Original article

Prospective, randomized study of seven versus fourteen days omeprazole quadruple therapy for eradication of Helicobacter pylori infection in patients with duodenal ulcer after failure of omeprazole triple therapy

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SUMMARY

Objective: To evaluate the efficacy and compliance with quadruple omeprazole as a second-line therapy for eradication of *H. pylori* in duodenal ulcer patients.

Methodology: This is a prospective, randomized, single-centre trial. One hundred and fifteen consecutive patients with active duodenal ulcer who had failed to eradicate *H. pylori* infection on omeprazole (20 mg b.d.), amoxycillin (1 g b.d.), and clarithromycin (500 mg b.d.) (OAC_{10}) for 10 days were randomized to receive as second-line therapy omeprazole (20mg *bd*), colloidal bismuth subcitrate (120mg *qid*), metronidazole (0.5g *tid*) and tetracycline hydrochloride (0.5g *qid*) for 7 ($OBMT_7$, $n=54$) or 14 days ($OBMT_{14}$, $n=61$). Failure of OAC_{10} had been confirmed by CLO-tests, histology and immunohistochemistry on gastric biopsies taken at endoscopy two months after therapy, and, in doubtful cases by ^{13}C-Urea-breath test (UBT). Compliance with treatment and treatment-related side effects were assessed. Eradication of *H. pylori* was confirmed by UBT 6 weeks after therapy. Patients with a negative UBT were re-evaluated at 6 and 12 months after treatment when a new UBT was performed whereas those with dyspepsia or *de novo* reflux symptoms were re-endoscoped.

Results: At baseline, there were no significant differences in any patient- or disease-related parameters between treatment groups. Six and four patients in the $OBMT_7$ and $OBMT_{14}$ groups, respectively, were lost to follow up. Three and seven patients in the $OBMT_7$ and $OBMT_{14}$ groups, respectively, were non-compliant. By intention-to-treat (ITT) analysis no significant differences were found in eradication rates between $OBMT_7$ and $OBMT_{14}$ [66.7% (36/54) *vs* 80% (36/45), respectively, 95% CI -5% to 27%, $p=0.215$). However, by per-protocol (PP) analysis eradication rates with $OBMT_{14}$ were significantly higher than with $OBMT_7$ [96% (48/50) *vs* 78.7% (48/61), respectively, 95% CI 14.7% to 17.3%, $p=0.035$]. Side effects were more common with $OBMT_{14}$.

Conclusions: $OBMT_7$ appears to be equally effective to $OBMT_{14}$ as second-line therapy for *H. pylori* after failure of OAC_{10} because a considerable number of patients cannot tolerate $OBMT_{14}$. However, if tolerated, $OBMT_{14}$ is an excellent second-line therapy for eradication of *H. pylori*.

Key words: omeprazole triple therapy, omeprazole quadruple therapy, duodenal ulcer, *Helicobacter pylori*.

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INTRODUCTION

Eradication of *H. pylori* infection in patients with duodenal ulcer heals the ulcer and cures the ulcer diathesis.[1,2] However, in routine clinical practice the optimal anti-*H. pylori* regimen remains uncertain. Because re-treatment is difficult and often ineffective it is vital to choose the best available first-line therapy in order to avoid future problems. Based on local conditions, it is

recommended that the combination of a proton pump inhibitor (PPI), clarithromycin and amoxicillin be the first-line therapy in areas where metronidazole resistance is high because patients are usually compliant to this regimen and achieve high eradication rates.[3-6] However, after the first enthusiastic results it was soon realized that in the clinical setting PPI-triple therapies achieve eradication rates ranging from 75% to 87% but 13% to 25% of patients will finally fail to eradicate *H. pylori* infection.7[6]

After failure of PPI-triple therapy a consecutively applied quadruple regimen (a PPI combined with classical triple therapy) is considered the best second-line therapy.[8-12] PPI triple therapies using alternative antibiotics for 10-14 days also claim equally good results but they are used as 'rescue' rather than second-line therapies.[13,14] However, the duration of PPI-quadruple therapy is a key issue because prolonging the treatment period in order to achieve higher eradication rates may compromise compliance with treatment.[15-18] Thus, the aim of this study was to evaluate the efficacy and assess compliance with 7-day and 14-day omeprazole quadruple therapy as a consecutive second-line therapy for *H. pylori* infection after failure of omeprazole triple therapy.

MATERIAL AND METHODS

Between January 1999 and December 2003, consecutive patients with *H. pylori* infection and an active duodenal ulcer who had been unsuccessfully treated for duodenal ulcer and *H. pylori* infection with omeprazole (20 mg twice daily before meals), amoxicillin (1 g twice daily with meals) and clarithromycin (500 mg twice daily with meals) for 10 days (OAC_{10}) were screened for this prospective, randomized, single-centre, investigator-blind study. Failure of OAC_{10} to eradicate *H. pylori* was confirmed at endoscopy two months later by means of a rapid urease test (CLO test, Delta West Ltd, Bentley, Australia), histology (modified Giemsa) and immunohistochemistry (rabbit anti-*H. pylori* monoclonal antibody, Dako) on mucosal biopsies taken from the gastric antrum and body/fundus, as has been previously described.[2,10] In case these three tests were discordant a ^{13}C-urea breath test (UBT) was performed. Patients with no-eradicated *H. pylori* infection were eligible for this study. All patients gave written informed consent before study entry. Exclusion criteria were chronic alcoholism, chronic renal or hepatic failure, malignant disease, previous gastric surgery, treatment with anticoagulants, treatment with antibiotics other than those prescribed for the study, regular treatment with nonsteroidal anti-inflammatory drugs, and well-documented allergy to any of the study drugs.

Eligible patients were randomized to receive as second-line therapy a quadruple therapeutic regimen consisting of omeprazole (20 mg twice daily before meals), bismuth subcitrate (CBS, De-Nol, one swallowable tablet containing 120 mg bismuth four times a day before meals and at night, 2h after dinner), metronidazole (500 mg three times a day before meals) and tetracycline hydrochloride (500 mg tablets four times a day, before meals and at bedtime) for seven ($OBMT_7$) or fourteen days ($OBMT_{14}$). No other acid-suppressive drugs were allowed during the trial or afterwards.

Patients were seen in the Outpatient clinic upon completion of therapy when 1) compliance with treatment was assessed by counting the returned tablets of each study medication, 2) treatment-related side effects were recorded using a standard questionnaire form, and 3) a further appointment for UBT was arranged 6 weeks later. Patients with a negative UBT were seen in the outpatient clinic at 6 and 12 months after completion of therapy. If dyspeptic symptoms were not reported a new UBT was arranged one year after quadruple therapy to assess for asymptomatic recrudescence of *H. pylori*. However, whenever patients reported recurrence of dyspeptic and/or *de novo* reflux symptoms during the annual follow up period an endoscopy was arranged to assess for recrudescence of *H. pylori* infection and/or relapse of duodenal ulcer.

Endoscopies and CLO tests were performed by a single physician (GJM) unaware of the patient's treatment category. Physicians unaware of the patient's history and endoscopy performed randomization, assessment of symptoms and compliance with treatment. Histopathology was assessed by two experienced pathologists unaware of the patients' status or treatment category.

The primary end-points of this study were compliance with treatment and eradication rates of *H. pylori* at week 6 after completion of quadruple therapy. Secondary endpoints were the influence of demographic and clinical parameters on eradication of *H. pylori*, the annual rate of *H. pylori* recrudescence and, finally, the rate of dyspeptic and/or *de novo* reflux symptoms indicating relapse of duodenal ulcer or post-eradication reflux esophagitis, respectively, during the annual follow up period.

The results of treatment were analyzed by the intention-to-treat (ITT) and per-protocol (PP) methods. The former included patients with confirmed evidence of *H. pylori* before treatment but also included as treatment failures patients who did not return for re-evaluation with UBT after treatment. The latter included only patients who were eligible for evaluation at each specific visit.

Comparisons between the two treatment groups were made using the Mann-Whitney U test and the Chi-square test or the Fisher's exact test where appropriate. Exact binomial 95% confidence intervals were calculated for *H. pylori* eradication. Multivariate logistic regression analysis was performed to evaluate the effect of potential risk factors on treatment, such as age (<40/>40 years), gender, disease duration, ulcer size (<1cm, >1cm) and number (single/multiple), past bleeding ulcer (yes/no), smoking (yes/no), social drinking (yes/no), occasional use of nonsteroidal anti-inflammatory drugs (NSAID) (yes/no), and **duration of treatment (7 *vs* 14 days)**.

RESULTS

Overall, 134 patients were screened for the study but 115 patients were randomized to receive $OBMT_7$ ($n=54$) or $OBMT_{14}$ ($n=61$) (Fig. 1). Six and four patients in the $OBMT_7$ and $OBMT_{14}$ groups, respectively, did not return for UBT 6 weeks after completion of therapy. Three and seven patients in the $OBMT_7$ and $OBMT_{14}$ groups were non-complaint (<95% of drugs taken). Thus, PP analysis was based on 45 patients in the $OBMT_7$ group and 50 patients in the $OBMT_{14}$ group. The demographic and clinical characteristics of patients at randomization (ITT analysis) and at completion of the trial (PP analysis) are given in table 1. There were no significant differences in any patient- or disease-related parameters between treatment groups at baseline.

At entry, none of the patients had unhealed duodenal ulcers. Histology and immunohistochemistry were 100% concordant for the presence of *H. pylori*. A UBT was performed in six patients (three patients in each treatment group) because the CLO-tests were negative and discordant to histology and immunohistochemistry. All UBTs confirmed the presence of *H. pylori* infection.

The ITT and PP rates for eradication of *H. pylori* based on results of UBT are given in table 2. By PP analysis, significantly more patients eradicated *H. pylori* infection with $OBMT_{14}$ than $OBMT_7$ ($p=0.035$). However, this difference was eliminated when results were analyzed by

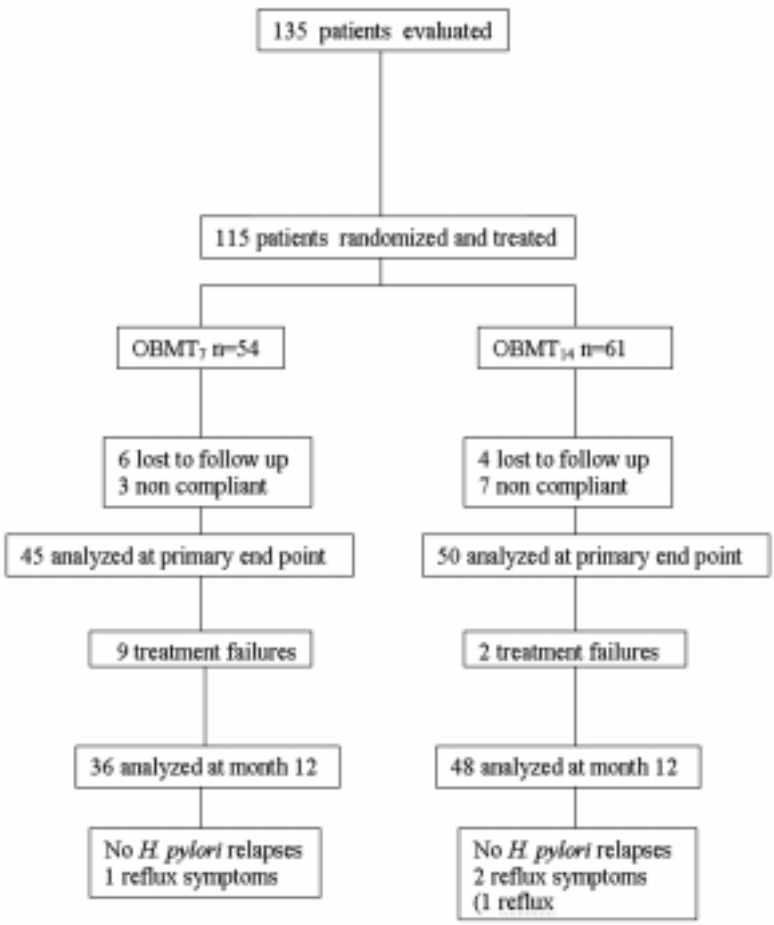

Figure 1. Flowchart of patients and reasons for discontinuation

Table 1. Patient demographic and clinical characteristics*

	Intention to treat		Per protocol	
	$OBMT_7$ (n=54)	**$OBMT_{14}$** (n=61)	**$OBMT_7$** (n=45)	**$OBMT_{14}$** (n=50)
Age (years) (mean, range)	38.5 (18-69)	40.5 (19-68)	38 (19-67)	40 (20-66)
Sex (M/F)	30/24		33/28	25/20 27/23
Disease duration				
(years) (mean, range)	4.2 (1-19)	5.0 (1-17)	4.1 (1-19)	4.9 (1-16)
Ulcer size (</>1cm)	23/31	24/37	17/28	19/31
Ulcer number (1/>1)	44/10	46/15	36/9	37/13
Past bleeders	18	25	18	25
Smokers	34	38	33	37
Social drinkers	30	39	28	36
Occasional NSAID users	21	29	21	28

******Differences between groups were not significant*

NSAID, nonsteroidal anti-inflammatory drug

Table 2. *H. pylori* eradication rates

	H. pylori eradication rate (n, %, $CI_{95\%}$*)	
Treatment group	**ITT**	**PP**
$OBMT_7$	36/54 (66.7%)	36/45 (80%)
$OBMT_{14}$	48/61 (78.7%)	48/50 (96%)
	(-5% to 27%)	(14.7% to 17.3%)
***p* value**	0.215	0.035

CI, confidence interval; ITT, intention to treat; PP, per protocol

ITT (p=0.215). Multiple logistic regression analysis did not reveal any other demographic or clinical independent factor(s) significantly related to eradication failure (data not shown).

Ten patients (8.7%) were non-compliant. Seven had received $OBMT_{14}$ but stopped treatment because of nausea (4), metallic taste (4), headache (3), vomiting (1), dizziness (1), and diffuse abdominal pain (1). Four of these 7 patients developed side effects leading termination of treatment during the second week of therapy. On the other hand, three patients receiving $OBMT_7$ stopped therapy because of nausea (3), metallic taste (3) and vomiting (1) during the first four days of therapy. None of the adverse events leading onto treatment discontinuation was graded as severe. Although twice as more of patients receiving $OBMT_{14}$ were non-compliant differences between groups were not significant. However, $OBMT_{14}$ was associated with a higher incidence of adverse events than $OBMT_7$ ($p<0.05$) but these were mostly minor, easily tolerated and did not interfere with the daily activities of patients nor did they prevent patients from completing the trial.

None of the patients with a negative UBT after therapy (n=84) developed any dyspeptic symptoms during the annual post eradication follow-up period. However, three patients (3.6%), one on $OBMT_7$ and two on $OBMT_{14}$ developed reflux symptoms 8-11 months after therapy but at endoscopy only one (1.2%) was found to have oesophagitis grade A (Los Angeles classification); no *H. pylori* infection was detected by means of the CLO-test, histology and immunohistochemistry. Eighty-one patients had remained entirely asymptomatic throughout this period.

Eradication failures (n=11) as well as non-compliant patients (n=10) were followed up in the Outpatient clinic. When dyspeptic symptoms recurred, these patients underwent endoscopy that revealed a relapse of ulcer and the presence of *H. pylori*. All relapses occurred between 8-16 months after treatment failure.

DISCUSSION

In this prospective, randomized, single-centre, investigator-blind study we have assessed the efficacy and compliance with a widely used second-line quadruple therapy, OBMT, for 7 or 14 days for eradication of *H. pylori* and prevention of duodenal ulcer recurrence in unselected, consecutive patients after failure of OAC_{10} to eradicate the infection. Although this trial was planned and started before the Maastrich-1 Consensus Conference, the choice for a PPI quadruple therapy was based on available evidence that this therapeutic regimen is highly efficacious for eradication of *H. pylori* infection.[7,15,16,18] In fact, this regimen has now been widely accepted and is the recommended choice by the Maastricht-2 Consensus Conference when PPI triple therapies have failed to eradicate *H. pylori* infection.[5,8-12,19]

The results that have emerged reflect common medical sense (table 2). First, $OBMT_{14}$ is more effective than $OBMT_7$ in eradicating *H. pylori* infection. In fact, when only patients able to complete treatment were compared (PP analysis) the difference in eradication rates between $OBMT_{14}$ and $OBMT_7$ achieved significant levels; even by ITT analysis there was a trend in favor of $OBMT_{14}$ to achieve better eradication rates than $OBMT_7$ (table 2). Second, longer treatment compromises compliance.

Thus, duration of treatment is the dominant factor determining eradication rates in this study. Patients receiving $OBMT_{14}$ achieved very high eradication rates (96%) and gained a 16% plus over $OBMT_7$ (PP analysis, table 2). Multivariate logistic regression analysis did not reveal any patient- or disease-associated factors other than duration of treatment to be independently associated with eradication failure. Antibiotic resistance is a crucial factor that determines the outcome of PPI triple therapies containing clarithromycin and/or metronidazole. However, quadruple therapies may overcome to a certain degree metronidazole-resistance.[8,9,12,19-21] This may be solely due to duration of treatment. The primary resistance of *H. pylori* strains to metronidazole in our country was reported to range from 46% to 54% between 1991 and 2002.[4,6,9,20] Assuming that roughly 45% of our patients carried metronidazole-resistant strains and were equally distributed in the two arms of this study, $OBMT_{14}$ but not $OBMT_7$ has largely overcome metronidazole-resistance. This is also supported by strikingly contrasting eradication rates with 7-day quadruple therapies in areas of high and low prevalence of metronidazole-resistant *H. pylori* strains, respectively.[7-9,16,17,22,23] In routine clinical practice, pretreatment susceptibility testing is not necessary when a PPI quadruple therapy is offered as a consecutive, second-line treatment.[12,21,22]

Compliance was the second important determinant of the outcome of treatment: twice as more patients receiving $OBMT_{14}$ were non-compliant compared with $OBMT_7$. Undoubtedly, 2- to 7-day quadruple therapies are associated with fewer side effects and better compliance than longer therapies.[7,9,10,15,16]

De novo post eradication reflux symptoms/oesophagitis developed in very few patients. No single factor could be accounted for but these patients had moderate corpus gastritis before treatment and had gained considerable body weight after treatment. All eradication failures as well as non-compliant patients had endoscopically confirmed relapse of duodenal ulcer and recrudescence of *H. pylori* 8-16 months after treatment failure.

In conclusion, $OBMT_7$ was better tolerated and produced equally good results with $OBMT_{14}$ in eradicating *H. pylori* and preventing relapses of duodenal ulcer after failure of OAC_{10}. However, for patients able to tolerate $OBMT_{14}$ eradication rates reached 96% whereas $OBMT_7$ was less effective. Based on this evidence, $OBMT_{14}$ is an excellent option for patients failing to eradicate *H. pylori* on PPI triple therapy even in areas with a high prevalence of metronidazole-resistance.

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