Digestive and Liver Disease 46 (2014) 980–984

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

A randomised clinical trial of 10-day concomitant therapy and standard triple therapy for *Helicobacter pylori* eradication

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ARTICLE INFO

Article history:
Received 8 April 2014
Accepted 20 July 2014
Available online 12 August 2014

Keywords:
Concomitant therapy
Helicobacter
Standard therapy

ABSTRACT

Background: As a result of increased resistance to antibiotics, *Helicobacter pylori* eradication rates using standard triple therapy have been declining.
Aim: To validate the efficacy and tolerability of a concomitant regimen as a first-line treatment for *H. pylori* infection.
Methods: A total of 348 naïve *H. pylori*-infected patients from six hospitals in Korea were randomly assigned to concomitant therapy and standard triple therapy groups. The concomitant regimen consisted of 30 mg of lansoprazole, 1 g of amoxicillin, 500 mg of clarithromycin, and 500 mg of metronidazole, twice daily for 10 days. The standard triple regimen consisted of 30 mg of lansoprazole, 1 g of amoxicillin, and 500 mg of clarithromycin, twice daily for 10 days.
Results: Concomitant and standard eradication rates were 78.7% (137/174) vs. 70.7% (123/174) by intention-to-treat ($p = 0.084$) and 88.7% (133/150) vs. 78.4% (120/153) by per-protocol ($p = 0.016$), respectively. The two groups were similar with regard to the incidence of adverse events.
Conclusions: Although 10-day concomitant therapy was validated as a suboptimal treatment option for the treatment of *H. pylori* infection, this regimen is expected to be a promising starting point in the development of an optimal treatment regimen for *H. pylori* infection.

1. Introduction

It is thought that the eradication of *Helicobacter pylori* (*H. pylori*) can partially reduce the incidence of gastric cancers as well as that of benign diseases such as peptic ulcers and gastritis [1,2]. Among the regimens used for *H. pylori* eradication, triple therapy (proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole) was accepted by international guidelines in 1996 as the first-line of "standard treatment" worldwide [3,4].

However, the eradication rate resulting from standard triple therapy has declined to less than 80% in recent years [5,6] and thus can no longer be considered "standard treatment". Therefore, it has been necessary to identify and validate combination regimens that are more efficacious. In a previous study by our group, sequential therapy showed higher effective eradication than the standard regimen (87.9% vs. 77.8%, respectively, $p = 0.013$) [7]. However, an eradication rate of over 90%, regarded as the optimal eradication cut-off therapy for per-protocol analysis, was not achieved using sequential therapy [5]. Consequently, another optimal treatment regimen is still required.

A concomitant therapy using PPI plus clarithromycin, amoxicillin, and tinidazole (or metronidazole) has been gaining attention

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http://dx.doi.org/10.1016/j.dld.2014.07.018
1590-8658/

as an effective eradication regimen again [8,9]. In this study, we aimed to validate the efficacy and safety of a concomitant regimen compared with the standard triple regimen for the efficient eradication of *H. pylori*.

2. Patients and methods

2.1. Study design

This prospective, randomised, controlled, open-label trial was conducted in six medical centres in the Daegu and Kyungsang territories, Korea from April 2012 to November 2013. This study was approved by the institutional international review board in each participating centre and the study was registered as a clinical trial (www.cris.nih.go.kr, approved number: KCT0000613). The trial was conducted in accordance with good clinical practices under the principles of the Declaration of Helsinki.

2.2. Participants

Patients presenting with *H. pylori* infection were recruited from the Daegu and Kyungsang territories in Korea. The patients underwent endoscopy and biopsies were taken for a rapid urease test, histological analysis, and a urea breath test (UBT) before treatment. *H. pylori* infection was defined as positive if any two tests among the rapid urease test, histological assessment and UBT were positive. The following criteria were used to exclude patients from the trial: younger than 18 years of age, previous *H. pylori* eradication therapy, previous gastric surgery, pregnancy, lactation, major systemic diseases, receipt of anti-secretory therapy, proton pump inhibitor, H2-receptor antagonist, bismuth, non-steroidal anti-inflammatory drug, anti-platelet agents, or antibiotics in the preceding 2 weeks, or allergy to any one of the medications in the eradication regimens. All enrolled patients provided written informed consent.

2.3. Randomisation and intervention

A randomisation list of patients, organised into six blocks, was computer-generated by an external statistician using SPSS software (version 18.0, Chicago, IL, USA). The randomised list was maintained by the study coordinator. The study coordinator was involved only in the randomisation in one of the participating centres. The patients were enrolled and the treatment assignment was ascertained by the study investigators. The patients were randomly assigned to one of these two groups, the concomitant group and the standard group. The concomitant regimen consisted of 30 mg of lansoprazole, 1 g of amoxicillin, 500 mg of clarithromycin, and 500 mg of metronidazole twice daily for 10 days. The standard therapy group received 30 mg of lansoprazole, 1 g of amoxicillin, and 500 mg of clarithromycin twice daily for 10 days.

2.4. Outcomes

The primary outcome of the study was a comparison of the eradication rates of *H. pylori* infections resulting from concomitant and standard triple therapy. The secondary outcome was treatment adherence and the frequency of adverse events resulting from the two different eradication regimens.

2.5. Follow-up procedures and rescue therapy

Four weeks after completion of the therapy, *H. pylori* eradication was assessed by UBT. A negative UBT was used as the readout to indicate successful eradication of infection. Medication adherence was assessed through pill counts and patients' entries in medication diaries. Adverse events were evaluated using a structured questionnaire and open-ended questions that the patients recorded in their medication diaries. In the event of treatment failure after initial concomitant or standard regimen, bismuth-containing quadruple therapy (30 mg of lansoprazole twice daily, 300 mg of bismuth subcitrate four times daily, 500 mg of metronidazole three times daily, and 500 mg of tetracycline four times daily) was administered as a rescue treatment regimen.

2.6. Sample size and statistical methods

According to the results of previous studies performed using concomitant and standard triple therapies, we calculated that a sample size of 156 would be necessary to detect a 10% difference between an 80% eradication rate for the standard triple therapy and a 90% eradication rate for the concomitant therapy with a power of 0.80 and a 2-sided $\alpha = 0.05$. If a dropout rate of 10% was to be expected, at least 174 patients per treatment group would be needed. To calculate the intention to treat (ITT) eradication rates, all patients who entered the study were considered. To calculate per-protocol (PP) eradication rates, only those patients who completed the entire protocol with more than 90% compliance were considered in the analysis. Data were analysed using SPSS software (version 18.0, Chicago, IL, USA), and the Chi-squared test, the *t*-test, and logistic regression analysis were used as appropriate. *p* values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Three hundred and forty-eight patients were enrolled in the study. The baseline demographic and clinical characteristics of the two groups of patients were not statistically significantly different (Table 1). Three hundred and three patients completed the study: 150 patients in the concomitant group and 153 in the standard group. Thirty (8.6%) patients missed follow-up and did not return for the UBT (16 in the concomitant group and 14 in the standard groups; Fig. 1).

3.2. Eradication rate

The ITT eradication rates were 78.7% (137/174 patients, 95% confidence interval (CI): 72.6–84.8) in the concomitant group and 70.7% (123/174 patients, 95% CI: 63.9–77.5) in the standard group ($p = 0.084$). PP eradication rates were 88.7% (133/150 patients, 95% CI: 83.6–93.8) and 78.4% (120/153 patients, 95% CI: 71.9–84.9%, $p = 0.016$) respectively. Lower compliance

Table 1
Baseline demographic and clinical characteristics of the patients.

Characteristic	Concomitant therapy ($n = 174$)	Standard therapy ($n = 174$)	*p* value
Gender			0.825
Male	109 (62.6%)	107 (61.5%)	
Age (mean ± SD), years	58.2 ± 9.8	57.5 ± 11.8	0.534
Smoking	73 (42%)	72 (41.4%)	0.243
Endoscopic findings			
Gastric ulcer	31 (17.8%)	34 (19.5%)	0.680
Duodenal ulcer	8 (4.6%)	16 (9.2%)	0.091
Gastric ulcer + duodenal ulcer	3 (1.7%)	3 (1.7%)	1.000
Peptic ulcer scar	96 (55.2%)	83 (47.7%)	0.163
Gastritis	36 (20.7%)	38 (21.8%)	0.793