Influence of *Helicobacter pylori* Eradication Therapy on the Occurrence of Gastrointestinal Events in Patients Treated with Conventional Nonsteroidal Antiinflammatory Drugs Combined with Omeprazole

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ABSTRACT. ***Objective.*** To evaluate the effect of eradication treatment of *Helicobacter pylori* and the influence of *H. pylori* status on the incidence of gastrointestinal (GI) events in rheumatic patients receiving longterm conventional nonsteroidal antiinflammatory drug (NSAID) therapy combined with omeprazole.

Methods. Patients (n = 919) requiring longterm NSAID therapy entered this multicenter, open label, parallel group study. *H. pylori* positive patients were randomized to receive either eradication therapy (omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 7 days) or no therapy. Both these groups and the *H. pylori* negative patients were given omeprazole, 20 mg once daily, along with NSAID for the study duration (5–8 weeks). Treatment failure (primary outcome variable) was defined as the occurrence of severe GI event (symptomatic ulcer, bleeding, perforation) or dyspepsia leading to discontinuation of NSAID therapy, unscheduled consultation, or upper GI tract endoscopy.

Results. Treatment failure was recorded in 9/294 (3.06%) infected patients receiving eradication therapy, 8/219 (3.65%) infected patients receiving omeprazole alone, and 5/391 (1.28%) *H. pylori* negative patients ($p > 0.05$). *H. pylori* eradication did not appear to influence the incidence and severity of dyspeptic symptoms in infected patients.

Conclusion. Our results do not support the use of *H. pylori* eradication therapy in rheumatic patients receiving conventional NSAID along with omeprazole. (J Rheumatol 2002;29:1975–80)

Key Indexing Terms:
NONSTEROIDAL ANTIINFLAMMATORY DRUGS — *HELICOBACTER PYLORI*
GASTRODUODENAL SIDE EFFECTS — OMEPRAZOLE

The gastrointestinal (GI) hazards of conventional nonsteroidal antiinflammatory drugs (NSAID), which inhibit both cyclooxygenase 1 (COX-1) and COX-2, are well established. Prospective, cross sectional endoscopic studies have shown that the combined prevalence of gastric and duodenal ulcers is 10–25% in rheumatic patients treated with these agents, which is 5–15 times the expected prevalence in an age matched healthy population[1]. Epidemiological studies have suggested roughly 4-fold enhancement of the risk of ulcer bleeding and perforation in patients taking conventional nonaspirin NSAID[2]. Further, dyspeptic symptoms are very common during NSAID therapy, their prevalence ranging from 5 to 50%[1]. Although such symptoms are poorly correlated with the endoscopic appearance and severity of mucosal injury, they are a major cause of discontinuation of NSAID therapy[1].

Various measures have been proposed to prevent NSAID associated gastropathy[3]. In this respect, the prostaglandin analog misoprostol, the proton pump inhibitor (PPI) omeprazole, and double dose H_2-receptor antagonists appear to be efficacious in preventing NSAID associated ulcers[4]. Only misoprostol 800 μg/day has been directly shown to reduce the occurrence of NSAID related ulcer complications[4]. On the other hand, omeprazole 20 mg once daily was as effective as misoprostol 200 μg qid in healing NSAID associated peptic ulcers, and significantly more effective compared with misoprostol 200 μg bid in preventing their recurrence[4,5]. Morever, omeprazole was better tolerated than misoprostol[4,5], and provided greater relief of symptoms, particularly abdominal pain and heartburn, in patients with NSAID associated dyspepsia[1].

The use of NSAID and infection with the bacterium

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Helicobacter pylori are 2 etiological factors that account for nearly all peptic ulcer disease. Unfortunately, studies of the interaction between NSAID and *H. pylori* have reported conflicting findings[6]. As a result, different treatment strategies have been recommended. For instance, a European consensus report recommended that *H. pylori* should be eradicated from infected patients in whom NSAID treatment is planned or in progress[7]. Conversely, a French task force recommended *H. pylori* eradication in patients with a gastroduodenal ulcer while taking NSAID, but advised against testing for or eradication of *H. pylori* before starting treatment with an NSAID[8].

We investigated the effect of an *H. pylori* eradication treatment on the incidence of GI adverse events in *H. pylori* positive patients receiving longterm conventional NSAID therapy along with omeprazole. A secondary objective was to evaluate the influence of *H. pylori* status on the incidence of NSAID associated GI adverse events.

MATERIALS AND METHODS

The study was conducted in accord with the standard codes of ethical practices. The protocol was approved by the Regional Ethics Committee of Bordeaux-B, France.

Patient selection. Patients aged 18 years and over were recruited in the community by rheumatologists or general practitioners. They were experiencing flare of osteoarthritis (OA), inflammatory spondyloarthropathies (SpA), or rheumatoid arthritis (RA) requiring regular NSAID therapy (≥ 5 days/week) for at least 5 weeks, at dosages equal to or greater than half the maximum recommended doses. At the time of this study, only dual COX-1/COX-2 inhibitors were available in France. Patients provided written informed consent, and were given a copy of their signed consent.

Patients were excluded if they had received NSAID therapy within the 2 preceding weeks, as were patients with a history of gastroduodenal ulcer or malignancy or gastric surgery. Other exclusion criteria included: GI symptoms necessitating endoscopy of the upper GI tract at the screening visit, *H. pylori* eradication therapy during the 12 months prior to entry to the study, a known allergy to the study drugs, and pregnancy. Finally, patients were ineligible if they were taking prednisone at dosages > 15 mg daily.

Study design. This was an open label trial. All patients underwent a rapid serological test for *H. pylori* in capillary blood (QuickVue®, Quidel) on entry to the study. *H. pylori* positive patients were allocated to either eradication therapy consisting of omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 7 days, or no eradication. Patients were randomized in consecutive order according to a list generated by AstraZeneca, Rueil-Malmaison, France; randomization was stratified for center. All patients, including *H. pylori* negative patients, were treated with omeprazole 20 mg once daily along with the NSAID throughout the study. Dyspeptic symptoms (defined as upper abdominal pain or discomfort, heartburn, or nausea/vomiting) during the 7 preceding days were recorded at the start of the study, after 4 weeks of treatment, and at study termination (Weeks 5 to 8). The severity was determined by the physician according to the following 4 point scale: 0 = absent; 1 = mild (awareness of symptoms but easily tolerated); 2 = moderate (sufficient discomfort to interfere with normal activities); or 3 = severe (incapacitating with inability to perform normal activities)[9]. Severe GI events (symptomatic gastroduodenal ulcer, hematemesis, melena, or perforation) were also recorded. The primary endpoint was the cumulative rate of "treatment failure," defined as the occurrence of severe GI events (as above) and/or dyspepsia leading to discontinuation of NSAID therapy, an unscheduled consultation and/or upper GI tract endoscopy. Secondary measures of efficacy included the incidence and severity of dyspeptic symptoms.

Sample size and statistical analysis. To calculate sample size, we assumed that the treatment failure would be 9% in patients receiving omeprazole alone[9]. Assuming a 4% difference between this group and the eradication group to be clinically meaningful, and with an alpha set at 0.05 (2 tailed) and power set at 80%, a total of 687 patients per group would be required. Again assuming a 10% dropout rate, a minimum of 2290 patients across the study sites was calculated to be required.

Statistical analysis was performed on the intention-to-treat population, which included all patients who received at least one dose of study medication and were treated with NSAID for at least one day. Differences in failure rates were analyzed using chi-square tests and Fisher's exact test. Ninety-five percent confidence intervals (95% CI) for the differences in treatment failure rates between groups were also calculated. Changes in incidences of dyspepsia were compared by the Mantel-Haenszel test. Secondary quantitative variables were analyzed using Student's t test. All tests were 2 sided. A p value < 0.05 was taken as significant.

RESULTS

A total of 919 patients were enrolled. Since 9 patients were not randomized, 3 did not receive study medication, and 3 were not given any NSAID, 904 patients (531 women, 373 men) were included in the intention-to-treat analysis. Patients were aged between 19 and 93 years (mean ± SD = 57.1 ± 14.2 yrs). There were 154 smokers (17%) and 62 (6.9%) were daily alcohol users. Ninety patients (10%) had RA, 118 (13.1%) SpA, and 455 (50%) OA of the knee or hip. Except for the proportion of women, which was higher in the *H. pylori* negative group, the characteristics of the patients were similar in the 3 groups, as was the mean duration of NSAID therapy (Table 1). Patients were given a large variety of NSAID, piroxicam (32.5%), diclofenac (21.1%), ketoprofen (10.4%), meloxicam (9.4%), tenoxicam (8.4%), and naproxen (8.3%) being the most commonly prescribed drugs among the 17 conventional NSAID available in France. The proportions of patients receiving the different types of NSAID were roughly similar between the 3 groups. *H. pylori* was detected in 513 patients, of whom 294 were allocated to eradication therapy followed by omeprazole and 219 to omeprazole alone.

Treatment failure. A total of 22 treatment failures occurred in the study, with causes of failure as shown in Table 2. The only severe GI event was one case of upper GI bleeding in an *H. pylori* negative patient. The cumulative rates of treatment failure were 3.06% (95% CI 1.09–5.03) in the *H. pylori* positive group with eradication therapy, 3.65% (95% CI 1.17–6.14) in the *H. pylori* positive group without eradication therapy, and 1.28% (95% CI 0.17–2.39) in the *H. pylori* negative patients. Accordingly, there were no significant differences between groups, although a numerical trend toward a lower rate of failures was evident in *H. pylori* negative patients compared with the *H. pylori* positive groups (Table 3).

Dyspepsia. The baseline incidence of dyspeptic symptoms was significantly higher in the *H. pylori* positive cohort (65.9%) than in the *H. pylori*-negative group (49.6%) ($p < 0.001$). However, dyspeptic symptoms were graded 1 (mild)

Table 1. Patient characteristics and duration of NSAID therapy.

	Hp +, with Eradication Therapy, n = 294	*Hp* +, No Eradication Therapy, n = 219	*Hp* –, n = 391
Age, yrs, mean ± SD	56.87 ± 13.20	58.74 ± 14.36	56.24 ± 14.76
Sex, male/female, n (%)	134/160 (46/54)	101/118 (46/54)	138/253 (35/65)
Caucasian, n (%)	288 (97.96)	214 (97.72)	381 (97.44)
Smoking habit, n (%)			
Nonsmoker	197 (67.01)	145 (66.21)	274 (70.08)
Ex-smoker	52 (17.69)	37 (16.89)	45 (11.51)
Occasional/current smoker	45 (15.30)	37 (16.90)	72 (18.41)
Rheumatic disease, n (%)			
Rheumatoid arthritis	23 (7.82)	23 (10.50)	44 (11.25)
Ankylosing spondylitis	42 (14.29)	26 (11.87)	50 (12.79)
Arthrosis of the knee	94 (31.97)	76 (34.70)	130 (33.25)
Arthrosis of the hip	54 (18.37)	36 (16.44)	65 (16.62)
Other	124 (42.18)	83 (37.90)	172 (43.99)
Time in the study, days, mean ± SD	57 ± 14	56 ± 13	56 ± 14

Hp+: infected with *H. pylori* at entry to the study; *Hp*– not infected.

Table 2. Causes of treatment failure.

	Hp+, with Eradication Therapy	*Hp*+, No Eradication Therapy	*Hp*–
No. of failures (%)	9/294 (3.06)	8/219 (3.65)	5/391 (1.28)
95% (CI)	1.09, 5.03	1.17, 6.14	0.17, 2.39
Cause of failure, n			
Withdrawal of NSAID	7	6	5
Unscheduled consultation	4	4	1
Endoscopy	1	1	1
Gastroduodenal ulcer	0	0	0
Upper GI bleeding	0	0	1
Perforation	0	0	0

Table 3. Differences in failure rates between groups.

	Difference, %	95% CI	p
HP+ with eradication therapy versus *HP*+ without eradication therapy	0.59	–2.54, 3.72	0.805
HP+ with eradication therapy versus *HP*–	1.78	–0.36, 3.92	0.111
HP+ without eradication therapy versus *HP*–	2.37	–0.01, 4.76	0.076

in 33.3% and 30.4% of the patients, respectively. The percentages of patients experiencing grades 2 and 3 dyspepsia decreased to the same extent in the *H. pylori* positive group with eradication and the *H. pylori* positive group without eradication (33.3% and 31.5% at visit 1, and 4.4% and 2.7% at visit 3, respectively). Both the incidence and severity of dyspepsia tended to decrease with time in all 3 groups of patients (Figure 1). The mean (SD) severity scores among *H. pylori* positive patients were 1.04 (0.88) at visit 1 and 0.36 (0.6) at visit 3 in the group given eradication therapy versus 0.98 (0.86) at visit 1 and 0.45 (0.57) at visit 3 in the group without eradication, compared with 0.69 (0.79) at visit 1 and 0.28 (0.52) at visit 3 in the *H. pylori* negative group.

Tolerability. The treatments were well tolerated in the 3 groups. Apart from the primary and secondary outcome measures, patients experienced few adverse events (Table 4). These consisted mostly of diarrhea (n = 19) and bronchitis (n = 11). There were also 4 serious adverse events: 2 (lumbosciatica, bronchospasm) in the *H. pylori* positive with eradication group, one (deep venous thrombosis) in the *H. pylori* positive without eradication group, and one (fatigue) in the *H. pylori* negative group. None was considered drug related.

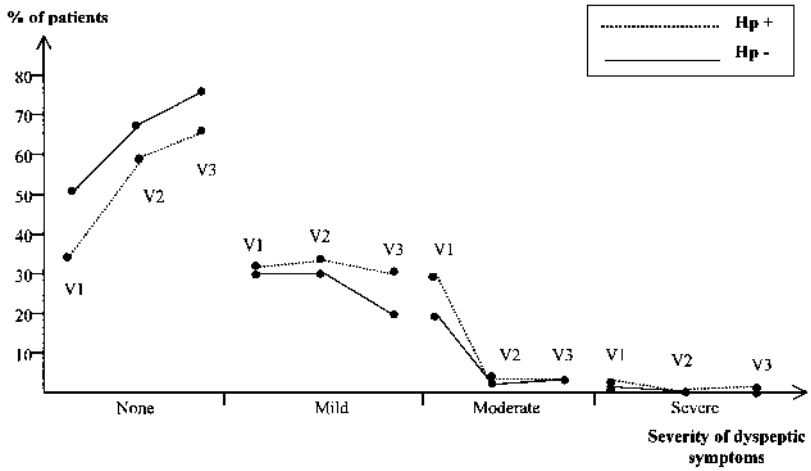

Figure 1. Incidence of dyspeptic symptoms during the study. V: visit.

Table 4. Summary of adverse events.

	HP+ with Eradication Therapy	*HP*+ without Eradication Therapy	*HP*–
No. of patients with adverse events (%)	60 (20)	32 (14)	52 (13)
No. of serious adverse events	2	1	1
Withdrawals due to adverse events (%)	14 (5)	7 (3)	9 (2)
Most frequently reported adverse events			
Diarrhea	8	7	4
Bronchitis	5	3	3
Nausea	3	3	3
Epigastric pain	3	4	1

DISCUSSION

The results of this study show that *H. pylori* eradication therapy in addition to prophylaxis with omeprazole does not reduce the incidence of treatment failure related to NSAID associated GI side effects, compared with *H. pylori* positive and *H. pylori* negative patients treated with omeprazole alone.

The interaction between *H. pylori* infection and NSAID in the pathogenesis of upper GI symptoms and GI ulcers and complications remains unclear, despite many studies. It has been reported that *H. Pylori* infection is associated with increased dyspeptic symptoms, but that it does not potentiate NSAID gastropathy in patients with RA receiving NSAID[10]. Other studies found no differences in frequency and severity of GI mucosal damage between *H. pylori* positive and negative healthy subjects given NSAID for 1–4 weeks[11,12]. Of 7 epidemiologic studies that investigated whether *H. pylori* infection influences the risk of ulcer complications in patients who are taking NSAID, one found an increase[13] and 3 reported a decrease in that risk (at least for bleeding due to gastric ulcers)[14–16], and 3 found no effect[17–19]. Overall, these findings suggest that NSAID and *H. pylori* act as independent risk factors. Conversely, a metaanalysis of endoscopic studies showed a small but significant enhancement of ulcer risk in NSAID users infected with the bacterium compared with those uninfected[20].

Among patients taking NSAID who have had a peptic ulcer, *H. pylori* eradication tended to delay gastric ulcer healing, but not duodenal ulcer healing, by a proton pump inhibitor[21–23]. After initial healing of an ulcer, *H. pylori* eradication alone appeared to have no significant effect on ulcer recurrence[21,22,24,25]. *H. pylori* eradication alone was also ineffective in preventing recurrent gastric ulcer bleeding compared with maintenance therapy with omeprazole[26]. Eradicating *H. pylori* infection has been recently reported to be equivalent to maintenance therapy with omeprazole in preventing recurrent GI bleeding in patients with *H. pylori* infection who were taking low dose aspirin[27]. In contrast, omeprazole was superior to eradication of *H. pylori* for the secondary prevention of upper GI bleeding in patients who were taking naproxen 1 g/day[27].

Few studies have investigated the influence of eradicating the bacterium from infected patients before beginning NSAID therapy or, as in the present study, at the time of initiation of NSAID therapy in patients with no history of

peptic ulcer disease. Chan, *et al*[28] reported that eradication of *H. pylori* before beginning NSAID therapy reduced the occurrence of NSAID induced peptic ulcers. In that study, the absence of preexisting ulcers was confirmed endoscopically, and *H. pylori* infection was assessed using the rapid urease test confirmed by the histology. Eradication therapy of *H. pylori* consisted of a one week course of a combination of bismuth subcitrate, tetracycline, and metronidazole, which was successful in 89% of the treated patients. Only 7% of the patients in the eradication group developed peptic ulcers after 8 weeks of treatment with naproxen 750 mg/day compared with 26% in the control group[28]. It has, however, been suggested that the use of cytoprotective bismuth in the eradication regimen may have confounded the results[29].

Our results indicate that *H. pylori* eradication therapy has no effect on failure rates due to NSAID associated adverse GI events in patients receiving prophylactic omeprazole therapy. Since the number of patients enrolled was less than the minimum number calculated as being required for statistical power, our results could be ascribed to a type II error. The inclusion rate was lower than expected, mainly because of one exclusion criterion. As no endoscopy was performed prior to entry to the study, the patient population was restricted to subjects who were not given NSAID during the 2 preceding weeks. This may have limited the number of patients with a preexisting ulcer at study entry. Another limitation of our study is that *H. pylori* status was assessed serologically. Although there is some concern about the sensitivity and specificity of this approach, the *H. pylori* infection rate of 57% was in agreement with that expected in a Western population of similar age[21]. Although *H. pylori* status was not reassessed in our study, the expected eradication rate with the triple-therapy regimen used is in the area of 90%[30,31], which is comparable to that achieved by Chan, *et al*[28]. Despite these weaknesses, it seems unlikely that their effect would be sufficient to completely obscure any clinically relevant benefit of *H. pylori* eradication in our large study. Indeed, treatment failure occurred in less than 2.5% of all patients during the course of the study. Despite the absence of a placebo arm, the low failure rate observed in our trial might be explained by the combination of NSAID with omeprazole, which proved effective at preventing endoscopic gastroduodenal ulcers and reducing NSAID related dyspepsia[4]. Although poorly correlated with NSAID induced GI complications, NSAID related dyspepsia is an important cause of drug discontinuation[1,4].

The incidence of dyspeptic symptoms appeared to be higher in our *H. pylori* positive cohort compared to the *H. pylori* negative group[32]. A pivotal question is whether curing the infection will lead to a sustained improvement in dyspeptic symptoms[32]. A systematic review of randomized controlled clinical trials concluded that *H. pylori* eradication might be cost effective although providing only a small benefit in patients experiencing dyspepsia[33]. However, treatment of *H. pylori* infection in non-ulcer dyspepsia remains controversial[34,35]. It should be noted that dyspepsia was not related to NSAID therapy in the above mentioned trials. Our investigation included a very different group of patients. It showed that eradication of *H. pylori* had no influence on the rate of "dyspepsia cure" as usually defined (no symptoms or mild symptoms not interfering with daily activities)[9,33] in patients receiving NSAID along with omeprazole. Overall, *H. pylori* eradication did not appear to influence the incidence and severity of dyspeptic symptoms in our infected patients.

Finally, our study suggests that *H. pylori* eradication therapy does not confer any clear advantage with regard to GI adverse events in patients taking conventional NSAID in combination with omeprazole.

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