

Seven versus Ten Days of Rabeprazole Triple Therapy for *Helicobacter pylori* Eradication: A Multicenter Randomized Trial

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BACKGROUND: Ten-day triple therapy is somewhat more effective than 7-day treatment for curing *Helicobacter pylori* infection. Recent studies have suggested that rabeprazole—a proton pump inhibitor with fast onset of acid inhibition—could raise the efficacy of 7-day therapies to the levels obtained with 10-day treatment.

OBJECTIVE: To compare the efficacy of 7- and 10-day rabeprazole-based triple therapy for *H. pylori* eradication.

PATIENTS AND METHODS: Four hundred and fifty-eight patients were randomized to 7 or 10 days of triple therapy, including rabeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1 g, all twice a day. Cure rates were evaluated by urea breath test.

RESULTS: Two hundred and thirty-seven patients received 7-day and 221 received 10-day therapy. Groups were comparable in terms of demographic variables. Intention to treat cure rates were 73.8% (95% CI: 67–79%) for 7-day and 79.6% (95% CI: 74–85%) for 10-day therapy ($p = 0.09$). Per-protocol cure rates were 81.8% (95% CI: 76–86%) and 89.3% (95% CI: 84–93%), $p = 0.02$, respectively. Cure rates were similar in peptic ulcer patients but in subjects without ulcer they were clearly lower for 7-day therapy: 66% versus 77% by intention to treat ($p = 0.08$) and 73% versus 91% in the per-protocol analysis ($p = 0.004$). Side effects and compliance in the two groups were comparable.

CONCLUSIONS: Seven- and 10-day triple therapies seem equally efficient in peptic ulcer patients. In contrast, 7-day therapy is significantly less effective in nonulcer dyspepsia patients. Ten-day therapy, therefore, seems preferable when treating nonulcer patients.

(Am J Gastroenterol 2005;100:1696–1701)

INTRODUCTION

Although triple therapy combining a proton pump inhibitor and two antibiotics is the standard care for *Helicobacter pylori* infection treatment, the ideal length of therapy has been a matter of debate for several years. The most frequently recommended length of treatment in Europe is 1 wk (1, 2). In contrast, in the United States, 10–14 day treatment is recommended because the results of 7-day therapies are inconsistent (3–6). In a previous metaanalysis, we observed that lengthening triple therapy slightly enhanced cure rates; improvement was 3–6% when therapy was increased from 7 to 10 days and 2–4% when increased from 10 to 14 days. The improvements in cure rates reached statistical significance only in the comparison of 7- and 14-day therapies (7). A later cost-effectiveness analysis of the two therapies favored the 7-day regimen (8).

However, other aspects have emerged since these studies were published, that have aroused controversy. First, some studies have suggested that short treatment regimens may be effective in patients with ulcer disease, but that eradication rates may be lower in patients with *H. pylori* infection without ulcer disease and that these patients may require longer courses of therapy (9–11). Since current guidelines recommend noninvasive testing and argue against the use of endoscopy to treat dyspeptic patients (1, 5, 6, 12–14), the underlying disease (peptic ulcer disease or nonulcer dyspepsia) is frequently unknown and the treatment cannot be tailored accordingly.

Second, some proton pump inhibitors such as rabeprazole have proved more effective than omeprazole in inhibiting acid secretion in the first days of treatment (15–17). It has been hypothesized that this rapid onset of action means that shorter regimens may be possible (18). In fact, a recent paper

of Vakil *et al.* (19), apparently found no differences between 7- and 10-day rabeprazole-based triple therapies. In the light of these results, the Food and Drug Administration (FDA) approved the 7-day rabeprazole-based triple therapy for *H. pylori* eradication in the United States.(20).

The present study was designed to compare the efficacy of 7- and 10-day rabeprazole-based triple therapy for *H. pylori* eradication.

PATIENTS AND METHODS

From September 2002 to November 2003, 458 patients were included in a randomized, multicenter trial.

PROTOCOL. All patients had diagnoses of peptic ulcer or nonulcer dyspepsia by endoscopy. *H. pylori* infection was established by histology, rapid urease test, or urea breath test. Exclusion criteria were: (i) age under 18; (ii) inability to attend follow-up; (iii) previous failed eradication therapy; (iv) antibiotic treatment during the 4 wk prior to the study; (v) previous ulcer surgery; (vi) pregnancy or inadequate contraception; and (vii) allergy to any of the drugs used in the study.

Closed envelopes produced using a random number generator were sent to participating centers. Randomization was stratified according to the presence or absence of an ulcer at endoscopy. Patients were randomized to receive a 7- or 10-day course of rabeprazole (20 mg) amoxicillin 1 g and clarithromycin (500 mg) (RCA) all twice daily.

MASKING. No blinding method was used, although the personnel performing the posteradication evaluation did not know the treatment received by the patient.

PARTICIPANT FLOW AND FOLLOW-UP. Compliance was evaluated by interview and pill count, and side effects were recorded by means of a structured clinical interview immediately after finishing therapy. Ranitidine (300 mg daily) was indicated after treatment in patients with prior history of bleeding peptic ulcer until cure of *H. pylori* infection was confirmed at the first control. Proton pump inhibitors were not allowed after treatment. Efficacy of the treatment was evaluated at least 2 months after therapy. Cure of *H. pylori* infection was determined by histology in 24 (5%) patients with gastric ulcer who underwent endoscopy to rule out malignancy. In the remaining patients with ulcer and in those without ulcer, cure was checked by a ¹³C-urea breath test performed following the standard European protocol (21).

The Institutional Review Board of the participating hospitals approved the study. Patients gave informed consent on entering the trial.

Statistical Methods

ANALYSIS. Proportions were compared using the χ^2 test and quantitative variables using the Student's *t*-test or the Mann-Whitney U-test when appropriate. The results of previous studies led us to expect better cure rates with 10-day triple therapy (7). For this reason, the one-sided Fisher test was used to compare cure rates. The number needed to treat

(NNT) and the difference (D) between treatments and 95% confidence intervals (95% CI) were also calculated for the major comparisons in the study. Data are given as mean \pm standard deviation. Primary outcome was eradication of *H. pylori* infection. Both intention to treat (all patients included in the study) and per-protocol (all patients who performed a valid posteradication evaluation) analysis were performed. Secondary outcomes were compliance and side effects. Calculations were performed using the SPSS for Windows statistical package.

Sample Size Calculation

Accepting an α -risk of 0.05 and a β -risk of 0.20 in a one-sided test, 173 subjects were necessary in the first group and 173 in the second to recognize a difference greater than or equal to 10% as statistically significant. Cure rates were estimated, on the basis of previous experience, to be 0.9 for 10-day and 0.8 for 7-day therapy. A drop-out rate of 25% was anticipated. The final number of patients was, therefore, 215 per group.

RESULTS

Two hundred and thirty-seven patients were assigned to the 7-day group and 221 to the 10-day group. The demographic and clinical characteristics of the groups were comparable (see Table 1).

Cure Rates

Forty-six patients—23 (10%) in the 7-day group and 23 (11.7%) in the 10-day group—did not return for follow-up. A CONSORT flow diagram is shown in Figure 1. Intention to treat cure rates were 73.8% (95% CI: 67–79%) for 7-day and 79.6% (95% CI: 74–85%) for 10-day therapy ($p = 0.09$). NNT was 17 and the D and its 95% confidence interval were 5.8% (95% CI: –2–14%). In the per-protocol analysis, 175 of 214—81.8% (95% CI: 76–86%)—patients in the 7-day group versus 176 of 197—(89.3% [95%CI: 84–93%, $p = 0.02$;

Table 1. Characteristics of the Groups. UBT: Urea Breath Test. PPI: Proton Pump Inhibitor

	7 days (n = 237)	10 days (n = 221)
Age (mean \pm SD)	51.3 \pm 15	51.4 \pm 16
Sex (male/female)	148/89	145/76
Peptic ulcer/dyspepsia	161/76	142/79
Ulcer bleeding	80	70
Diagnosis of <i>Helicobacter pylori</i> at entry		
Histology	115	115
UBT	75	63
Urease test	47	43
Smoking habit	74	75
Alcohol >40 g/day	27	39
Use of NSAID or AAS	26	18
Previous PPI use	63	51
Months between the end of treatment and control test (mean \pm SD)	3 \pm 1.4	2.9 \pm 1.3

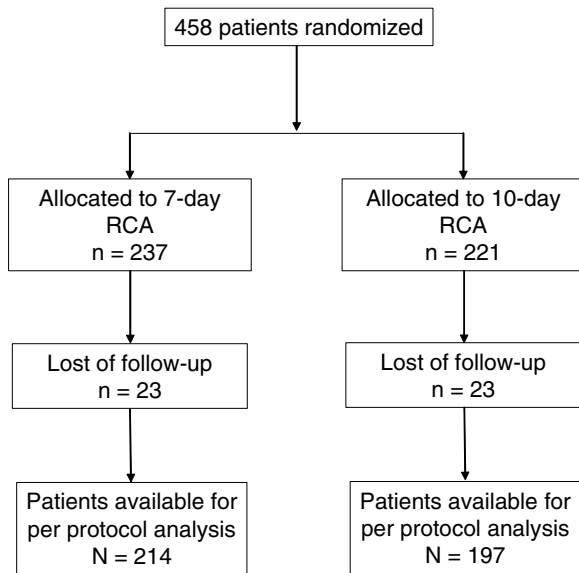


Figure 1. CONSORT flow diagram showing entries and withdrawals from the study.

NNT: 13; D 7.5%, 95% CI: 1–14%])—were cured at the 2-month follow-up test. Both Intention to treat (77.6% vs 81%, $p = 0.28$, NNT: 29, D: 3.4%, 95% CI: –1–13%) and per-protocol cure rates (86.2% vs 88.5%, $p = 0.35$, NNT: 43, D: 2.3%, 95% CI: –6–10%) were fairly similar in both treatment arms for peptic ulcer patients. Additionally, there were no differences between duodenal and gastric ulcers. Cure rates, however, were clearly lower for 7-day therapy in nonulcer individuals: (65.8% vs 77.2%, $p = 0.08$, NNT: 9; D: 11.4%, 95% CI: –3–26%) by intention to treat analysis, and 72.5% vs 91%, $p = 0.004$, NNT: 5, D: 18.5%, 95% CI: 6–31%); in the per-protocol analysis (Fig. 2).

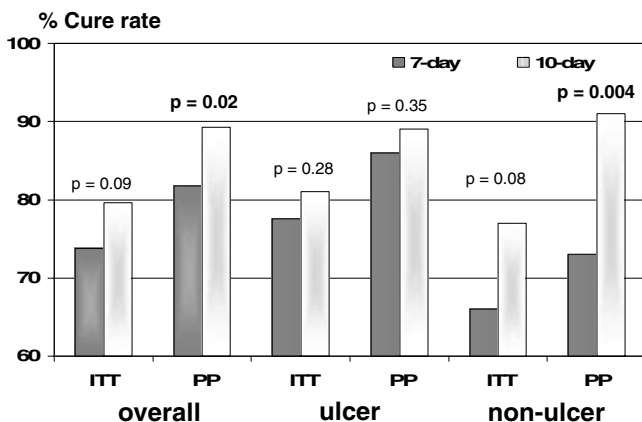


Figure 2. Intention to treat and per-protocol cure rates for 7-day and 10-day triple therapies. Ten-day therapy was homogeneously better in all comparisons, although the differences only reach statistical significance in the per-protocol analysis in the overall group and in the nonulcer patients.

Compliance and Side Effects

Compliance was fairly good in both groups. Ninety percent of the patients in the 7-day RCA group versus 88% in the 10-day group took all the prescribed treatment ($p = 0.6$). Compliance was also similar between ulcer and nonulcer patients: 90% versus 86% ($p = 0.18$).

No severe side effects were reported. Mild to moderate side effects were reported by 62 patients (26%) in the 7-day group and by 52 (23.5%) in the 10-day group ($p = 0.51$). Most frequent symptoms were metallic taste or oral mucositis in 19% of patients, and diarrhea in 7%. Less frequent symptoms were nausea (4%), abdominal pain (4%), heartburn (3%), and vomiting and reduced appetite (1% each). No differences according to type of symptoms were found. Symptoms were limited to the duration of treatment in most patients, and no differences in the duration of symptoms were found between groups.

DISCUSSION

Eradication therapy should be modified according to the changing scenario of the treatment of peptic ulcer and dyspepsia. Approaches to *H. pylori* treatment have moved from the restrictive recommendation of treating patients with a documented peptic ulcer only to the current proposal for non-invasive testing and treatment in uninvestigated dyspepsia (1, 5, 6, 12–14) or even to the well supported arguments in favor of preventing gastric cancer by screening and treating *H. pylori* in populations at risk (22, 23). It has been shown that there are geographical variations in response to eradication treatment, which have been attributed to differences in the prevalence of antibiotic resistances and to genetic differences in the metabolism of proton pump inhibitors (24). However, to confront the new challenges of the expanding indications for eradication therapy, a therapy with demonstrated efficacy in all patients and settings is necessary.

The results of the present study strongly suggest that 7-day triple therapy did not achieve these goals. Its performance in ulcer patients is acceptable, with per-protocol cure rates around 85%, but the results in the whole population of infected individuals are poor, mainly because of the low cure rates in nonulcer patients. The reasons for the low eradication rates with short treatments in nonulcer patients remain unknown. It has been suggested that compliance may depend on symptom severity or the perceived severity of the underlying illness; for instance, patients told they have an ulcer at endoscopy may be more compliant (19). The results of our study did not suggest that compliance played a major role in the differences in cure rates. Furthermore, compliance could not explain the increased efficacy of longer therapies in nonulcer patients. An alternative explanation is that the higher degrees of mucosal inflammation induced by more aggressive *H. pylori* strains present in ulcer patients may improve the efficacy of triple therapy (24, 25).

The differences in cure rates of triple 7- and 10-day therapies are especially relevant when patients with uninvestigated dyspepsia are treated with a “test and treat” strategy. On the basis of the accumulated evidence (26, 27), this strategy is now recommended by many guidelines as the initial management strategy for patients with uninvestigated dyspepsia (1, 5, 6, 12–14). Approximately 25–35% of uninvestigated dyspepsia patients with a positive *H. pylori* test bear a peptic ulcer at endoscopy (28), meaning that 65–75% are nonulcer patients. Therefore, the use of 7-day triple therapy in this setting would be expected to fail in a large group of patients. Obviously, patients who need further testing and second line therapy represent an important medical and economic burden.

Some of the results of this paper challenge those of the previous paper by Vakil *et al.* (19). The differences however, are more to do with the interpretation of the data than with the results themselves. As in our study, Vakil *et al.* (19) found the cure rates of 7-day triple therapy to be 9% better in ulcer than in nonulcer patients. A 9% difference in cure rates is, certainly, clinically relevant, even though the numbers in their study were probably too small to allow this difference to reach statistical significance.

The present study has some particularities that merit comment. It was performed mainly in county hospitals with busy outpatient clinics and a high volume of peptic ulcer patients. Many patients had presented bleeding and received antisecretory treatment prior to inclusion in the study. This meant that their ulcer had healed before entry, whereas others were treated immediately after diagnostic endoscopy. These conditions may well give a more accurate idea of how the treatments work in the real world than studies performed in selected patients and tertiary centers. However, the availability of specific resources was limited and antimicrobial resistances could not be tested. Therefore, we lack information about clarithromycin resistance in our patients. However, resistance to this antibiotic in our area is around 10% and has remained stable in recent years (29–33). These values seem quite similar to those observed in U.S. recent studies with triple therapy (19).

A striking finding in the study is that intention to treat eradication rates did not reach 80% even for 10-day therapies. This does not seem to be a local trend. Per-protocol cure rates in the Vakil *et al.* study were 77% for rabeprazole 10-day therapy and 73% for omeprazole 10-day triple therapy (19). In a recent multicenter study, ITT eradication rates of 77% were achieved with a combination of esomeprazole 40 mg q.d., clarithromycin 500 mg b.d., and amoxicillin 1,000 mg b.d. administered for 10 days (34). In three multicenter U.S. trials with omeprazole 20 mg b.d. combined with amoxicillin 1,000 mg b.d. and clarithromycin 500 mg b.d. administered for 10 days in patients with duodenal ulcer, ITT eradication rates ranged from 69% to 83%, with a combined eradication rate of 75% (4). Data with 10-day therapy from the present study are, therefore, comparable to other recent trials. These data convincingly show that even

using 10-day schedules, triple therapy achieves insufficient cure rates and that more effective alternatives must be sought. Recently, there has been exciting progress in eradication therapy. Firstly, new antibiotics were added to the anti-*H. pylori* arsenal: rescue therapies using rifabutin (35–39) or the new quinolones (39–42) have demonstrated their efficacy, broadening the choice for the recommended second line quadruple therapy. The availability of new rescue therapies would make it possible to combine the classical drugs, amoxicillin, clarithromycin and metronidazole in first line therapy. Among the new promising alternatives to triple therapy, a 10-day sequential therapy combining a five day course of amoxicillin and a proton pump inhibitor with five days of clarithromycin, metronidazole and a proton pump inhibitor was recently described (43–46). This treatment seems to be effective even in patients with clarithromycin resistance and is the first therapy that has proved superior to triple therapy in a large randomized trial (47). Future studies on eradication will probably compare these new alternatives to the triple therapy that is standard today.

In conclusion, 7- and 10-day triple therapies seem equivalent in peptic ulcer patients. However, 7-day therapy is significantly less effective in nonulcer dyspepsia patients. Ten-day therapy seems, therefore, preferable for treating nonulcer patients. However, even 10-day triple therapies achieve suboptimal intention to treat cure rates of below 80%. There are many promising new therapies for *H. pylori* treatment. Their effectiveness must be tested and compared to that of 10-day triple therapy, as 7-day therapies seem quite ineffective in some subgroups of patients.

APPENDIX

Other members of the *Helicobacter pylori* Study Group of the Asociación Española de Gastroenterología were Dr. Jordi Guardiola (Hospital Comarcal de l'Alt Penedès, Vilafranca del Penedès), Dr. Angel Cosme (Hospital de Donosti, San Sebastian), Dr. Fuentes (Hospital Miguel Servet, Zaragoza), Dr. Mur (Hospital Clínico Universitario, Zaragoza), Dr. Joan Saló and Dr. Ramón Barniol (Hospital Comarcal de Vic), Dr. Daniel Carpio (Complejo Hospitalario, Pontevedra), Dr. Lluçia Titó (Hospital de l'Esperit Sant, Santa Coloma de Gramanet), Dr. Ramon Guirao (Hospital de San Jorge, Huesca), Dr. Ramon Barniol (Hospital Comarcal de Vic), Dr. Fernando Gomollón (Hospital Miguel Servet, Zaragoza), Dr. Albert Tomas (Hospital General de Catalunya, San Cugat del Vallès), Dr. Jose Luis Ulla (Complejo Hospitalario, Pontevedra).

ACKNOWLEDGMENTS

This study was supported in part by a grant from the Instituto de Salud Carlos III (C03/02). We are indebted to Michael

Maudsley for his help with the English and to María José López for her efficient secretarial assistance.

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Received January 5, 2005; accepted March 7, 2005.

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