Gut 1996; **39**: 22–26

Role of *Helicobacter pylori* in ulcer healing and recurrence of gastric and duodenal ulcers in longterm NSAID users. Response to omeprazole dual therapy

G Bianchi Porro, F Parente, V Imbesi, F Montrone, I Caruso

Abstract

***Background*—The relation between *Helicobacter pylori* infection and non-steroidal anti-inflammatory drug (NSAID)-associated peptic ulcers remains unclear; in particular, it is not known whether *H pylori* plays a part in the healing and recurrence of these ulcers.**

***Aims*—To evaluate prospectively in a consecutive series of arthritis patients receiving longterm NSAID treatment the prevalence of peptic ulcer as well as the effect of *H pylori* eradication on the healing and recurrence of gastric and duodenal ulcer found.**

***Patients*—Some 278 consecutive patients underwent gastroscopy with multiple biopsies of the gastric antrum and corpus for histological examination and rapid urease test. One hundred peptic ulcers (59 gastric ulcers, 39 duodenal ulcers, and two gastric ulcers concomitant with a duodenal ulcer) were found. Seventy per cent of these ulcers were *H pylori* positive.**

***Methods*—According to their *H pylori* status, ulcer patients were randomised to one of the following treatments: *H pylori* negative ulcers received omeprazole 20 mg twice daily for four to eight weeks, whereas *H pylori* positive lesions were treated with omeprazole 20 mg twice daily plus amoxycillin 1 g twice daily (the second of these for the first two weeks) or omeprazole alone for four to eight weeks while continuing NSAID therapy. Patients with healed ulcers were endoscopically followed up for six months after stopping antiulcer therapy while continuing NSAIDs.**

***Results*—Endoscopic healing rates for gastric and duodenal ulcers in the three different groups were similar both at four and eight weeks. *H pylori* eradication did not influence healing, which occurred in 14 of 20 (70%) of patients in whom *H pylori* was eradicated, compared with 14 of 17 (82%) of patients with persistent infection. Cumulative recurrence rates at six months did not statistically differ among the three different groups (27% in *H pylori* negative, 46% in *H pylori* positive, and 31% in those where *H pylori* was eradicated during the healing phase), although a numerical trend in favour of a higher recurrence rate in infected patients was evident.**

***Conclusions*—*H pylori* eradication does not confer any significant advantage on the healing of gastric and duodenal ulcers associated with longterm NSAID use. It remains to be established with certainty whether eradication may be helpful in the reduction of recurrence in a specific subset of NSAID associated ulcer.**

(*Gut* 1996; **39**: 22–26)

Keywords: *H pylori*, NSAIDs, peptic ulcers, arthritis.

Departments of Gastroenterology
G Bianchi Porro
F Parente
V Imbesi

and Rheumatology
F Montrone
I Caruso

L Sacco University Hospital, Milan, Italy

Correspondence to:
Professor G Bianchi Porro, Gastrointestinal Unit, Ospedale L Sacco, Via GB Grassi, 74, I-20157 Milan, Italy.

Accepted for publication 31 January 1996

Although *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly considered the most important exogenous factors in the aetiology of peptic ulcer disease, little is known about the relation between these two agents in patients with NSAID associated peptic ulcers.[1]

Indeed, very few prospective studies have dealt with the possible interaction between NSAIDs and *H pylori* on the clinical course of NSAID induced gastroduodenal lesions, yielding conflicting results. Lanza *et al*[2] found that *H pylori* infection has no influence on the development of gastroduodenal mucosal lesions after the short-term administration of naproxen or aspirin in healthy volunteers. Similarly, Kim *et al*[3] showed that *H pylori* infection does not confer increased risk of ulceration in arthritic patients receiving NSAIDs in the long term. In contrast, Taha *et al*[4] showed that peptic ulcers in longterm NSAID users are more likely to develop in the presence of *H pylori* infection and duodenal erosions. To date, no prospective study has evaluated whether the eradication of *H pylori* might influence the healing process of peptic ulcer induced by NSAIDs. In addition, no firm data are yet available on peptic ulcer recurrence in arthritic patients who receive NSAIDs daily after initial healing, although Seppala *et al* have recently shown that the eradication of *H pylori* seems to reduce gastric ulcer recurrences even in patients taking NSAIDs more than once a week.[5] The question is not irrelevant if we consider that at least 50% of gastroduodenal ulcers in longterm NSAID users are associated with *H pylori* infection[3 6 7] and, therefore, they might benefit particularly from an antibacterial treatment if a synergistic relation between this bacterium and NSAID could be confirmed.

Therefore, we have aimed at investigating prospectively the effect of *H pylori* eradication

on healing and recurrence of NSAID associated peptic ulcers in a group of arthritic patients receiving NSAIDs in the long term.

Methods

Patients

Patients aged 18 years or over were recruited from the Rheumatology Outpatients' Clinic provided that they had osteoarthritis, adult rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or Reiter's syndrome. Daily NSAID therapy had to have been taken for at least four weeks before baseline endoscopy and was expected to continue for at least an additional six months. Patients were excluded if they had had gastric surgery, gastrointestinal malignancy, or if they had taken antiulcer agents or antibiotics within three weeks of endoscopy. Other exclusion criteria included pyloric obstruction, recent acute upper gastrointestinal bleeding, and severe renal impairment. In addition, patients taking anticoagulants, cytotoxic drugs or prednisone at dosages >10 mg/day were excluded. Demographic data including age, sex, smoking habits, alcohol consumption, and history of ulcer disease were specifically looked for and recorded.

Informed consent was obtained at baseline endoscopy, which was performed using diazepam for sedation. An ulcer was defined as a localised defect in gastric or duodenal mucosa of at least 5 mm in diameter and with perceptible depth, whereas smaller lesions were considered as erosions. Ulcer dimensions were measured using standard Olympus biopsy forceps, with the fully open spoon being equivalent to 5 mm.

Study design

H pylori was determined by a biopsy urease test and histological assessment. For this purpose, apart from specimens from gastric ulcer edges, three biopsy specimens were taken from the antrum and two from the corpus. One antral biopsy specimen was used for the rapid urease test (CP test, Brocades, Milan, Italy), whereas the remaining formalin fixed specimens were used for histological assessment. The specimens were embedded in paraffin wax and stained with haematoxylin and eosin and modified Giemsa methods. Gastric histopathology was classified according to a personal modification of the Sydney system as previously described.[8] A patient was considered *H pylori* positive when *H pylori* was found at histological examination and rapid urease test was positive.

Patients with active gastric or duodenal ulcer at initial endoscopy were asked to participate in a prospective trial to evaluate the effect of *H pylori* on ulcer healing and recurrence. The presence of concurrent gastric or duodenal erosions did not constitute a criterion for exclusion from the trial.

According to their *H pylori* status they were assigned to the following ulcer healing treatments: *H pylori* positive patients received omeprazole 20 mg twice daily for four weeks and amoxycillin 1 g twice daily during the first two weeks or omeprazole 20 mg twice daily alone for four weeks according to a randomised single blind scheme. *H pylori* negative patients were all treated with omeprazole 20 mg twice daily for four weeks. Patients also continued to take NSAIDs at the same dose given prior to the study during both the ulcer healing and ulcer recurrence phases of the study. Patient compliance to antiulcer treatment was determined by counting all the unused tablets reported by the patients at fortnightly clinical assessments; during these visits side effects were specifically asked for and recorded.

After four weeks patients were endoscoped again to assess ulcer healing; if the ulcer was still active they received an open therapy with omeprazole 20 mg twice daily for a further four weeks.

Patients were considered to have been cured of *H pylori* if both rapid urease test and histological examination in the antrum and corpus were negative. In patients whose ulcer had healed at four weeks, *H pylori* eradication was assessed after one month from stopping treatment; in patients whose ulcer healed at eight weeks, because of the possibility of a false negative result at this time while receiving omeprazole, *H pylori* status was taken on the basis of the result of biopsies done at three months during the follow up. Similarly, in patients with unhealed ulcer after eight weeks, *H pylori* status was re-evaluated one to three months afterwards while they were receiving alternative therapy (sucralfate, misoprostol) after stopping NSAIDs.

Patients with healed ulcers at eight weeks, irrespective of their *H pylori* status, were asked to participate in the second part of the study. During this phase patients continued to take NSAIDs at the same dose given during the ulcer healing phase for a further six months but stopped any antiulcer therapy. Endoscopy was repeated at 12 and 24 weeks of follow up or before in the case of a recurrence of ulcer symptoms, with the endoscopist unaware of the *H pylori* status of the patients. Patients who took at least 85% of the antiulcer treatment, who missed no more than two consecutive days of NSAID therapy, and who had both the second and third endoscopic examination were considered evaluable for the first end point of the study.

Any patient who took at least 70% of NSAID therapy and did not miss more than three consecutive days of treatment during the longterm phase was considered evaluable for the second end point of the study.

Statistical analysis included the Student's t test for unpaired samples, and the χ^2 and Fisher's exact test where appropriate. Ninety five per cent confidence intervals for the difference in healing and recurrence rates between groups were also calculated.

Results

A total of 278 consecutive arthritic patients taking longterm NSAID treatment underwent

TABLE I *Demographic and clinical characteristics of the evaluable patients in relation to the presence of a gastric or duodenal ulcer*

Characteristic	*Ulcer*	*No ulcer*
Patients (n)	100	146
Age (y) (mean)	59	56
Sex		
Women (%)	78 (78)	120 (82)
Men (%)	22 (22)	26 (18)
Gastric erosions present (%)	52 (52)	76 (52)
Duodenal erosions present (%)	28 (28)	32 (22)
History of ulcer disease (%)	34 (34)	25 (17)*
Arthritic condition		
Osteoarthritis (%)	24 (24)	36 (25)
Rheumatoid arthritis (%)	68 (68)	98 (67)
Other (%)	8 (8)	12 (8)
H pylori status		
Positive (%)	70 (70)	72 (49)*
Negative (%)	30 (30)	74 (51)

*$p<0.01$.

diagnostic upper gastrointestinal endoscopy in our unit over the study period, and 246 of these satisfied the inclusion criteria and were therefore recruited into the study.

Some 142 of these patients (58%) had *H pylori* infection identified by histology and rapid urease test. At initial endoscopy, 59 patients had gastric ulcer alone, 39 duodenal ulcer alone, and two both duodenal and gastric ulcer. Table I shows the demographic and clinical characteristics of these patients compared with those without ulcers. Patients in both groups were comparable with respect to their age, sex, smoking and drinking habits, number of gastric or duodenal erosions, and type of arthritic condition, whereas a previous history of ulcer disease and *H pylori* infection was significantly more frequent in the ulcer than in the non-ulcer group. In contrast, no significant difference in the types, dose or length of NSAID intake was found between the two groups.

Site and size of gastric ulcers

Most ulcers (53 (83%) of 64) were located at the gastric antrum; seven (11%) occurred in the angulus area and four (6%) in another part of the corpus. The mean ulcer size, 6 mm (range 5–15) was similar in all three study groups.

Ulcer healing phase

Of the 70 patients with *H pylori* positive gastric or duodenal ulcer, 36 received omeprazole 20 mg twice daily for four to eight weeks and amoxycillin 1 g twice daily during the first two weeks, whereas the remaining 34 were treated with omeprazole 20 mg twice daily alone for four to eight weeks. All the 30 patients with *H pylori* negative gastric or duodenal ulcer received omeprazole 20 mg twice daily for four to eight weeks. Table II shows the healing rates for gastric and duodenal ulcers in the three different groups at four and eight weeks of treatment. There were no significant differences in the percentages of healing between the different groups of treatment for both gastric and duodenal ulcers.

H pylori infection was cured in 20 of 36 (56%) patients who received the antibiotic regimen and in none of those treated with omeprazole alone but did not significantly influence the healing process. Indeed, healing occurred in 14 of 20 patients (70%) who were cured of *H pylori* and in 14 of 17 (82%) patients with persistent infection.

Eleven patients with gastric ulcer and five with duodenal ulcer were still unhealed after eight weeks of treatment. However, in both groups the maximum ulcer diameter significantly reduced during treatment, thus suggesting a slow response rather than resistance to treatment. Indeed, for these gastric ulcers the mean diameter fell from 7 (before therapy) to 3·6 mm (at eight weeks) with a 49% reduction and, similarly, for the duodenal ulcers, it reduced from 6·2 to 3·5 mm corresponding to a reduction of 42%.

TABLE II H pylori *and healing of gastric and duodenal ulcers*

Population	*Healing at four weeks*	*Healing at eight weeks*	*CI 95%*
H pylori negative			
All ulcers (n=30) (%)	21/30 (70)	22/27 (81)	
Gastric ulcers (n=19) (%)	13/19 (68)	13/17 (76)	
Duodenal ulcers (n=11) (%)	8/11 (73)	9/10 (90)	−0·25, +0·11
H pylori positive (OM alone)			
All ulcers (n=34) (%)	25/34 (74)	28/32 (88)	
Gastric ulcers (n=23) (%)	15/23 (65)	19/21 (90)	−0·19, +0·20
Duodenal ulcers (n=11) (%)	10/11 (91)	10/11 (91)	
H pylori positive (OM+amoxycillin)			−0·09, +0·25
All ulcers (n=36) (%)	27/36 (75)	28/35 (80)	
Gastric ulcers (n=22) (%)	15/22 (68)	16/21 (76)	
Duodenal ulcers (n=14) (%)	12/14 (86)	12/14 (86)	

OM=omeprazole.

TABLE III H pylori *and recurrence of NSAID associated gastric or duodenal ulcer*

Population	*Cumulative recurrence at six months*	*CI 95%*
Group A (n=19) (%) (*H pylori* negative)	5/18 (27)	−0·48, +0·10
Group B (n=29) (%) (*H pylori* positive)	13/28 (46)	−0·36, +0·28
Group C (n=14) (%) (*H pylori* eradicated)	4/13 (31)	−0·17, +0·28

Ulcer recurrence phase

A total of 62 patients with healed peptic ulcer after eight weeks of acute antiulcer treatment entered this phase of the study. They were subdivided into three different groups according to their baseline *H pylori* status: 19 patients were *H pylori* negative (group A), 29 patients had persistent *H pylori* infection after short-term therapy (group B) whereas 14 patients had been cured of *H pylori* after the short-term phase (group C). Fifty nine patients completed the study correctly and were therefore evaluable: 18 in group A, 28 in group B, and 13 in group C. Three patients defaulted: one in group A failed to attend the three month endoscopic control, another in group B refused to have another endoscopy at six months, and one in group C did not adhere strictly to NSAID treatment. Table III shows the cumulative recurrence rate at six months for the three different groups. There were no significant differences between groups although a numerical trend towards a lower rate of recurrence was evident in *H pylori* negative and patients cured of *H pylori*

compared with those with persistent *H pylori* infection.

Discussion

Despite the fact that it is now well accepted that NSAIDs and *H pylori* have distinct pathogenic roles in peptic ulcer disease, the relation between these two factors remains unclear.[1] Current evidence seems to show that the presence of *H pylori* infection does not constitute a significant additional risk factor for NSAID gastropathy,[2 3 6 7 9–11] but it is suspected that NSAID use exacerbates *H pylori* ulcers and therefore the existence of a small group of patients whose ulcers results from an interaction between *H pylori* and NSAIDs could be hypothesised. This is indirectly supported by a study that showed that peptic ulcers in longterm NSAID users are more likely to develop in patients with *H pylori* positive duodenal erosions.[4]

Whether or not *H pylori* and NSAIDs have a synergistic relation in NSAID associated ulcers can be best considered by a prospective study evaluating the role of eradicating *H pylori* in the healing and recurrence of these ulcers such as reported here. In a large population of arthritic patients taking longterm NSAID treatment we found a prevalence of longterm gastric or duodenal ulceration of 36% (100 of 278). This is consistent with previous studies performed by us and by other authors reporting that NSAID associated peptic damage occurs in approximately 30% of NSAID users.[12 13] Fifty eight per cent of the patients studied were *H pylori* positive, which is what can be expected in a Western control population of similar age and in line with the data previously reported by others in arthritic patients.[3 7 14]

Most (70%) NSAID associated ulcers were associated with *H pylori* infection and antral gastritis; this concurs well with that seen by Shallcross *et al*[6] who showed that in ulcer patients taking NSAIDs, approximately three quarters are *H pylori* positive. However, the fact that as many as 30% of these ulcers occurred in uninfected patients strengthens the theory that these drugs exert an ulcerogenic effect that does not necessarily require the presence of *H pylori* or gastritis.[15]

One of the most important results of the ulcer healing phase of our study was that the cumulative healing at eight weeks, especially for gastric ulcers, was fairly poor (approximately 80%), considering that these patients were all receiving 40 mg omeprazole per day. This finding differs from that seen by Walan *et al*[16] in a multicentre trial comparing ranitidine with omeprazole in gastric ulcers, where omeprazole seemed more effective. However, in the second study NSAIDs were used simply on demand and not daily as for our patients. Our results, therefore, suggest that irrespective of the cause, the regular use of NSAIDs delays ulcer healing even with omeprazole treatment and not only under treatment with less potent agents (ranitidine) as already reported.[17 18]

Unlike non-NSAID associated peptic ulcers where healing is increased by *H pylori* eradication,[19] we found that *H pylori* infection has not a clear influence on healing of NSAID associated peptic ulcers. Indeed, healing rates of both duodenal and gastric ulcers did not significantly differ between patients with persistent *H pylori* infection and those in whom the organism had been eradicated. On the other hand, it should be emphasised that the *H pylori* cure rate obtained with omeprazole/amoxycillin in these patients (that is 56%) is comparable with that we and others have reported in non-NSAID related peptic ulcers using the same combination.[19–22]

In addition, we showed that *H pylori* eradication did not significantly reduce the frequency of recurrence in patients who continued to receive longterm NSAID treatment but stopped antiulcer medications. Unfortunately, the comparatively small number of ulcers (mainly duodenal ulcers) included in the longterm phase of our study does not completely exclude the possibility that *H pylori* infected patients taking NSAIDs would not have an increased risk of developing ulcer recurrence compared with *H pylori* negative patients; this is particularly true if we consider the existence of a numerical trend but not statistically significant in favour of a higher recurrence rate in infected compared with uninfected patients or those cured from the infection and the fact that we did not compare each one of the two common causes of ulcer with both together. The question could have been better tackled by including a third control population constituted by *H pylori* positive healed ulcers not receiving NSAID in the longterm phase.

However, the finding that eradication of *H pylori* was not associated with the cure of NSAID associated peptic ulcers suggest that the additional risk induced by the presence of *H pylori*, if any, tends to be small and eventually its eradication would be worthwhile only in a subset of patients receiving longterm NSAID treatment. The results of this study, if confirmed, may have important consequences in clinical practice as they suggest that the determination of *H pylori* status in a patient with NSAID associated gastric or duodenal ulcer does not provide any relevant additional information concerning ulcer healing; in contrast, it remains to be established, in further studies including larger numbers of *H pylori* infected and uninfected patients with NSAID associated peptic ulcers, whether a subset of ulcers caused by both agents does exist and whether these ulcers might benefit in the long run from *H pylori* eradication.

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