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Original Article

Randomized clinical trial comparing ten day concomitant and sequential therapies for *Helicobacter pylori* eradication in a high clarithromycin resistance area☆

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ABSTRACT

Background: Currently only a few studies compare sequential and concomitant non-bismuth *Helicobacter pylori* therapies referring to high antibiotic resistance populations.
Materials and methods: This multicenter prospective randomized clinical trial included 353 *H. pylori* positive, treatment naïve, patients. All patients had positive CLO-test and/or histology and culture. They received sequential (esomeprazole 40 mg, amoxicillin 1 g/bid for 5 days, followed by 5 days of esomeprazole 40 mg, clarithromycin 500 mg and metronidazole 500 mg bid), or concomitant treatment (all drugs taken concomitantly bid for 10 days). Eradication was confirmed by ^{13}C-urea breath test or histology 4–6 weeks after treatment. Adverse events and adherence were evaluated.
Results: Allocated to concomitant were 175 (72F/103M, mean 52.3 years, 38.3% smokers, 25.7% ulcer disease) and 178 (87F/91M, mean 52 years, 31% smokers, 19.1% ulcer disease) patients to sequential treatment. There were 303/353 (85.8%) positive cultures, with the following resistances: 34% metronidazole, 27.7% clarithromycin, and 7.9% dual. Eradication rates were, respectively, 89.1% (156/175) vs. 78.7% (140/178) by intention to treat ($p = 0.01$, 95% CI = 2.7–18) and 93.4%(156/167) vs. 82.8% (140/169) per protocol ($p = 0.004$, 95% CI = 3.6–17.6). Overall, adherence was (98.9%, 95% CI = 97–100). Eradication rates according to resistance were the following: dual susceptible strains 67/69 (97.1%), 62/67 (92%) ($p = 0.4$), metronidazole single resistant 38/39 (97.4%), 31/39 (79.5%) ($p = 0.03$, 95% CI = 3.5–33), clarithromycin single resistant 25/28 (89.3%), 26/31 (83.9%) ($p = 0.8$), and dual resistant 9/12 (75%), 4/11 (36.4%) ($p = 0.1$) for concomitant and sequential regimens, respectively. Side effects were comparable among regimens, except from diarrhea being more frequent among patients treated with concomitant treatment.
Conclusions: Concomitant treatment eradication rate overcomes 90% per protocol and has a significant advantage over sequential therapy. This is probably due to its better efficacy on metronidazole resistant strains. Both regimens were well tolerated and safe.

1. Introduction

Helicobacter pylori (*H. pylori*) is a global human pathogen implicated in the pathogenesis of prevalent and serious diseases mainly peptic ulcer disease and gastric malignancy [1]. Therefore, *H. pylori* infection should be properly and effectively treated as any other infection [2]. Triple regimens based on clarithromycin, the mainstay of *H. pylori* treatment for the last two decades all over the world, have lost their efficacy in several countries [3] due to globally increasing rates of clarithromycin resistance [4,5]. Therefore, they should be abandoned as first line therapies, in several parts of the world including most European countries and Greece [6–8]. Accordingly, the current European guidelines recommend bismuth based or alternatively non-bismuth quadruple regimens (the so called "concomitant" and "sequential") as first line treatments, in areas with high prevalence (over 20%) of clarithromycin resistance [9]. As bismuth salts and tetracycline are

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largely unavailable, the use of non-bismuth quadruple therapies becomes inevitable in several countries including ours [10,11]. Up to date, there is no study comparing both regimens in a trial setting with documented (by culture and antibiotic susceptibility tests) high rate of clarithromycin resistance. Most of the studies published so far, either concerned populations with levels of clarithromycin resistance below the cutoff level of 20% set by the recent Maastricht IV consensus [12–14] or compared regimens of different duration [15–18]. The former is of pivotal importance because some well designed, culture based, studies have shown that both sequential and concomitant therapy are influenced, although at a different extend, by antibiotic resistances to clarithromycin, metronidazole or both [11,19–21]. The latter represents an unfair comparison among regimens not only in terms of efficacy as prolongation of treatment seems to favorably affect concomitant and not sequential treatment [22–24] but also in terms of side effects, adherence and costs [16,17].

The aim of our study was to randomly compare the effectiveness of 10-day concomitant and sequential regimens, as first line *H. pylori* treatments, in a population with documented high levels of clarithromycin resistance and to evaluate the influence of bacterial resistance to clarithromycin (CLA) and metronidazole (MET), on *H. pylori* eradication rates.

2. Methods

2.1. Study design

This study was designed as a three center prospective, open label, and randomized trial. The study was conducted as part of a national multicenter ongoing protocol aiming at recording the nationwide prevalence of *H. pylori* antibiotic resistance. Our study was carried out between September 2012 and September 2015 in the GI departments of three participating hospitals (Athens Medical Paleo Faliron Hospital, Alexandra General Hospital and Central Clinic of Athens). The study protocol was approved by the ethics committees of the three involved hospitals and conformed to the principles of the Declaration of Helsinki and the ICH standards of Good Hospital Practice. A written, fully informed consent was obtained from each patient included in the study before enrolment.

2.2. Role of the funding source

This study was in part funded by a Hellenic Society of Gastroenterology grant. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the paper. All authors had full access to the study data, reviewed and approved the final manuscript.

2.3. Patients' recruitment

Patients of 18 years or older with dyspepsia/or iron deficiency anemia, who were referred for upper gastrointestinal endoscopy and found to be infected with *H. pylori* (positive rapid urease test), naïve to *H. pylori* eradication treatment, fulfilled eligibility criteria and were invited to participate in the study. Exclusion criteria were the following: age below 18 years, presence of severe co-morbidities (i.e. liver cirrhosis, renal failure, hematological, neurological, psychiatric, cardiovascular or pulmonary disease), previous gastric surgery, gastric malignancies, Zollinger–Elisson syndrome, known allergy or other contraindications to the study medications, previous *H. pylori* treatment, use of antibiotics, bismuth salts, NSAIDS or aspirin in the preceding month, use of PPI in the preceding 2 weeks and not willing to participate in the study. Pregnant or lactating women were also excluded.

We selected 365 eligible patients. Twelve patients refused to sign the informed consent and were excluded. The remaining 353 patients were included in the study. A careful medical history was obtained and complete clinical examination performed (including appropriate blood or other tests if indicated) prior to inclusion into the study.

2.4. H. pylori detection

During upper GI endoscopy two antral biopsies were taken for a rapid urease test (CLO-test). In those who tested positive two additional specimens (from the antrum and corpus) were sent to a reference laboratory (Hellenic Pasteur Institute) for culture and antibiotic susceptibility tests. In cases with indication for histology or equivocal CLO-test results, at least two specimens were taken from the antrum and corpus respectively, to confirm *H. pylori* gastritis using hematoxylin–eosin and modified Giemsa staining. Patients who tested positive by the urease test and/or histology were allocated to either treatment group.

2.5. Randomization and masking

Participants who had a positive test for *H. pylori* and met eligibility criteria were randomly assigned, in a 1:1 basis, to one of two treatment groups namely sequential or concomitant. Randomization was organized centrally by an independent assistant investigator using a computer generated randomization method, with a block size of four, which produced a separate number for each patient sealed in an opaque envelope and kept in his office throughout the study. After obtaining informed consent, the investigators would call the research assistant to open the envelope for the allocated regimen. All data were inserted in a computer database and elaborated by the participating investigators. The trial was not blinded for patients and recruiting physicians, regarding treatment regimen, as in most randomized controlled *H. pylori* eradication trials [25].

2.6. Interventions

After the confirmation of *H. pylori* infection, eligible patients were randomly assigned to either sequential or concomitant treatment group, for 10 days. The sequential composed 40 mg of esomeprazole bid and amoxicillin of 1 g bid, for the first 5 days followed by esomeprazole 40 mg bid, clarithromycin 500 mg bid and metronidazole 500 mg bid, for another 5 days. The concomitant composed 40 mg of esomeprazole bid, amoxicillin 1 g bid, clarithromycin 500 mg bid and metronidazole 500 mg bid. Esomeprazole was given before and antibiotics after meals, in both regimens. The patients were provided with a printed handout in order to take the medications correctly and better adhere to treatment. In the post-treatment period, symptomatic patients were allowed to use antacids on demand. Antibiotics or other medications interfering with the treatment results were prohibited during the study period. Efficacy of treatment was evaluated 4–6 weeks after completion of antibiotic therapy by ^{13}C-urea breath test performed according to the standard European protocol [26]. In patients requiring a follow-up endoscopy due to peptic ulcer disease with persisting or recurring symptoms, the diagnostic test of choice was histological examination of the four samples taken, in pairs, from the antrum and from the corpus and stained by modified Giemsa.

2.7. Tolerability and adherence

Side effects of treatment were assessed on a structured clinical interview with a specific questionnaire completed immediately after the end of eradication therapy and at the final re-evaluation. During the interview, the patients were asked to grade the severity of each adverse event experienced as “mild” (transient and well tolerated), “moderate” (causing discomfort and partially interfering with common everyday activities), or “severe” (causing considerable interference with patients' daily activities). Incapacitating or life threatening complications were classified as serious and required reporting to regulatory agency (National Organization of Medicines). Adherence to treatment was assessed