"7, 10 and 14-days rabeprazole-based standard triple therapies for H. pylori eradication : Are they still effective ? A randomized trial"

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Abstract

Background & study aims : **Increasing data suggests that the efficiency of standard triple therapies of 7-10-14 days duration has fallen below the threshold for acceptability (80% cure rates in intention to treat analysis). Use of rabeprazole, a PPI less influenced by CYP2C19 gene polymorphisms is reported to lead to improved eradication rates. This study aims to re-examine the effectiveness of 7-10-14 days triple therapies based on rabeprazole in Greek patients.**

Patients and methods : **307 patients, from 2 endoscopic centers in Greece, were randomized to receive Rabeprazole 20 mg bid, Clarithromycin 500 mg bid, and Amoxycillin 1gr bid for 7-days, for 10-days or for 14-days. Cure rates were assessed by CLO-test and histology. Clarithromycin sensitivity tests were carried out in the cultured pre-treatment H. pylori strains. The success rates were calculated by both intention-to-treat (ITT) and per protocol (PP) analyses.**

Results : **The eradication rates according to ITT analyses were 74.5% (95% CI : 66.5-82.9%) for 7-days, 80.6% (95% CI : 73.2-88.2%) for 10-days and 90.2% (95% CI : 84.5-95.9%) for 14-days treatment. PP cure rates were 76% (95% CI : 68.4-85.0%) for 7-days, 83% (95% CI : 76.6-91.0%) for 10-days and 93.9% (95% CI : 86.7-97.3%) for 14-days treatment. Side effects were generally minor and comparable in all treatment groups.**

Conclusions : **Both 10- and 14-days rabeprazole-based triple regimens reached eradication rates above the threshold of 80% on an intention to treat basis. In our setting, the current regimen using rabeprazole, amoxicillin and clarithromycin was well tolerated, is still effective and should continue to be recommended as first-line therapy for H. pylori eradication.** (Acta gastroenterol. belg., **2011**, 74, **407-412**).

Key words : helicobacter pylori, triple therapy, rabeprazole, greece.

Introduction

It is widely accepted that Helicobacter pylori infection is an important risk factor for chronic gastritis, gastroduodenal ulcer disease and gastric malignancy (1). Despite more than 20 years of experience on H. pylori treatment, the ideal eradication regimen still remains uncertain. According to the Maastricht 1 consensus, a 7-days triple therapy consisting of a proton pump inhibitor (PPI) bid plus amoxicillin 1000 mg bid. and clarithromycin 500 bid. or metronidazole 400 or 500 mg qid. is recommended (2). In the United States, the same regimens are given for 10-14 days (3). These recommendations, which date from 1996 and 1998, remain unchanged in subsequent guidelines. Today, indications for H. pylori eradication are developed by an international consensus of experts (Maastricht 3 consensus report) (4). Successful therapy has been defined as one that cures more than 80% of patients on an ITT basis (4,5). During the last decade we are witnessing a progressive decline in cure rates below that threshold (6-9). The main, but not the only reason, for the lower eradication rates is antimicrobial resistance. According to recent trials, eradication rates with 7-day triple therapy have been ranging from 57 to 73%, compared to 67-79% for 10-day triple therapy (10). In the light of this disappointing data, some experts have proposed that standard triple regimens should possibly be abandoned as no longer effective (7) while others claim that they cannot yet be considered obsolete (11). Promising treatment strategies, such as sequential therapies, have been proposed as superior to standard triple therapies, but their use is limited to certain countries (12).

In Greece triple regimens remain the standard of care in every day clinical practice for H. pylori eradication. To our knowledge, there are no national clinical trials to monitor the effectiveness of 7-10-14 days standard therapy, so as to guide the choice of appropriate therapy in the new high antimicrobial resistance era. Whether triple therapy is still effective or should be abandoned as obsolete remains obscure. Rabeprazole is a relatively newer PPI less influenced by CYP2C19 gene polymorphisms with higher anti H. pylori and antisecretory activity as compared to omeprazole (13-15).

We conducted a randomized study designed to re-examine the effectiveness of triple therapies (7 vs. 10 vs. 14-days) based on rabeprazole and their acceptability as first-line H. pylori eradication regimens in Greek patients.

Patients and methods

This study is a prospective, open-label, multicenter randomized trial. From January 2005 to February 2007, 307 consecutive symptomatic patients (173 males,

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Table 1. — **Clinical and Demographic characteristics of patients in the three groups**

	Group A (n=102)	Group B (n=103)	Group C (n=102)
Age (mean, range)	47 (20-72)	48 (22-77)	47 (24-73)
Sex (M/F)	55/47	60/43	58/44
Smokers	49/102 (48%)	45/103 (43.6%)	44/102 (43.1%)
DUD	59/102 (57.8%)	58/103 (56.3%)	58/102 (56.8%)
NUD	43/102 (42.1%)	45/103 (43.6%)	44/102 (43.1%)
Alcohol use	15/102 (14.7%)	19/103 (18.4%)	13/102 (12.7%)

M ; males, F ; Females, DUD ; Duodenal ulcer disease, NUD ; Non-ulcer dyspepsia.

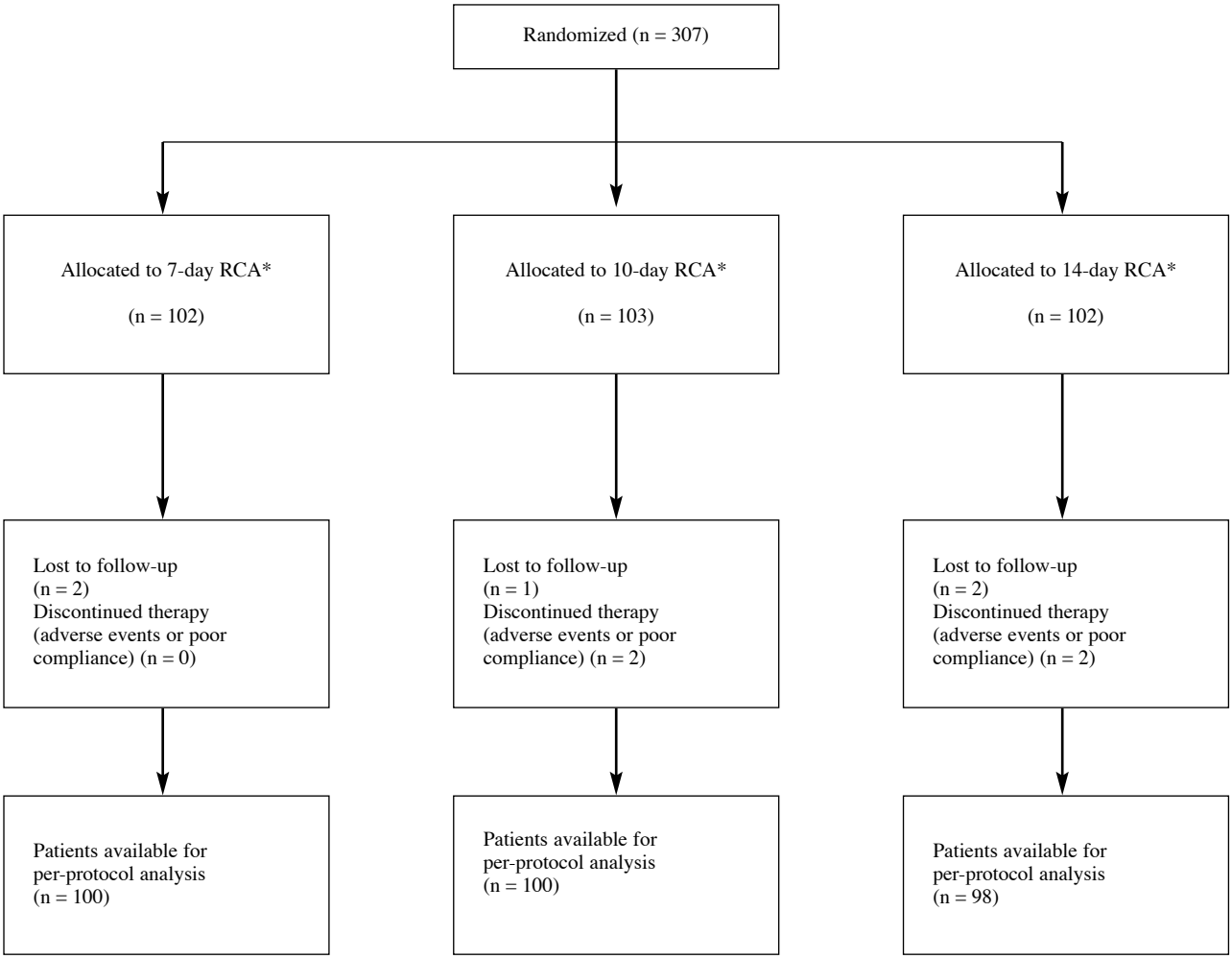
134 females ; mean age 47.7 years ; range : 20-77) with H. pylori infection were enrolled. The diagnosis of H. pylori was determined by at least a positive test using CLO-test or histology. Endoscopy revealed duodenal ulcer in 175 patients and non-ulcer dyspepsia in 132. The clinical and demographic data are presented in Table 1. Previous H. pylori eradication therapy was an exclusion criterion for the study. We also excluded patients with liver cirrhosis, renal failure, other serious concomitant diseases, patients who had been treated in the preceding 2 months with antibiotics, bismuth preparations, PPIs, and NSAIDs, patients with known allergy to the medications used, patients with previous gastric surgery and pregnant women. The study was approved by the Ethics Committee of our hospital and informed written consent was obtained from all patients prior to the study. Using a computer-generated numeric sequence, patients were randomized to one of the following treatment groups : 1) Group A : Rabeprazole (RAB) 20 mg bid plus Clarithromycin (CLA) 500 mg bid plus Amoxycillin (AMO) 1 gr bid for 7 days 2) Group B : RAB 20 mg bid plus CLA 500 mg bid plus AMO 1gr bid for 10 days and 3) Group C : RAB 20 mg bid plus CLA 500 mg bid plus AMO 1gr bid for 14 days. During the first endoscopy 6 biopsy specimens (3 from the corpus and 3 from the antrum) were taken. Two biopsy specimens (1 from the antrum and 1 from the corpus) were used for rapid urease test (CLO test, Ballard Medical Products, UT), 2 were sent for culture and the remaining 2 were sent for histological assessment of H. pylori status by haematoxylin and eosin and modified Giemsa stain. The Warthin-Starry technique was employed for negative cases. Repeat endoscopy was also performed 4-6 weeks after completion of therapy to assess H. pylori eradication (4 biopsy specimens were taken ; 2 from the corpus and two from antrum for CLO-testing and histology). H. pylori eradication was considered successful if both urease test and histology were negative. Due to the limited availability of specific resources, antibiotic susceptibility tests were not carried out in all 307 patients but in a satisfactory majority of 209 (209/307, 68.08%). No blinding method was used, although the personnel performing the post-treatment evaluation were not aware of the treatment received by the patient. Treatment side-effects were investigated by means of a structured clinical interview immediately after of completing therapy. Compliance with therapy was assessed by the number of tablets returned by each patient to final follow-up. Patients were considered to be non-compliant if less than 80% of the medication was taken.

Statistical analysis

Analysis of the results was performed by statistical package SPSS 11.0.0 (SPSS Inc., Chicago, IL, USA). Data in the text and labels are presented as medians and ranges. Percentages are given with 95% confidence intervals (CI). Numerical data were analysed by either two-tailed t-test or the non-parametric Mann-Whitney U-test as appropriate. Qualitative data were evaluated by two sided- Pearson's chi-squared test or Fisher's exact test as appropriate, with both "per protocol" and "intention-to-treat" analysis. The former considers only patients completing the study and the latter includes all patients abandoning the study as treatment failures. Assuming a difference of 15% in eradication efficacy between the two treatment groups to be clinically relevant, at least 100 hundred patients should be included per treatment group, based on a two-sided test with a power of 80% and an alpha error of 5% (Statistical package, GraphPad StaMate 1.01, San Diego, CA, USA).

Results

Table 1 shows the patient characteristics. The three groups were comparable in terms of age, smoking, consumption of alcohol and proportion of duodenal vs. non-ulcer dyspepsia. Five patients were lost to follow-up after treatment. A CONSORT flow diagram is shown in figure 1. Among the 302 remaining patients, adverse effects were observed in 89 patients (29.5%) and most of them were of mild to moderate severity. In the three treatment groups adverse events were reported by 30 patients (29.4%) in Group A, 23 patients (22.3%) in group B and 36 patients (35.5%) in Group C. No significant differences in adverse event rates were observed in all groups. Most frequent symptoms were abdominal discomfort in 35.9% of patients and nausea in 21.3% (Table 2). Less frequent symptoms were taste disturbance (14.6%), vomiting (10.1%), diarrhea (5.6%) and headache (3.4%). No differences according to type of symptoms were found. Two patients (2/89, 2.2%) reported severe adverse events requiring suspension of treatment : 1 from Group B reporting vomiting and 1



*RCA : Rabeprazole-Amoxycillin-Clarithromycin.

Fig. 1. — Flow diagram showing entries and withdrawals from the study

Table 2. — **Type of adverse effects observed among patients treated with triple therapy for H. pylori infection (n = 89)**

Type of adverse effect	Frequency	Percent
Abdominal discomfort	32	35.9%
Nausea	19	21.3%
Taste disturbance	13	14.6%
Vomiting	9	10.1%
Diarrhea	5	5.6%
Headache	3	3.4%
Other	8	9%

from Group C reporting diarrhea. Overall compliance was satisfactory. Two patients took < 80% of the medication, 1 patient from Group B took 6 days out of the 10-days course (60% compliance) and 1 patient from Group C took 7 out of the 14-days course (50% compliance). Treatment failed for both patients as indicated by the positive CLO-test on the follow up endoscopy.

Overall, by intention to treat analysis (ITT), H. pylori was eradicated in 251/307 patients (81.8%) and by per protocol analysis (PP) in 251/298 patients (84.2%). The eradication rates according to intention to treat analysis were 74.5% (95% CI : 66.5-82.9%) for 7-days, 80.6% (95% CI : 73.0-88.2%) for 10-days and 90.2% (95% CI : 84.5-95.5%) for 14-days treatment. Per-protocol cure rates were 76% (95% CI : 68.4-85.0%) for 7-days, 83% (95% CI : 76.6-91.0%) for 10-days and 93.9% (95% CI : 86.7-97.3%) for 14-days treatment (Table 3). Statistically significant differences in the eradication rates were found between Group A and Group C (ITT analysis : 74.5% vs. 90.2%, $P < 0.05$; PP analysis : 76% vs. 93.9%, $P < 0.05$). Clarithromycin sensitivity tests were carried out in the cultured pre-treatment (209/307, 68.08%) H. pylori strains. Primary CL resistance was 20/209 (9.56%). Regarding the Clarithromycin resistant H. pylori strains the eradication rate was 6/20 (30%), whereas the eradication rate in the clarithromycin sensitive strains was 179/189 (94.7%) ($P < 0.0005$).

Discussion

Triple regimens based on the combination of a PPI with two antibiotics aim to achieve high H. pylori

Table 3. — **Eradication rates and 95% confidence intervals (CI) in the treatment groups**

Eradication	Group A	Group B	Group C
ITT analysis	76/102 (74.5%)	83/103 (80.6%)	92/102 (90.2%)*
95% CI (range)	(66.1-82.9)	(73.0-88.2)	(84.5-95.9)
PP analysis	76/100 (76%)	83/100 (83%)	92/98 (93.9%)**
95% CI (range)	(68.4-85.0)	(76.6-91.0)	(86.7-97.3)

*P < 0.05 as compared to Group A; **P < 0.05 as compared to Group A.

eradication rates with minimal side effects. These regimens have been used in various combinations in order to establish better selection among the available drugs, assess their optimal dosage and the duration of therapy. It is well known that in order to achieve high H. pylori eradication rates the effectiveness of the first line therapy remains the most significant factor (16). A successful therapy has been defined as one that cures more than 80% of patients on an ITT basis. This level was initially proposed by Graham *et al*. in 1989 and later accepted by the guidelines and consensus conferences. By 1995 it seemed that 90% was achievable and even 95% was considered realistic. After this initial high efficacy of triple standard regimens, during the last decade we are witnessing a progressive decline in cure rates. Resistance to Clarithromycin is increasing especially among adolescents and children representing the main risk factor for treatment failure (17). Treatment regimens and their duration are difficult to be standardized because eradication rates show significant geographical variation (18,19). Antibiotic resistance is a local phenomenon ; it shows significant differences not only between countries or continents but even within the confines of a single country. These geographical variations in the incidence of drug resistance do have an impact on the success of eradication regimens. Thus, antibiotic resistance in different geographical areas may be an important factor when choosing a first-line eradication therapy. In addition, individual factors such as patient's compliance to treatment, age less than 60 and presence of duodenal ulcer or the type of gastritis have been linked to therapy efficacy (20,21).

In Greece the incidence of resistance to CL is estimated to be between 6% and 20% in different studies, while that to MET is reported to be at the higher European levels of 49% (22-25, unpublished data). In contrast to the increased outpatient macrolide consumption registered in this country (26), we found a relatively low primary resistance of 9.56%. Our prevalence is in agreement with the 10.6% found by Boyanova *et al*. (24) or the 9.9% found by a European multicenter study (23) but is certainly low compared to those found in studies conducted almost concurrently, in neighbouring countries : 21.3% in Italy (27) or the markedly high 48.2% reported in Turkey (28). This wide geographical variation in the incidence of antibiotic resistance is a determinant for the success of eradication regimens, and underlines the need for local clinical trials aiming to guide the choice for appropriate therapy. According to the Maastricht 3 consensus, the threshold of clarithromycin resistance at which this antibiotic should not be used is 15-20% (4). It is worthy of note that to date there is no published data to support that this limit of 20% has been reached in Greece.

On the other hand, eradication rates for triple therapies are reported to depend on the degree of acid secretion suppression (29). The effectiveness of acid suppression by a PPI seems to depend on a polymorphism of the CYP2C19 gene (15). In our study we aimed to maximize our treatment outcomes by choosing rabeprazole in the therapeutic scheme. Owing to its non-enzymatic pathway of metabolism, rabeprazole is reported to be less influenced by genetic polymorphisms of the CYP2C19 in contrast to omeprazole or pantoprazole (30-33). In a recent retrospective study from 1995 to 2008 in Japan, significant declines in eradication rates were observed with omeprazole or lansoprazole, but not with rabeprazole (34). Also, RAB itself is noted to possess antibiotic effects against H. pylori (35), and this may have helped to achieve high anti-H. pylori eradication rates. However, we did not measure CYP2C19 polymorphism or intragastric pH variations in our study, so we lack further information regarding this issue.

In our study we showed that 14 days treatment with rabeprazole 20 mg bid, plus amoxicillin 1 gr bid plus clarithromycin 500 mg bid was more effective in the eradication of H. pylori as compared to the same regimen used for 7 days. This difference was observed both in ITT analysis (90.2% vs. 74.5%) as well as in per protocol analysis (93.9% vs. 76%). There was no significant difference between the groups who received therapy for 7 or 10 days, and between the groups who were treated for 10 or 14 days. We confirm other observations (36) that the 14 day triple regimen is more effective in the eradication of H. pylori as compared with the 7-day triple regimen (ITT difference $\approx$ 15%).

This is yet another report, which notes the failure of a seven-day triple therapy regimen to reach acceptable cure rates (ITT rate : 74.5%). These results compare favourably with those of older randomized trials, conducted by Calvet *et al*. (37) and Vakil *et al*. (38), showing the ineffectiveness of a 1-week triple regimen. In both of these studies, the suboptimal results of 7-days triple therapy were linked to the low cure rates obtained from nonulcer patients. In our study, eradication rates were not investigated separately between ulcer and

nonulcer disease, but both of these groups of patients were equally assigned to our 3 treatment groups and we can therefore safely affirm that treatment outcomes were not affected by this variable.

A notable finding in our study was that extending duration of treatment to 10-days allowed for acceptable ITT rates (80.6%), although the difference did not reach statistical significance. On the contrary, prolonging duration of treatment to 14-days significantly increased ITT to the satisfactory rate of 90.2%. It is worthy of note, that this extension of treatment duration did not significantly increase the rate of serious adverse events which could have adversely affected the eradication rates.

In conclusion, the present study strongly indicates the unacceptable eradication rate of a 7-day triple therapy. On the contrary, both 10- and 14-days rabeprazole-based triple regimens reached eradication rates above the threshold of 80% on an intention to treat basis (80.6% and 90.2% respectively). We believe that the current regimen using rabeprazole, amoxicillin and clarithromycin-with a minimum duration of ten days is highly tolerable and not yet obsolete in Greek patients and should therefore continue to be recommended as first-line therapy for H. pylori eradication.

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