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.), amoxicillin (1 g b.d.), and clarithromycin (500 mg b.d.) (OAC10) 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 (OBMT7, n=54) or 14 days (OBMT14, n=61). Failure of OAC10 had been confirmed by CLO-tests, histology and immunohistochemistry on gastric biopsies taken at endoscopy two months after therapy, and, in doubtful cases by 13C-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 OBMT7 and OBMT14 groups, respectively, were lost to follow up. Three and seven patients in the OBMT7 and OBMT14 groups, respectively, were non-compliant. By intention-to-treat (ITT) analysis no significant differences were found in eradication rates between OBMT7 and OBMT14 [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 OBMT14 were significantly higher than with OBMT7, [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 OBMT14.

Conclusions: OBMT7 appears to be equally effective to OBMT14 as second-line therapy for H. pylori after failure of OAC10 because a considerable number of patients cannot tolerate OBMT14. However, if tolerated, OBMT14 is an excellent second-line therapy for eradication of H. pylori.

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

INTRODUCTION

Eradication of H. pylori infection in patients with duodenal ulcer heals the ulcer and cures the ulcer dia- thesis.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. 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.

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. 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. 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. 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 (OAC10) were screened for this prospective, randomized, single-centre, investigator-blind study. Failure of OAC10 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. In case these three tests were discordant a 13C-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 (OBMT7) or fourteen days (OBMT14). 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 end-points 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-compliant (<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](image-url)
Table 1. Patient demographic and clinical characteristics*  

<table>
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<th></th>
<th>Intention to treat</th>
<th>Per protocol</th>
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<tr>
<td></td>
<td>OBMT₇ (n=54)</td>
<td>OBMT₁₄ (n=61)</td>
</tr>
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<td>Age (years) (mean, range)</td>
<td>38.5 (18-69)</td>
<td>40.5 (19-68)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<td>33/28</td>
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Disease duration  

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<th>OBMT₁₄ (n=61)</th>
</tr>
</thead>
<tbody>
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<td>(years) (mean, range)</td>
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<td>5.0 (1-17)</td>
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<td>Ulcer size (&lt;&gt;/=1cm)</td>
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<td>24/37</td>
</tr>
<tr>
<td>Ulcer number (&gt;1)</td>
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<td>46/15</td>
</tr>
<tr>
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<td>25</td>
</tr>
<tr>
<td>Smokers</td>
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<td>38</td>
</tr>
<tr>
<td>Social drinkers</td>
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<td>39</td>
</tr>
<tr>
<td>Occasional NSAID users</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

*Differences between groups were not significant  

NSAID, nonsteroidal anti-inflammatory drug  

Table 2. *H. pylori* eradication rates  

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ITT</th>
<th>PP</th>
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<tbody>
<tr>
<td>OBMT₇</td>
<td>36/54 (66.7%)</td>
<td>36/45 (80%)</td>
</tr>
<tr>
<td>OBMT₁₄</td>
<td>48/61 (78.7%)</td>
<td>48/50 (96%)</td>
</tr>
<tr>
<td>(*-5% to 27%)</td>
<td>(14.7% to 17.3%)</td>
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*p value*  

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<thead>
<tr>
<th></th>
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<tr>
<td></td>
<td>0.215</td>
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<tr>
<td></td>
<td>0.035</td>
</tr>
</tbody>
</table>

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 OBMT₁₄ 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 OBMT₇ 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 OBMT₁₄ were non-compliant differences between groups were not significant. However, OBMT₁₄ was associated with a higher incidence of adverse events than OBMT₇ (*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 OBMT₇ and two on OBMT₁₄ 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 to eradicate the infection. Although this trial was planned and started before the Maastricht-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. In fact, this regimen has now been widely accepted and is the recommended choice by the Maastricht Consensus Conference when PPI triple therapies have failed to eradicate *H. pylori* infection.

The results that have emerged reflect common medical sense (table 2). First, OBMT is more effective than OBMT, 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 and OBMT achieved significant levels; even by ITT analysis there was a trend in favor of OBMT to achieve better eradication rates than OBMT (table 2). Second, longer treatment compromises compliance.

Thus, duration of treatment is the dominant factor determining eradication rates in this study. Patients receiving OBMT achieved very high eradication rates (96%) and gained a 16% plus over OBMT, (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. 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. Assuming that roughly 45% of our patients carried metronidazole-resistant strains and were equally distributed in the two arms of this study, OBMT but not OBMT 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. In routine clinical practice, pretreatment susceptibility testing is not necessary when a PPI quadruple therapy is offered as a consecutive, second-line treatment.

Compliance was the second important determinant of the outcome of treatment: twice as many patients receiving OBMT were non-compliant compared with OBMT. Undoubtedly, 2- to 7-day quadruple therapies are associated with fewer side effects and better compliance than longer therapies.

*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 recurrence of *H. pylori* 8-16 months after treatment failure.

In conclusion, OBMT was better tolerated and produced equally good results with OBMT in eradicating *H. pylori* and preventing relapses of duodenal ulcer after failure of OAC. However, for patients able to tolerate OBMT eradication rates reached 96% whereas OBMT was less effective. Based on this evidence, OBMT 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.

REFERENCES