HELICOBACTER PYLORI

Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for *Helicobacter pylori* eradication: the HYPER Study

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Background: Triple therapy is recommended for *Helicobacter pylori* eradication, yet consensus on the duration of treatment is lacking.
Aim: To compare the efficacy and safety of 1- and 2-week regimens of omeprazole, amoxicillin and clarithromycin in a large, multicentre, double-blind and randomised study.
Methods: A total of 909 *H pylori*-positive patients with duodenal ulcer, enrolled in 81 endoscopy units in Italy, were randomised to receive omeprazole, amoxicillin and clarithromycin for either 1 week (OAC1W) or 2 weeks (OAC2W) or omeprazole and amoxicillin for 2 weeks. *H pylori* eradication was assessed by histological examination and carbon-13 urea breath test 4 weeks after treatment.
Results: Both the intention-to-treat (ITT; n = 907) and per protocol (PP; n = 661) analyses showed no significant differences between the eradication rates of OAC1W (ITT 79.7%; PP 83.6%) and OAC2W (ITT 81.7%; PP 84.9%; ITT p = 0.53; PP p = 0.71). Both triple omeprazole, amoxicillin and clarithromycin regimens gave significantly higher eradication rates compared with omeprazole and amoxicillin treatment (ITT 44.6%; PP 42.8%; p<0.001). Poor compliance was reported in 18.6%, 17.3% and 15.1% (p = 0.51) of patients for OAC2W, OAC1W and omeprazole and amoxicillin, respectively. Adverse events occurred in 9.9% and 9.6% (p = 0.88) of patients for OAC2W and OAC1W, respectively, and in 5.9% for omeprazole and amoxicillin (p = 0.11).
Conclusions: 1-week and 2-week triple treatments for *H pylori* eradication are similar in terms of efficacy, safety and patient compliance.

Helicobacter pylori infection is now recognised as a major cause of peptic ulcer disease, and several studies have shown that its eradication markedly reduces the rate of ulcer relapse.[1 2] Multicentre studies have shown that triple therapy with omeprazole, clarithromycin and either amoxicillin or metronidazole is one of the most effective and well-tolerated treatments for *H pylori* eradication.[3–6] However, a consensus on the length of treatment is still lacking. In Europe, guidelines for treatment of *H pylori* infection recommend 1 week of treatment,[7] whereas in the USA it is recommended that triple regimens be given for 10–14 days.[8 9] In recent years, a decrease in the efficacy of 1 week of triple therapy has been reported.[10–12] A longer duration of treatment could provide better eradication rates. Some large, multicentre studies have recently reported that prolonging the duration of triple therapy from 7 to 10 days does not improve its results.[12–14] Individual studies comparing treatment with a proton pump inhibitor (PPI) and two antibiotics for 1 and 2 weeks have generally shown little difference between the two regimens.[11 15–21] However, two meta-analyses have concluded that 2-week triple therapies achieve considerably better results than 1-week schedules.[22 23] Overall, few studies have directly compared 1- and 2-week triple regimens and the sample sizes of those that have been performed are not sufficiently large to detect any noticeable difference in efficacy.[11 15–19 21]

To overcome this shortcoming, we performed a large, randomised, multicentre trial involving >900 consecutive patients with duodenal ulcer enrolled in 81 Italian endoscopy units. The aim of this double blind, placebo-controlled study was to compare the efficacy and safety of 1 week and 2 weeks of omeprazole-based triple therapy, including amoxicillin and clarithromycin, in *H pylori* eradication in patients with duodenal ulcer. A standard dual therapy (omeprazole and amoxicillin) was included as a control arm with a low-eradication rate. This was included both as a measure of the internal validity of the study, and as part of a second long-term follow-up study which had the aim of evaluating factors associated with the recurrence of duodenal ulcer, such as sex, age, smoking, positive family history for peptic ulcer, and dyspeptic and reflux symptoms.

MATERIALS AND METHODS

Patients

Patients with a symptomatic duodenal ulcer who were *H pylori*-positive according to rapid urease testing were enrolled in the study between May 1996 and June 1998. Patients with a prepyloric ulcer within 2 cm of the pylorus were also accepted. The following exclusion criteria were applied: previous treatments for *H pylori* eradication; allergy to penicillin or macrolides; significant liver or kidney disease; severe cardiac or pulmonary disease; suspected or confirmed malignancy; concurrent gastric ulcer or reflux oesophagitis; active upper gastrointestinal bleeding; history of gastric surgery; pregnancy or breast feeding; and clinically significant abnormalities in the predrug laboratory screen. Patients using antibiotics in the month before inclusion, bismuth-containing compounds

Abbreviations: ^{13}C-UBT, carbon-13 urea breath test; ITT, intention-to-treat; OAC1W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week, followed by omeprazole 20 mg twice daily and placebo for 1 week; OAC2W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 g twice daily for 2 weeks; PPI, proton pump inhibitor.

during the 3 months before inclusion, or PPIs, H_2-receptor antagonists, misoprostol or sucralfate in the 2 weeks before the pre-entry endoscopy were excluded. Patients receiving regular treatment with non-steroidal anti-inflammatory drugs (⩾5 days a week, for at least 2 weeks during the month before the start of the study) were also excluded.

This study was performed according to good clinical practice and the Declaration of Helsinki, and was approved by the research ethics committee of each participating centre. Written informed consent was obtained from all patients.

Study design

This study had a double blind, randomised, placebo-controlled, parallel-group design and involved 81 Italian endoscopy units. Patients were randomised using a computerised random-number generator to receive omeprazole 20 mg twice daily in combination with amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 (OAC1W) or 2 weeks (OAC2W), or omeprazole 20 mg twice daily, amoxicillin 1 g twice daily and clarithromycin placebo twice daily for 2 weeks (hereafter referred to as omeprazole and amoxicillin). Patients in the OAC1W group were treated for one additional week with omeprazole 20 mg twice daily and amoxicillin and clarithromycin placebos twice daily. Treatments were assigned to patients using numbered containers and the randomisation was centralised and implemented by AstraZeneca, Italy. The computer-generated randomisation list was blocked by centre into blocks of size 2; the block size was unknown to the investigators. Patient numbers were allocated consecutively at the different centres at the time of enrolment.

Endoscopy was performed at the end of the 2-week administration period for the evaluation of ulcer healing, which was defined by the presence of white scars or complete re-epithelisation in the area where the ulcer was present earlier. In patients without healed ulcers, endoscopy was performed again after 4 weeks of treatment with omeprazole 20 mg twice daily. At 2 weeks, adverse events and treatment compliance were evaluated by personal interview. Treatment compliance was also measured by counting the returned pills. Patients were considered to be non-compliant if <75% of study medication was taken.

Assessment of *H pylori* status

Biopsy specimens were taken during upper gastrointestinal endoscopy before the start of the study treatment. Two biopsy specimens, one from the corpus and one from the antrum, were taken for the rapid urease test (CP test, Yamanouchi Pharma SpA, Carugate, Milan, Italy). For histological assessment of *H pylori* infection, two biopsy specimens were taken from the corpus and three from the antrum. *H pylori* infection was also assessed by carbon-13 urea breath test (^{13}C-UBT). Although all patients with a positive result for the rapid urease test were enrolled, patients were considered *H pylori*-positive only if a positive result was confirmed by histological examination or ^{13}C-UBT. At least 4 weeks after the withdrawal of treatment, all patients with healed ulcers underwent endoscopy, where five biopsy specimens, two from the corpus and three from the antrum, were taken for histological examination. ^{13}C-UBT was also performed. Patients were considered *H pylori*-negative if both the histological assessment and the ^{13}C-UBT gave negative results.

For *H pylori* diagnosis, biopsy specimens were fixed in 10% formalin and stained with haematoxylin–eosin and Giemsa stain. The ^{13}C-UBT was performed using 100 mg of ^{13}C-urea and a single post-urea breath sample at 30 min according to the European standard protocol.[24]

Statistical analysis

Statistical analysis was performed using the SAS statistical package (V.6.12). The primary efficacy variable was the eradication rate of *H pylori*. Assuming true eradication rates of 85% and 94% for 1 and 2 weeks respectively for the OAC regimen, 203 patients in each group would be necessary to detect, with 80% power, a minimum difference of 9% between the two groups. This sample size was calculated using the normal approximation to the binomial distribution at a significance level of 0.05. Allowing for a 20% dropout rate, at least 254 patients for each group were required to be enrolled.

Intention-to-treat (ITT) and per protocol (PP) statistical analyses were performed. ITT analysis included all randomised patients who had taken at least one dose of study medication, except those in whom positive *H pylori* infection status at entry was not confirmed by either histological examination or ^{13}C-UBT. PP analysis included all patients who took at least 75% of the study medication, except those who were lost to follow-up and those with major protocol violations that could have influenced treatment outcome. For example, patients were excluded if they used disallowed drug during the study, if the assessment of post-treatment *H pylori* status was performed too early, if their *H pylori* status was unknown due to missing data, or if they had concurrent gastric ulcer or related diseases. The treatment groups were compared using the normal approximation to the binomial distribution. A χ^2 test or Fisher's exact test, as appropriate, was performed to compare demographics characteristics and eradication rates between treatment groups, and the analyses were prespecified in the trial protocol. A p value of <0.05 was considered to be significant.

RESULTS

A total of 909 patients (621 males, 288 females; mean (range) age, 46 (18–72) years) were randomised in this study: 302 patients in the OAC1W group, 302 in the OAC2W group and 305 in the omeprazole and amoxicillin group. No differences were observed among the three groups in terms of sex, age, smoking and alcohol use as shown in table 1.

Two patients were excluded from the ITT analysis: one patient from the OAC1W group, who received no treatment, and one patient from the OAC2W group who was *H pylori*-negative at entry. This last patient was only included in the safety analysis. A total of 11 patients from the OAC1W group, 10 patients from the OAC2W group and 12 patients from the omeprazole and amoxicillin group were excluded from the PP analysis due to major protocol violations. In all, 19 patients from the OAC1W group, 17 patients from the OAC2W group and 23 patients from the omeprazole and amoxicillin group were lost to follow-up. Poor compliance also lead to exclusion from the PP analysis for a further 52 (17.3%) patients from the OAC1W group, 56 (18.6%) patients from the OAC2W group and 46 (15.1%) patients from the omeprazole and amoxicillin group. Treatment compliance was similar in the three groups ($p = 0.51$). Therefore the PP analysis of *H pylori* eradication included 219 patients in the OAC1W treatment group, 218 in the OAC2W group and 224 in the omeprazole and amoxicillin group (fig 1).

Table 2 shows the eradication rates for the three groups according to ITT and PP analysis. There was no significant difference between OAC1W and OAC2W regimens in either ITT ($p = 0.53$) or PP ($p = 0.71$) analyses. As expected, both triple OAC treatments resulted in significantly higher eradication rates compared with omeprazole and amoxicillin treatment in both ITT and PP analyses ($p<0.001$). The difference in eradication rate between the OAC1W and OAC2W groups was 2% (95% CI –4% to 8%) in the ITT analysis, and 1.3% (95% CI –5.5% to 8.1%) in the PP analysis.

Table 1 Baseline characteristics of study patients

	OAC1W (n = 301)	OAC2W (n = 302)	OA (n = 305)	p Value
Sex (male)	206 (68.4%)	216 (71.5%)	198 (64.9%)	0.19
Age (years; mean (SD))	45.5 (11.8)	46.7 (11.6)	45.5 (11.5)	—
Smoking				
Yes	172 (57.1%)	166 (55.0%)	151 (49.5%)	0.15
No	85 (28.2%)	94 (31.1%)	102 (33.4%)	0.38
Ex-smoker	44 (14.6%)	42 (13.9%)	52 (17.0%)	0.53
Alcohol use	133 (44.2%)	153 (50.7%)	139 (45.6%)	0.24

OA, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and placebo for 2 weeks; OAC1W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week, followed by omeprazole 20 mg twice daily and placebo for 1 week; OAC2W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 g twice daily for 2 weeks.

According to the ITT analysis, 235 of 301 patients in the OAC1W group (78.1%; 95% CI 73 to 82.3%), 243 of 301 patients in the OAC2W group (80.7%; 95% CI 75.9 to 84.8%), and 253 of 305 patients in the omeprazole and amoxicillin group (83.0%; 95% CI 78.3 to 86.7%) had healed ulcers after 2 weeks of treatment. According to the PP analysis, 200 of 227 patients in the OAC1W group (88.1%; 95% CI 83.2 to 91.7%), 212 of 233 patients in the OAC2W group (91.0%; 95% CI 86.6 to 94.1%) and 216 of 235 patients in the omeprazole and amoxicillin group (91.9%; 95% CI 87.7 to 94.7%) had healed ulcers after 2 weeks of treatment. As expected, there was no significant difference between the three regimens in terms of ulcer healing in either the ITT analysis ($p = 0.31$) or in the PP analysis ($p = 0.35$). A further 4 weeks of omeprazole treatment was given to patients without healed ulcers after 2 weeks and at the third visit, ulcer healing rates >90% were observed in all treatment groups in both the ITT and PP analyses.

The three treatments were well tolerated. The adverse events reported were mild or moderate and never severe. The proportions of patients experiencing adverse events was not significantly different in OAC1W and OAC2W groups, being 9.6% and 9.9% ($p = 0.88$), respectively (table 3). In the omeprazole and amoxicillin group, only 5.9% of patients experienced adverse events, but this was not significantly different from the other groups ($p = 0.11$). Similar proportions of patients from the three groups discontinued treatment due to adverse event ($p = 0.48$), as shown in table 3. The most frequent adverse events were diarrhoea, glossitis and stomatitis, as shown in table 4.

DISCUSSION

There is still no general consensus regarding the optimal duration of triple therapy for *H pylori* eradication. European guidelines indicate that triple therapy for 1 week is acceptable[7] whereas, in the USA, 10–14 days of treatment is still preferred.[8 9] This difference in recommended treatment duration owes much to the fact that few studies have directly compared 1- and 2-week triple treatment regimens. Of those that exist, almost all have been conducted in individual centres and with few patients.[11 15–21] Most of these studies[11 15–19 21] reported a trend towards better results with 2-week eradication treatments, showing an increase in eradication rates of 4–11% in 2-week when compared with 1-week regimens. However, these increases were not statistically relevant. These trials also did not have the power to detect a difference of <15–20% due to the small numbers of patients enrolled. For example, Laine *et al*[15] included 50 patients in each treatment group, but showed that 250 patients would be required to achieve statistical significance at the eradication rates (OAC1W = 86%; OAC2W = 92%; $p = 0.11$, by ITT analysis) achieved in their study. In a study in India, significantly higher rates of *H pylori* eradication were reported for a 2-week triple treatment (95%) compared with a 1-week regimen (54%).[20] However, this study used a low dose of clarithromycin (250 mg twice daily), which could be

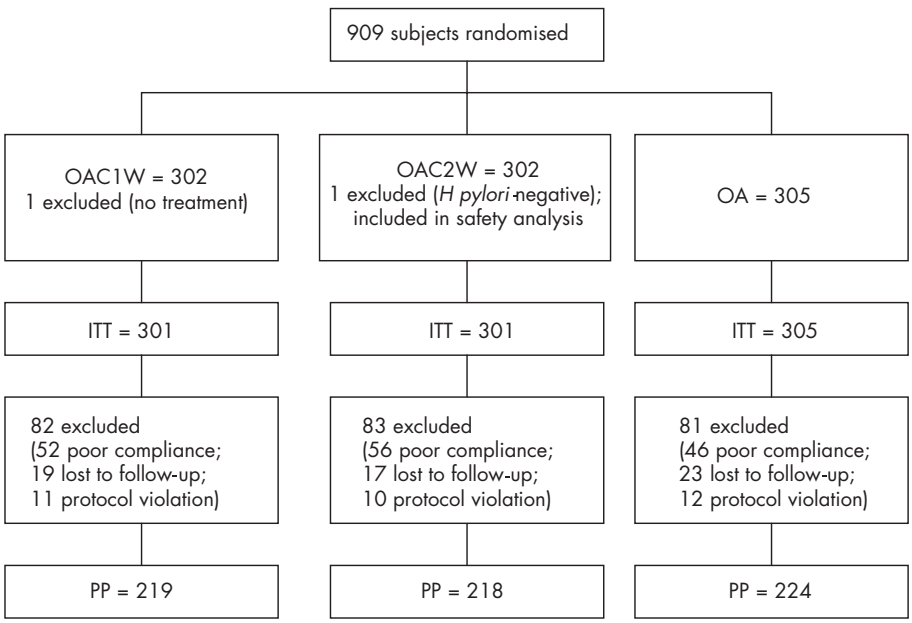

Figure 1 Flow of participants through each phase of the study. ITT, intention to treat; OA, omeprazole; PP, per protocol.

Table 2 *H pylori* eradication rates for each treatment regimen

	ITT		PP	
	n	% (95% CI)	n	% (95% CI)
OAC1W	240/301	79.7 (74.8 to 83.9)	183/219	83.6 (78.1 to 87.9)
OAC2W	246/301	81.7 (77 to 85.7)	185/218	84.9 (79.5 to 89.0)
OA	136/305	44.6 (39.1 to 50.2)	96/224	42.9 (36.5 to 49.4)

ITT, intention-to-treat; PP, per protocol; OA, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and placebo for 2 weeks; OAC1W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week, followed by omeprazole 20 mg twice daily and placebo for 1 week; OAC2W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 g twice daily for 2 weeks.

responsible for the lower effectiveness of the 1-week regimen. The general consensus is that, in a 1-week PPI, clarithromycin and amoxicillin triple regimen, a twice daily dose of 500 mg clarithromycin is preferable.[25]

Just one multicentre study has compared the efficacy of 1 week and 2 weeks of triple therapy, but this study used metronidazole rather than clarithromycin in association with amoxicillin.[26] Triple therapy with metronidazole and amoxicillin is recognised as having lower efficacy compared with PPI and clarithromycin-based triple therapies and so it is not recommended by guidelines as part of triple therapy for *H pylori* eradication.[7–9]

The problem of small patient numbers has led some investigators to conduct meta-analyses, which can be helpful because they represent a formal method for pooling large groups of patients from different studies. Two meta-analyses have concluded that 2 weeks of triple therapy was significantly more effective than a 1-week regimen, and reported an increase in the *H pylori* eradication rate of 9–12%.[22 23] However, the results of both these meta-analyses might have been biased by the fact that about half of the studies included had been published in abstract form.[27–30] These abstracts do not report methods in detail and therefore an accurate evaluation of the quality of the study is not possible.[31] One of the roles of meta-analysis is to encourage better quality studies in the future and the authors of these two meta-analyses suggested the need for studies that include many more patients.

Our study is the first large, multicentre, randomised, double blind, placebo-controlled study directly comparing the efficacy of 1 and 2 weeks of triple therapy in patients with duodenal ulcer that is recommended by guidelines for *H pylori* eradication. We show that 1 week of treatment with omeprazole, clarithromycin and amoxicillin achieves *H pylori* eradication rates of 80% and 84% by ITT and PP analyses, respectively in duodenal ulcer patients, and that extending treatment to 2 weeks does not enhance eradication. The difference between eradication rates achieved with 1 and 2 weeks of triple therapy is not statistically significant.

The eradication rates reported in our study are consistent with data from other studies, which show that the efficacy of triple therapy for the eradication of *H pylori* has decreased in recent years.[10–12] An increase in the prevalence of clarithromycin resistance seems to be the most important cause of this reduced efficacy.[32] Novel agents and new and modified eradication regimens have been reported to improve eradication rates, but their efficacy still needs confirmation.[33] One week of triple therapy remains the recommended first line treatment for *H pylori* eradication.

In our study, the tolerability of triple therapy was good and similar for both 1- and 2-week regimens and was not significantly different from double therapy. It has been reported that increasing the duration of triple therapy decreases patient treatment compliance. However, the study reporting this finding could have been biased by the small number of patients included. We show that compliance was not significantly different for 1 and 2 weeks of triple therapy.

In conclusion, this study shows that the efficacy and safety of 1 week of triple therapy including amoxicillin and clarithromycin is not significantly different from 2 weeks of treatment for the eradication of *H pylori* in patients with duodenal ulcer.

Table 3 Patients with adverse events and the frequency of withdrawal due to adverse events in the three treatment groups

	OAC1W (n = 301), n (%)	OAC2W (n = 302), n (%)	OA (n = 305), n (%)
Patients with AE	29 (9.6)	30 (9.9)	18 (5.9)
Treatment discontinuation due to AE	4 (1.3)	5 (1.7)	2 (0.7)

AE, adverse event; OA, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and placebo for 2 weeks; OAC1W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week, followed by omeprazole 20 mg twice daily and placebo for 1 week; OAC2W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 g twice daily for 2 weeks.

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Table 4 Frequency of adverse events in the three treatment groups

Adverse event	OAC1W (n = 301), n (%)	OAC2W (n = 302), n (%)	OA (n = 305), n (%)
Diarrhoea	10 (3.3)	10 (3.3)	6 (2.0)
Glossitis	7 (2.3)	10 (3.3)	3 (1.0)
Stomatitis	4 (1.3)	5 (1.7)	2 (0.7)
Abdominal pain	2 (0.7)	4 (1.3)	2 (0.7)
Allergic cutaneous reactions	4 (1.3)	2 (0.7)	2 (0.7)
Dry mouth/throat	3 (1)	3 (1.0)	0
Tongue discoloration	2 (0.7)	1 (0.3)	0
Nausea	0	2 (0.7)	2 (0.7)
Vomiting	0	1 (0.3)	0
Headache	2 (0.7)	2 (0.7)	2 (0.7)
Monilia	1 (0.3)	1 (0.3)	0
Herpes simplex labialis	0	1 (0.3)	1 (0.3)

OA, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and placebo for 2 weeks; OAC1W, omeprazole 20 mg twice daily and amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week, then omeprazole 20 mg twice daily and placebo for 1 week; OAC2W, omeprazole 20 mg twice daily + amoxicillin 1 g twice daily and clarithromycin 500 g twice daily for 2 weeks.

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