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Duodenal ulcer healing with 1-week eradication triple therapy followed, or not, by anti-secretory treatment: a multicentre double-blind placebo-controlled trial

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SUMMARY

Background: In the management of *Helicobacter pylori* induced duodenal ulcer, it is still controversial whether anti-secretory treatment needs to be continued following a 1-week course of eradication therapy.

Methods: 150 patients with *H. pylori* active duodenal ulcer (diameter ≥ 5 mm) were included. After a 1-week eradication treatment combining omeprazole 20 mg b.d., amoxicillin 1000 mg b.d. and clarithromycin 500 mg b.d. (OAC), patients were randomized to omeprazole 20 mg or placebo for 3 additional weeks. The primary variable was ulcer healing assessed at 4 weeks. Eradication was verified 4 weeks after cessation of study drugs by ^{13}C-urea breath test. Intention-to-treat analysis (ITT) included 131 patients with positive histopathology at inclusion.

Results: Healing rates were not statistically different, at 89% and 87%, respectively, in the OAC–omeprazole and OAC–placebo groups (95% CI: –8.7; 13.7). Numerically, healing rates in patients with successful eradication was higher [94/104 (90%)] than in patients with failed eradication [21/27 (78%)]. However, the difference was not statistically significant ($P < 0.1$).

Conclusions: One-week OAC eradication triple therapy achieves excellent healing rates in patients with uncomplicated duodenal ulcer disease. Although the confidence interval of the difference in healing suggests little or no benefit of continued omeprazole treatment after 1 week, larger studies are needed to address this issue definitively.

INTRODUCTION

The combination omeprazole of amoxicillin and clarithromycin (OAC) for 1 week is currently the reference treatment for the eradication of *Helicobacter pylori*. Following this 1-week course, a prolongation of anti-secretory treatment for patients with active duodenal ulcer is often recommended. However, several studies have suggested that treatment for eradication of *H. pylori* without prolongation of anti-secretory treatment is sufficient to heal most of the duodenal ulcer.[1–9] The present study tests the hypothesis that the 1-week triple therapy for eradication of *H. pylori* alone is a convenient therapy regimen for uncomplicated *H. pylori*-associated duodenal ulcer.

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PATIENTS AND METHODS

This study was designed as a multicentre, prospective, randomized, double-blind study with two parallel groups. The study was conducted in France according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethical Committee of Haute Normandie. Informed consent was obtained from each patient.

Patients

Patients more than 18 years old, with an endoscopically proven duodenal ulcer (≥ 5 mm diameter), and positive urease test (HUT test; ASTRA Chemicals GmbH, Germany) were eligible for this study.

Exclusion criteria were: current or recent (in the previous month) complication of duodenal ulcer (bleeding, perforation or stenosis); previous gastric surgery; concomitant oesophagitis or gastric ulcer at endoscopy; failure of a previous eradication treatment combining an anti-secretory agent and two antibiotics; undergoing treatment with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs); pregnancy or lactation; suspicion of poor compliance or a known allergy to the study drugs.

Study design

All eligible patients were initially treated with 1 week of eradication therapy, combining omeprazole 20 mg b.d., amoxicillin 1000 mg b.d. and clarithromycin 500 mg b.d. (OAC). Following the eradication therapy, patients were allocated randomly by drawing consecutive sealed envelopes to omeprazole 20 mg o.d. (OAC–omeprazole group) or placebo (OAC–placebo group) for 3 additional weeks. Concomitant treatment with anti-secretory agents, sucralfate, misoprostol, NSAID or aspirin was forbidden during this study. However, patients were allowed to take antacid (Rennie) for the treatment of gastrointestinal complaints.

Compliance assessment was evaluated by questioning at visits 2 and 3. Endoscopic examination was performed at the discontinuation of study drugs (day 28); however, an endoscopy was performed at day 14 in cases of mild or severe symptoms for at least 2 days during week 2.

Detection of H. pylori *status*

Four antral and four corpus biopsy specimens were taken at inclusion. *H. pylori* status was determined by urease test (HUT test) readings after 3 h for two antral biopsies and two corpus biopsies, and by centralized histopathological examination for the two antral biopsies and two corpus biopsies. The ^{13}C-urea breath test (^{13}C-UBT) was performed as described in a previous study[10] and centralized at Inbiomed, Lyon, France. An increase of $^{13}CO_2$ excretion in the breath of more than 3% above baseline values at 30 min was considered positive for *H. pylori.* The eradication of *H. pylori* was assessed on the basis of a negative breath test 4–6 weeks after the end of treatment.

Symptoms and safety considerations

Symptoms were assessed by the investigator at inclusion (baseline), during treatment (study days 7 and 14), at the end of the treatment (day 28) and at follow-up (4–6 weeks after the completion of study medication) according to a four-grade Liker scale (none/mild/moderate/severe). The following symptoms were recorded: overall assessment of dyspeptic symptoms; abdominal/epigastric pain; epigastric burning; hunger pain; belching; nausea; vomiting. Drug tolerability was investigated at each visit.

Statistical considerations and analysis

The size of the sample was based on the hypothesis that the healing rate with omeprazole would be 95%, and the difference between the group with omeprazole and the group with placebo would be 15%. Calculation using the continuity corrected χ^2-test, with a type I error of 0.05 and a type II error of 0.1 (two-sided correlation) estimated that each group should consist of at least 113 patients. According to the probability of a loss of about 5% of patients, a total of 240 randomized patients should have been included.

Eradication treatments were compared by calculating a 95% confidence interval for the difference in healing rates. The analysis rules were as follows: the intention-to-treat (ITT) analysis included all patients randomized with *H. pylori* infection, confirmed by histopathology at inclusion. In ITT, patients without a final assessment of healing and/or *H. pylori* status were recorded as a failure.

The per protocol healing (PP healing) analysis excluded patients without a final assessment of healing and/or patients with a major deviation from the protocol, such as the concomitant intake of aspirin, NSAIDs or anti-secretory agents, vagotomy, compliance < 75%, final endoscopy performed more than 7 days after discontinuation of study drugs, or a duration of healing treatment outside 14–28 days.

The per protocol eradication (PP eradication) analysis excluded patients without final assessment of *H. pylori* status or with a major deviation from the protocol, such

as concomitant intake of antibiotics or anti-secretory agents, ^{13}C-UBT performed < 26 days following the discontinuation of study drugs, compliance < 75% or vagotomy.

RESULTS

Study population

One hundred and fifty patients (76 in the OAC–omeprazole group and 74 in the OAC–placebo group) were randomized. One hundred and thirty-one patients (64 in the OAC–omeprazole group and 67 in the OAC–placebo group, 65% male, median age [range] 45 [20–86] years) were included in the ITT population. One hundred and eleven and 99 patients, respectively, met the criteria for PP healing analysis and PP eradication analysis. The disposition of patients during the study is summarized in Figure 1. There were no significant differences in between the demographic characteristics of the patients in the two groups (Table 1).

H. pylori *eradication*

Eradication was defined as a negative ^{13}C-UBT at 4–6 weeks after the discontinuation of study drugs. The results are summarized in Table 2. In the ITT analysis, *H. pylori* eradication was achieved in 104 out of the 131 patients, giving an ITT eradication rate of 79.3%, and demonstrating no difference between the OAC–omeprazole group and the OAC–placebo group. In the PP analysis, 90 of the 99 patients (90.9%) had a successful *H. pylori* eradication.

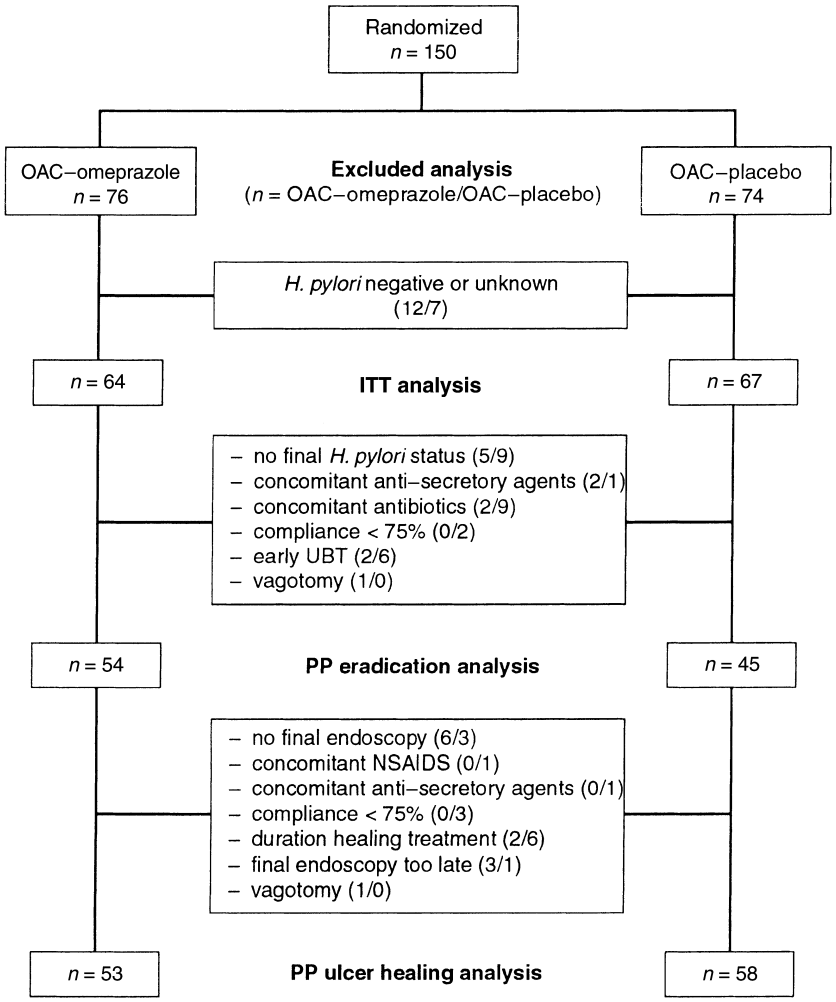

Figure 1. Disposition of all patients (number of patients in OAC–omeprazole group/OAC–placebo group).

Table 1. Clinical characteristics of the ITT population

	Treatment group		
	OAC–omeprazole $n = 64$	OAC–placebo $n = 67$	*P*-value
Mean age (years)	64	67	N.S.
Ethnic group			
Caucasian	56	63	N.S.
Black and others	8	4	N.S.
Non-smoker (%)	33	46	N.S.
History of peptic ulcer disease			
< 1 years (%)	35	51	N.S.
> 5 years (%)	48	33	N.S.
History of complicated peptic ulcer disease (%)	5	0	N.S.

OAC–omeprazole: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by omeprazole 20 mg o.d. for 3 weeks.
OAC–placebo: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by placebo for 3 weeks.

Table 2. Eradication of *H. pylori*

Eradication *n* (%)	OAC–omeprazole	OAC–placebo	[95% CI] difference
ITT	53/64 (82.8%)	51/67 (76.1%)	[−7.20; 20.5]
PP	50/54 (92.6%)	40/45 (88.9%)	[−7.8; 15.2]

OAC–omeprazole: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by omeprazole 20 mg o.d. for 3 weeks.
OAC–placebo: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by placebo for 3 weeks.

Ulcer healing

In ITT, healing was achieved within 28 days in 57 of 64 patients (89.1%) in the OAC–omeprazole group and in 58 of 67 (86.6%) in the OAC–placebo group. The percentage difference was 2.5%, 95% CI: [−8.7; 13.7] ($P = 0.663$). For the PP analysis, healing occurred in 46 of 47 patients (97.8%) in the OAC–omeprazole group vs. 41 of 44 patients (93.2%) in the OAC–placebo group. The difference was 4.6%, 95% CI: [−0.6; 17.5] ($P = 0.11$). Overall, the healing rate was 87.8% in the ITT population and 93.7% in the PP population. Overall healing rates were 94/104 (90.4%) in patients with a successful eradication vs. 21/27 (77.8%) in patients where eradication failed ($P < 0.1$). (Table 3).

Symptoms and safety

The evolution of symptom relief is shown in Figure 2. A rapid clinical improvement was obtained in both groups. No patients had moderate or severe symptoms at the end of the treatment regimen and only 18.6% had mild residual symptoms. In the same manner, there was no difference in adverse event occurrence in the ITT population between the two groups.

DISCUSSION

The results of this study suggests that a 1-week triple therapy which combines omeprazole 20 mg b.d., amoxicillin 1000 mg b.d. and clarithromycin 500 mg b.d. with no additional acid suppression therapy achieves the healing of most uncomplicated active duodenal ulcers.

Table 3. Healing of duodenal ulcer according to *H. pylori* status

	Healed		Unhealed		*P*-values stratified on *H. pylori* status
	H. pylori+	*H. pylori*−	*H. pylori*+	*H. pylori*−	
ITT					
OAC–omeprazole	9/11	48/53	2/11	5/53	0.77
OAC–placebo	12/16	46/51	4/16	5/51	
PP					
OAC–omeprazole	3/3	43/44	0/3	1/44	0.26
OAC–placebo	4/4	37/40	0/4	3/40	

OAC–omeprazole: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by omeprazole 20 mg od for 3 weeks.
OAC–placebo: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by placebo for 3 weeks.

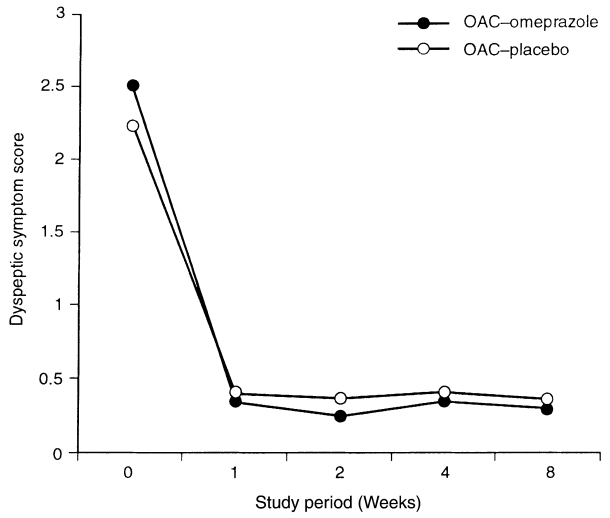

Figure 2. Evolution of dyspeptic symptoms. OAC–omeprazole: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by omeprazole 20 mg b.d. for 3 weeks. OAC–placebo: omeprazole 20 mg b.d., amoxicillin 1000 mg b.d., clarithromycin 500 mg b.d. for 1 week, followed by placebo for 3 weeks.

However, it should be noted that the number of patients previously calculated as being required for an adequate statistical power was not reached. This was due to difficulty in recruiting patients with active duodenal ulcer, who were not taking anti-secretory agents before endoscopy. Nevertheless, the number of patients included and analysed in each group was comparable to that of previous randomised and published studies.[1, 7, 11] Although the confidence interval of the difference in healing observed in our study suggests little or no benefit for continued omeprazole treatment after 1 week, on the other hand one cannot exclude the possibility that such treatment increases the healing rate by as much as 13.7%. Larger and adequately powered studies will be needed to definitively address this issue.

Several randomized studies have also previously suggested that the *H. pylori* eradication regimen currently used could be sufficient to obtain duodenal ulcer healing. Most of those studies were conducted with a 10–14-day regimen,[3, 4, 6, 8] or with a colloidal bismuth subcitrate.[11] However, one study using a 1-week triple therapy, without prolongation of the anti-secretory drug, has shown that approximately 80% of *H. pylori*-associated duodenal ulcers were healed after 28 days.[1] Furthermore, in this study, ulcers were healed in 28 out of 40 patients in whom *H. pylori* was not eradicated.[1] In another study, with a design similar to ours, all 52 patients had an ulcer, which was healed by 28 days, where the *H. pylori* cure rate was 96%.[2]

In our study, as for other studies, the percentage of patients with healed ulcer was no different whether *H. pylori* was eradicated or not. However, although not significant, there is a tendency to a lower healing rate in patients where eradication failed, as was suggested in another recent study.[9] The percentage of patients who were healed, despite the failure to eradicate *H. pylori*, was higher than that observed in the placebo groups of previous placebo-controlled studies in uncomplicated active peptic ulcer.[12]

These results suggest that the therapeutic impact of 1-week triple therapy is independent of the ultimate success of eradication. The question is whether the determining factor is the high dosage of 7-day anti-secretory treatment, or the antibiotic treatment, or a combination of both. The anti-secretory treatment reduces the hydrochloric acid–pepsin insult and promotes the repair process. It might also act by promoting the migration of *H. pylori* to the fundus, reducing acid secretion. The aim of the antibiotic is to eliminate one of the pathogenic factors involved in peptic ulcer. This objective can be reached not only when eradication is complete and definite, but also by decreasing bacterial density, even in the absence of eradication.[8]

The results from our study permit similar conclusions to be reached to those proposed in other studies.[1, 2] It suggests that 7-day triple therapy is a simple and sufficient treatment for the healing of an uncomplicated active peptic ulcer. However, this cannot be extended to complicated ulcers or those that have developed during NSAID treatment, which were excluded from our study, as well as from other published studies. Since successful eradication is the essential factor for the prevention of recurrence and complications of peptic ulcer disease.[13]

In conclusion, a 1-week omeprazole–amoxicillin–clarithromycin eradication triple therapy achieves excellent healing rates in patients with uncomplicated duodenal ulcer disease. Although the confidence interval of the difference in healing observed in our study suggests little or no benefit for continued omeprazole treatment after 1 week, the lack of a statistically significant difference cannot be seen as a confirmation of equivalence between the two treatments. Larger and better-resourced studies are needed to definitively address this issue.

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