

Evidence for the essential role of *Helicobacter pylori* in gastric ulcer disease

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Abstract

Helicobacter pylori (*H pylori*) eradication heals chronic active type B gastritis and dramatically changes the natural history of duodenal ulcer disease. There are few data concerning the role of anti-*H pylori* treatment in gastric ulcer disease. A total of 83 patients presenting with *H pylori* positive active gastric ulcer disease were treated with omeprazole and antibiotics (amoxicillin, ciprofloxacin, roxithromycin) in seven different clinical protocols, each of which included the attempt to eradicate *H pylori* infection and to evaluate the post-therapeutic course of ulcer disease. The overall proportion of *H pylori* eradication was 67.9% (53 of 78 patients available for follow up). Best results were obtained with two week treatment regimens comprising omeprazole 20 mg twice daily and amoxicillin 500 mg four times a day or 1000 mg twice daily (eradication >80%). Eradication of *H pylori* speeds up ulcer healing, with a six week healing rate of 84.9% compared with 60% in patients with persistent *H pylori* infection ($p=0.0148$). In a subgroup of 11 patients with refractory ulcers, *H pylori* eradication ($n=10$) was associated with ulcer healing on continued acid suppression in nine cases. One male patient with chronic antral ulcer did not respond to treatment within the next six months (*H pylori* and ulcer persistence), and in one female patient a resistant body ulcer was identified as gastric lymphoma. Fifty patients with healed ulcers were followed up for one year. Patients with ($n=32$) and without ($n=18$) bacterial eradication had similar demographic and clinical characteristics. *H pylori* eradication was associated with a statistically significant reduction of ulcer recurrences (3.1 v 55.6% , $p<0.001$). This study concludes that *H pylori* eradication considerably changes the natural history of *H pylori* associated gastric ulcer disease. In addition, *H pylori* eradication speeds up ulcer healing and is associated with healing of previously refractory ulcers. Thus, treatment aimed at bacterial eradication should be considered in all patients with gastric ulcers severe enough to contemplate further treatment options.

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The dramatic effect of eradicating *Helicobacter pylori* (*H pylori*) on the medium term natural course of duodenal ulcer disease is sufficiently well reported by now.¹⁻⁴ Therefore, *H pylori* treatment is recommended for patients with relapsing duodenal ulcer disease.⁵ In contrast, there is still a considerable dearth of knowledge on the post-therapeutic course of gastric ulcer

disease. In 1992, a first controlled study showed that *H pylori* positive gastric ulcer disease will respond in exactly the same way as duodenal ulcer disease does.² To shed further light on this issue, we report our short and medium term experience in patients with *H pylori* associated gastric ulcers treated with omeprazole and antibiotics.

Methods

In the past three years, a total of 83 patients presenting with *H pylori* positive (proved by culture or histological examination, or both) active gastric ulcer disease participated in seven different, not randomised and uncontrolled clinical protocols, each of which included the attempt to eradicate *H pylori*. The studies were designed to evaluate the *H pylori* eradication potency of the various regimens and the post-therapeutic course of ulcer disease. A refractory ulcer was defined as an ulcer that did not heal within three months on conventional treatment with full dose H_2 blockers or 20 mg omeprazole.

Five patients missed the first follow up investigation. The remaining 78 patients (Table I) were treated with either omeprazole (40 mg every morning) and ciprofloxacin (500 mg twice daily) for one week ($n=11$), omeprazole (40 mg every morning) and amoxicillin (500 mg four times daily) for one week ($n=8$), omeprazole (40 mg twice daily) and amoxicillin (500 mg four times daily) for one week ($n=12$), omeprazole (20 mg twice daily) and amoxicillin (500 mg four times daily) for two weeks ($n=20$), omeprazole (20 mg twice daily) day 1-14 and amoxicillin (500 mg four times daily) day 8-14 ($n=9$), omeprazole (20 mg twice daily) and amoxicillin (1 g twice daily) for two weeks ($n=15$) or with omeprazole (2×20 mg twice daily) and roxithromycin (300 mg twice daily) for two weeks ($n=3$). After the study period of treatment had ended, patients were treated with 300 mg ranitidine in the evening ($n=70$) or 20 mg omeprazole ($n=8$) up to the six week follow up investigation. In patients with incomplete ulcer healing at that time ($n=18$) treatment was continued with 20 mg omeprazole every morning until complete ulcer healing proved by endoscopy was achieved.

Patients routinely had an endoscopy before treatment and after six weeks. Patients with incomplete ulcer healing after six weeks were reinvestigated by endoscopy at four week intervals. During the follow up without any anti-ulcer treatment, patients were instructed to report to the study physicians with all symptoms related to their gastric ulcer disease, who suggested and performed repeat endoscopies. All endoscopically proved ulcer relapses were then registered. Beside these 'on demand' visits and endoscopies,

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TABLE I Demographic and clinical characteristics of the study patients (total group; subgroups with regard to the treatment regimens: group I: one week ciprofloxacin 500 mg twice daily plus omeprazole 40 mg every morning; group II-VI: amoxicillin 500 mg four times daily for one week (II, III), two weeks (IV), day 8-14 (V) or 1 g twice daily two weeks (VI) plus omeprazole 40 mg every morning (II), 40 mg twice daily (III), 20 mg twice daily (IV-VI); group VIII: roxithromycin 300 mg twice daily plus omeprazole 20 mg twice daily)

| | Total group (n=78) | Group I (n=11) | Group II (n=8) | Group III (n=12) | Group IV (n=20) | Group V (n=9) | Group VI (n=15) | Group VII (n=3) |
|---------------------------|-----------------------|-------------------|-------------------|---------------------|--------------------|------------------|--------------------|--------------------|
| Median age (y) (range) | 65.5 (29-86) | 53 (39-82) | 66.5 (46-86) | 64 (44-82) | 59 (35-83) | 67 (52-78) | 69 (29-86) | 80 (74-86) |
| Men/women (n) | 44/34 | 6/5 | 3/5 | 9/3 | 14/6 | 3/6 | 8/7 | 1/2 |
| Ulcer history (n) | 55 | 7 | 6 | 10 | 14 | 5 | 12 | 1 |
| First ulcer (n) | 23 | 4 | 2 | 2 | 6 | 4 | 3 | 2 |
| Aspirin or NSAID use (n)* | 16 | 3 | 1 | 2 | 4 | 2 | 2 | 2 |
| Smoker (n) | 35 | 7 | 3 | 4 | 9 | 3 | 8 | 1 |
| Ulcer location: | | | | | | | | |
| Antral ulcer (n) | 55 | 9 | 5 | 10 | 14 | 6 | 9 | 2 |
| Body ulcer (n) | 21 | 2 | 3 | 2 | 6 | 3 | 4 | 1 |
| Antral+body ulcer (n) | 21 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |

*Regularly before ulcer treatment, NSAID=non-steroidal anti-inflammatory drug.

a routine clinical examination and an upper gastrointestinal endoscopy were performed in 50 patients (Table II) after one year.

During each endoscopy, four antrum and four body biopsy specimens were taken and analysed for *H pylori* colonisation by an urease test, microscopy of a methylene blue stained mucosal smear, specific culture, and histological tests after modified Giemsa stain as described elsewhere.⁶⁷ Eradication was defined as inability to show *H pylori* four weeks or more after discontinuation of study treatment by all four tests.

The age distribution of the 50 patients followed up over one year was statistically compared with the Wilcoxon rank sum test. All categorial data were statistically compared with the χ^2 test or with Fisher's exact test, when appropriate. All statistical calculations were two tailed. Differences were considered significant at a 5% probability value.

Results

Eighty three patients with *H pylori* positive gastric ulcers entered the study. Five patients were lost to follow up. Before treatment, *H pylori* colonisation of the gastric mucosa was detected by urease test in all patients, histologically in 82, microscopically after methylene blue staining in 74, and by culture in 67 patients.

The overall proportion of *H pylori* eradication was 67.9% (53 of 78 patients). In patients treated with amoxicillin plus omeprazole, there was a trend (without statistical significance) towards better *H pylori* eradication rates after a two week antibiotic course compared with one week amoxicillin treatment (85.7 v 69%, $p>0.05$) and in patients with body ulcers compared with those

TABLE II Demographic and clinical characteristics of 50 patients with gastric ulcer disease prospectively followed up for one year with regard to their Helicobacter pylori (HP) state after treatment

| | HP negative (n=32) | HP positive (n=18) | p |
|---------------------------|-----------------------|-----------------------|----|
| Median age (y) (range) | 65.5 (49-87) | 68 (36-82) | NS |
| Men/women (n) | 19/13 | 10/8 | NS |
| Aspirin or NSAID use (n)* | 2 | 0 | NS |
| Location of index ulcer: | | | |
| Antral ulcer (n) | 24 | 13 | NS |
| Body ulcer (n) | 8 | 5 | NS |

*Regular treatment during the follow up, NS=not significant ($p>0.05$); NSAID=non-steroidal anti-inflammatory drug.

who had antral manifestation of their ulcer disease (94.4 v 72.7%, $p>0.05$). Ciprofloxacin was obviously ineffective as dual treatment with omeprazole (eradication rate 18.2% (2/11 patients)). The group of patients treated with roxithromycin in addition to omeprazole (n=3) was too small for a meaningful subgroup analysis of the eradication potency.

Six weeks after the beginning of the study treatment, complete ulcer healing was endoscopically seen in 60 of 78 patients (76.9%). Healing was significantly achieved more frequently in patients with successful *H pylori* eradication (84.9 (45/53 patients) v 60% (15/25 patients), $p=0.0148$, Table III) despite similar distributions of ulcer size in these two group (median ulcer size: 11.5 mm v 12 mm).

The total study group comprised 11 patients with *H pylori* positive refractory gastric ulcers (six men, five women, median age 53 years, median pretreatment with H₂ blockers (n=9) or omeprazole (n=2) six months (range: 3->12 months)) who were treated with an omeprazole plus amoxicillin regimen. After eradication of *H pylori* (n=10) from the gastric mucosa eight ulcers healed within the next six (n=6) to 10 weeks (n=2). A giant prepyloric ulcer (diameter 5 cm) was completely epithelised after five months. In one female patient, the body ulcer

TABLE III Six week ulcer healing rates with regard to the Helicobacter pylori (HP) state after treatment (total study group: n=78 patients)

| | HP eradication (n) | HP persistence (n) |
|----------------------------------|-----------------------|-----------------------|
| Ulcer healing after 6 weeks (n) | 45 | 15 |
| Residual ulcer after 6 weeks (n) | 8 | 10 |
| | 45/53 (84.9%)* | 15/25 (60%) |

* $p=0.0148$ (χ^2 test).

TABLE IV Medium term clinical course of gastric ulcer disease with regard to the Helicobacter pylori (HP) state after treatment (patients data are listed in Table II)

| | HP negative (n=32) | HP positive (n=18) | p |
|---------------------------------|-----------------------|-----------------------|--------|
| Follow up (months) | 12 | 12 | |
| <i>H pylori</i> reinfection (n) | 2 | - | |
| Ulcer relapse (n) | 1 (3.1%)* | 10 (55.6%) | <0.001 |

*Patient receiving non-steroidal anti-inflammatory drugs, but HP negative.

was later identified as a gastric lymphoma and surgical resection was done. In a 40 year male patient with persistent *H pylori* colonisation of the gastric mucosa, a chronic antral ulcer did not heal during the follow up of six months.

We prospectively followed up 50 patients with healed ulcers for one year. *H pylori* infection was eradicated in 32 patients and persisted in 18 patients. These two groups of patients had similar demographic and clinical characteristics (Table II). *H pylori* infection was a strong predictor of ulcer recurrences. Within the follow up period 10 of 18 post-treatment *H pylori* positive patients (55.6%) and only one of 32 patients with *H pylori* eradication (3.1%) had an endoscopically proved ulcer relapse ($p < 0.001$, Table IV). The ulcer recurrence after bacterial eradication was associated with diclofenac treatment. The *H pylori* reinfection rate in the first year after eradication was 6.25% (two of 32 patients).

Discussion

A very strong association of *H pylori* infection of the gastric mucosa with chronic active type B gastritis and duodenal ulcer has been clearly established by now. The prevalence of *H pylori* in gastric ulcer disease varies more widely, but has most consistently been found to be around 70%.⁸ After exclusion of patients with known causes of their ulcer disease, *H pylori* infection has been detected with a much higher frequency of 96% in subgroups with idiopathic gastric ulcers, which is equivalent to the *H pylori* prevalence in duodenal ulcer disease.⁹ A strong association, however, is not a proof of causation. Therefore, additional evidence clearly pointing to a causal relation between *H pylori* infection and gastric ulcer disease has to be provided. A powerful argument for causation could be the effect of treatment interventions. Thus, elimination of the putative causal agent (*H pylori*) should prevent the illness (gastric ulcer).

Indeed, a truly dramatic change of the natural course of *H pylori* associated gastric ulcer disease after bacterial eradication was shown by our study. In patients with *H pylori* eradication, the one year ulcer relapse rate was one of 32 (3.1%), while failure to eradicate *H pylori* resulted in an endoscopically proved ulcer recurrence rate of 10 of 18 patients (55.6%, $p < 0.001$). The one year re-infection rate determined by this study was 6.25%. These findings are in accordance with those reported by Graham *et al.*,² who randomly treated 26 patients with *H pylori* positive gastric ulcers with either ranitidine alone or triple therapy plus ranitidine. The only factors in Graham's and our studies associated with ulcer recurrence were *H pylori* infection and the use of non-steroidal anti-inflammatory drugs. Preliminary data of the German gastric ulcer study support these findings.¹⁰ Thus, in addition to duodenal ulcer disease, *H pylori* eradication may also cure gastric ulcer disease. Therefore, it seems to be warranted that a treatment aimed at bacterial eradication should be considered in all patients with *H pylori* associated gastric ulcer disease severe enough to contemplate further treatment options (for

example, frequent ulcer relapses, ulcer complications).

In addition, our data clearly suggest that – similar to duodenal ulcers¹¹ – eradication of *H pylori* infection speeds up gastric ulcer healing, with a six week healing rate of about 85% as opposed to 60% in gastric ulcer patients with persistent *H pylori* colonisation. Moreover, most of the previously refractory gastric ulcers heal within six to 10 weeks after eradicating *H pylori* on continued acid suppression. Both findings lend additional support to the assumption that *H pylori* plays an important, probably causative part in the pathogenesis of the formerly 'idiopathic' gastric ulcer disease.

Up to now, the 'how' of anti-*H pylori* treatment is still a matter of debate. Bismuth salts and treatment by a single antibiotic fail to eradicate *H pylori* in a noteworthy proportion, but combined treatment regimens comprising bismuth salts and two antibiotics (for example, metronidazole plus amoxicillin or tetracycline) eradicated *H pylori* in most of the treated patients and is recommended as the treatment of first choice to eradicate *H pylori* in duodenal ulcer disease.¹² Patients treated with such an elaborate regimen, however, complained of considerable side effects, clearly endangering a sufficiently high compliance rate in routine clinical practice. Recent studies have suggested that omeprazole enhanced single antibiotic (for example, amoxicillin, clarithromycin) regimens combine a sufficient simplicity and low complications with high rates of bacterial eradication.¹³⁻¹⁵ In our hands, double dose omeprazole (20 mg twice daily) plus amoxicillin 2 g for two weeks is at least equally effective in eradicating *H pylori* in gastric as it is in duodenal ulcer disease. Therefore, it seems to be justified to recommend amoxicillin/omeprazole as the treatment of first choice to eradicate *H pylori* in *H pylori* related duodenal and gastric ulcer diseases. Triple therapy may then be reserved as 'second line' therapeutic option for patients with treatment failure of omeprazole plus antibiotics or with suspected penicillin hypersensitivity.

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