triple therapy for *H. pylori* infection (n = 164)

Severity	Frequency	Percent
Mild	100	61
Moderate	58	35.3
Severe	6	3.7

Table 4. Type of adverse effects observed among patients treated with triple therapy for *H. pylori* infection (n = 164)

Type of adverse effect	Frequency	Percent
Abdominal pain	56	34.2
Nausea	13	7.9
Vomiting	6	3.7
Diarrhea	25	15.2
Taste perversion	12	7.3
Pruritus	5	3.1
Other	47	28.6

Discussion

During the last decade several therapeutic schemes for *H. pylori* eradication were evaluated by various authors from different countries. Due to its safety profile, cost, and efficacy, triple therapy with a PPI, amoxicillin, and clarithromycin was regarded by the first Maastricht Consensus as the first option for eradication, and this position was subsequently endorsed by the following editions of this panel [5,27] as well as by the Brazilian consensus on *H. pylori* [28].

According to current recommendations [29,30], which consider an effective therapeutic scheme that achieves an eradication rate of at least 80% based on an intention-to-treat analysis, or 90% based on per protocol analysis, the scheme PPI/AC is adequate as the primary option for *H. pylori* eradication in our country. In our study, the eradication rates were 88.8% (95% CI 86%-92%) per protocol and 82.7% (95% CI 79%-86%) according to the intention to treat. These results are similar to those observed in the works of Bellelis [20], and Coelho [22] in research studies also conducted in Brazil. Results in works from Taiwan [23], Kuwait [24], Hong Kong [25], Iran [26], and Chile [27] have presented similar results regarding the efficacy of triple therapy. Meta-analysis of published works regarding the differences between the PPI in *H. pylori* treatment regimens showed eradication rates between 82% and 84% when they were combined with amoxicillin and clarithromycin [15,16].

Despite concerns regarding an increasing resistance to the components of the PPI/AC treatment regimen, this is still a valuable alternative to eradicate *H. pylori* in our country. A recent work from our group has demonstrated low *in vitro* resistance rates to amoxicillin [36], but even the previously observed higher resistance rates to this antimicrobial agent do not seem to result in lower eradication rates *in vivo* [36]. We may attribute this variation to regional differences in a country of continental dimensions such as ours. Low resistance rates to clarithromycin have also been demonstrated before in Brazil [11,36-38,40]. Second- and third-generation macrolides have been commercially available for a long time, but they are not used widely due to their elevated cost, a fact which may suffice to explain these low resistance rates in our country. Conversely, the widespread use of nitroimidazolic compounds to treat parasitic infections, sexually transmitted diseases, and gynecological infections might be responsible for the significant reduction in *H. pylori* metronidazole

sensitivity as several authors have observed [11,12,25,36-39,41].

The safety profile of this therapeutic scheme is also remarkable, since only six patients from a cohort of 493 patients had to withdraw from the study protocol due to intolerable adverse effects. In North America, Vakil *et al.* have observed a drop-out rate of 4% due to intolerable side effects in a cohort of 193 patients treated with seven-day rabeprazole, amoxicillin and clarithromycin [42]. This is a particularly relevant feature of this therapeutic scheme, since schemes containing nitroimidazolic compounds, such as metronidazole, have a higher incidence of side effects, limiting their use as first-line regimens in clinical practice.

The present study shows data on the efficacy and safety of triple therapy with a PPI, amoxicillin, and clarithromycin in a large cohort of Brazilian patients with peptic ulcer disease and well-documented *H. pylori* infection. Dismissing classical treatment options in favour of others with an inadequate safety profile or lower patient adherence due to its intrinsic complexity is unwise. Further meta-analysis of properly designed clinical trials is required to determine if triple therapy with PPI, amoxicillin, and clarithromycin has survived the test of time.

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