

ATROPHIC GASTRITIS AND *HELICOBACTER PYLORI* INFECTION IN PATIENTS WITH REFLUX ESOPHAGITIS TREATED WITH OMEPRAZOLE OR FUNDOPLICATION

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Abstract *Background.* *Helicobacter pylori* infection plays an important part in the development of atrophic gastritis and intestinal metaplasia, conditions that predispose patients to gastric cancer. Profound suppression of gastric acid is associated with increased severity of gastritis caused by *H. pylori*, but it is not known whether acid suppression increases the risk of atrophic gastritis.

Methods. We studied patients from two separate cohorts who were being treated for reflux esophagitis: 72 patients treated with fundoplication in Sweden and 105 treated with omeprazole (20 to 40 mg once daily) in the Netherlands. In both cohorts, the patients were followed for an average of five years (range, three to eight). After fundoplication, the patients did not receive acid-suppressive therapy. The presence of *H. pylori* was assessed at the first visit by histologic evaluation in the fundoplication group and by histologic and serologic evaluation in the omeprazole group. The patients were not treated for

H. pylori infection. Before treatment and during follow-up, the patients underwent repeated gastroscopy, with biopsy sampling for histologic evaluation.

Results. Among the patients treated with fundoplication, atrophic gastritis did not develop in any of the 31 who were infected with *H. pylori* at base line or the 41 who were not infected; 1 patient infected with *H. pylori* had atrophic gastritis before treatment that persisted after treatment. Among the patients treated with omeprazole, none of whom had atrophic gastritis at base line, atrophic gastritis developed in 18 of the 59 infected with *H. pylori* ($P < 0.001$) and 2 of the 46 who were not infected ($P = 0.62$).

Conclusions. Patients with reflux esophagitis and *H. pylori* infection who are treated with omeprazole are at increased risk of atrophic gastritis. (N Engl J Med 1996;334:1018-22.)

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HELICOBACTER PYLORI causes chronic gastritis in virtually all infected people. In many of them, this persistent inflammation ultimately leads to loss of the normal architecture of the gastric mucosa, with disappearance of the gastric glands and specialized cells. The resulting atrophic mucosa and intestinal metaplasia increase the risk of dysplasia and gastric cancer.^{1,2} The hypothetical link between *H. pylori* and gastric cancer has been substantiated by a variety of studies. A recent consensus committee of the World Health Organization concluded that there is sufficient evidence that *H. pylori* has an etiologic role in gastric carcinogenesis.³ The development of atrophic gastritis induced by persistent *H. pylori* infection is an essential step in the cascade of events leading to gastric cancer.

Proton-pump inhibitors such as omeprazole influence the normal acidic habitat of *H. pylori* and have direct activity in vitro against the bacteria. Nevertheless, monotherapy with these drugs does not lead to the eradication of *H. pylori*.⁴ On the contrary, the activity of corpus gastritis increases in *H. pylori*-infected patients treated with omeprazole.⁵⁻⁷ A similar effect has been observed during H₂-blocker therapy⁸ and after vagotomy,^{9,10} as well as during treatment of mice with omeprazole.¹¹

One hypothesis is that the increased inflammation increases the speed of atrophic changes of the gastric mucosa during acid-suppressive maintenance therapy. We conducted a prospective histologic follow-up study to compare the effects of omeprazole maintenance treatment and fundoplication in patients with gastroesophageal reflux disease who were infected or not infected with *H. pylori*.

METHODS

Patients

We studied two cohorts of patients in whom grade I to IV reflux esophagitis, defined according to the classification of Savary and Miller,¹² had been diagnosed by endoscopy.

The first cohort consisted of 109 Dutch patients who were enrolled between 1986 and 1991 in an open, compassionate-use study to evaluate the long-term efficacy and safety of omeprazole (Losec) in patients with severe reflux disease. Patients were included if they had endoscopically verified persistent esophagitis despite at least three months of treatment with an H₂ blocker in a dose equivalent to at least 600 mg of ranitidine daily. All eligible patients participated. During follow-up, three patients died of unrelated diseases and one emigrated. No other patients withdrew. The final analysis involved all biopsy specimens collected up to July 1994 from 105 patients (56 men and 49 women; mean age at the initial visit, 62 years [range, 16 to 83]). The patients were treated with 40 mg of omeprazole a day for 4 to 16 weeks until esophageal healing was endoscopically verified. Thereafter, maintenance treatment with 20 mg of omeprazole a day was started. The maintenance dose was raised to 40 mg in subjects with endoscopic evidence of a relapse. The mean follow-up period was five years (range, three to eight). During this treatment period, all patients underwent gastroscopy at one year and then every two years. During the pre-entry and follow-up endoscopies, four to six biopsy specimens were obtained with standard biopsy forceps from the area 10 cm below the cardia. The endoscopist was not made aware of previous histologic results. The study was performed in four referral centers in the Netherlands. The protocol was approved by the ethics committees of the participating hospitals and by the scientific review committee of the Free University Hospital,

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Amsterdam. The data on the efficacy of the omeprazole treatment obtained before April 1991 in 91 of these patients have been published previously.¹³

The second cohort consisted of 137 Swedish patients who were treated between 1987 and 1992 with either a Nissen–Rosetti or a Toupet fundoplication procedure for recurrent, endoscopically verified reflux esophagitis. They participated in a randomized study of the clinical efficacy and side effects of these two types of fundoplication. The surgical results for this cohort are described elsewhere.¹⁴ All patients underwent gastroscopy with biopsy sampling preoperatively. Postoperatively, this procedure was repeated after one year and then every two years, according to the routine described for the Netherlands study. During follow-up, two patients died of unrelated diseases and three were lost to follow-up. Seven had a relapse of reflux disease requiring acid-suppressive medication. The series of biopsy specimens was incomplete for 53 patients. Thus, the histologic analysis involved 72 patients (28 men and 44 women; mean age at the initial visit, 53 years [range, 25 to 73]) all treated in the same hospital. The mean postoperative follow-up time was five years (range, three to eight). None of these 72 patients were treated with acid suppressors after surgery. The study was performed in one academic hospital in Sweden and was approved by the local ethics committee. Before inclusion in the study, all patients from both cohorts gave informed oral consent that was witnessed by two physicians.

Histologic Methods

Five-micrometer sections stained with hematoxylin and eosin were used for standard histologic evaluation. *H. pylori* was detected by a modified silver-impregnation method.¹⁵ Sevier–Munger silver staining,¹⁶ and sometimes Grimelius's staining as well,¹⁷ was used to detect argyrophil neuroendocrine cells (mainly enterochromaffin-like [endocrine-like] cells). Different staining techniques were used with adjacent sections. Slides from various visits were scrambled and stained together. All specimens from both cohorts were graded by one pathologist according to the Sydney classification.¹⁸ The pathologist was not aware of the clinical and endoscopic data. The following items were evaluated separately: *H. pylori* colonization, presence of an acute inflammatory component (especially the amount of neutrophilic infiltration), presence of a chronic inflammatory component (especially the amount of lymphoplasmacytic infiltration), mucosal atrophy, intestinal metaplasia, and argyrophil-cell changes. All these items were scored from 0 to 3. For the first five items, the scale ranged from absent (0) to slight (1), moderate (2), and severe (3). For the argyrophil-cell pattern, the classification of Solcia et al. was used.¹⁹ The scores ranged from normal (0) to diffuse (1), linear (2), and micronodular (3) hyperplasia. The results were scored blindly with the use of patient codes.

The presence of *H. pylori* infection at the first visit was determined by histologic evaluation in the cohort undergoing fundoplication and by histologic and serologic evaluation in the cohort receiving omeprazole. In the case of discrepant results, the histologic evaluation was considered definitive, unless no bacteria were observed in a sample of atrophic mucosa with a positive serologic result (a finding regarded as a sign of past infection).²⁰ Anti-*H. pylori* IgG serum antibodies were detected in the patients in the omeprazole cohort with an enzyme-linked immunosorbent assay.²¹

Statistical Analysis

Statistical analysis was performed with Fisher's exact test, McNemar's test, Wilcoxon's rank-sum test, and one-way analysis of variance by the unpaired Student's t-test.²² Two-tailed P values smaller than 0.05 were considered to indicate statistical significance.

RESULTS

Omeprazole Cohort

At the initial visit, 46 of the 105 patients in the omeprazole cohort were negative for *H. pylori* and 59 were positive. The two groups did not differ in age (mean age in both groups, 62 years; $P=0.96$ by Student's t-test). No new infections were observed, nor did any

infected patient become negative for *H. pylori*. Before entry, all 46 *H. pylori*-negative patients had either no histologic signs of gastritis (39 patients) or only mild histologic signs (7 patients) (Table 1), and none had signs of atrophic gastritis (Table 2). After an average follow-up of five years, moderate-to-severe corpus gastritis had developed in only 2 (4 percent) of these 46 patients (Table 1). *H. pylori* infection could not be detected in them. In these two patients, histologic signs of mild-to-moderate atrophic gastritis developed concomitantly (Table 2). Thus, the prevalence of atrophic gastritis in this group increased from 0 to 4 percent ($P=0.62$ by McNemar's test), corresponding to an annual increase of 0.8 percent (95 percent confidence interval, 0.2 to 3 percent). The prevalence of argyrophil-cell hyperplasia remained stable at 8.7 percent (Table 3), and there was no intestinal metaplasia.

In the 59 *H. pylori*-positive patients, the prevalence of gastritis in the corpus increased during therapy from 59 to 81 percent ($P=0.007$ by McNemar's test), and the median gastritis score increased from mild to moderate ($P<0.001$ by Wilcoxon's rank-sum test) (Table 1). During follow-up, the prevalence of atrophic gastritis in these infected patients increased from 0 to 31 percent (18 patients; $P<0.001$ by McNemar's test) (Table 2), corresponding to an annual increase of 6.1 percent (95 percent confidence interval, 3.8 to 8.8 percent). Atrophic gastritis was present at one year in 8 of 59 patients (14 percent; 7 mild and 1 moderate), at three years in 17 of 59 patients (29 percent; 7 mild, 8 moderate, and 2 severe), at five years in 12 of 43 patients (28 percent; 3 mild, 7 moderate, and 2 severe), and at seven years in 6 of 15 patients (40 percent; 1 mild, 1 moderate, and 4 severe). Figure 1 shows a Kaplan–Meier survival curve of these results.

The development of atrophy during follow-up was associated with significantly higher gastritis scores at the one-year visit ($P=0.008$ by Wilcoxon's rank-sum test). The prevalence of intestinal metaplasia increased from 1.7 percent (one patient) to 5.1 percent (three patients)

Table 1. Activity of Corpus Gastritis in 105 Patients with Gastroesophageal Reflux Disease Treated with Omeprazole Maintenance Therapy, According to *H. pylori* Status.*

CORPUS GASTRITIS AT BASE-LINE VISIT	CORPUS GASTRITIS AT LATEST FOLLOW-UP VISIT				TOTAL
	NONE	MILD	MODERATE	SEVERE	
	number of patients (percent)				
<i>H. pylori</i> -negative					
None	36	2	1	0	39 (85)
Mild	4	2	0	1	7 (15)
Total	40 (87)	4 (9)	1 (2)	1 (2)	46 (100)
<i>H. pylori</i> -positive					
None	7	5	9	3	24 (41)
Mild	3	10	9	3	25 (42)
Moderate	0	2	3	0	5 (8)
Severe	1	1	3	0	5 (8)
Total	11 (19)	18 (31)	24 (41)	6 (10)	59 (100)

*The mean follow-up time for the *H. pylori*-negative patients was 5.1 years (range, 2.7 to 7.7); for the *H. pylori*-positive patients, it was 5.2 years (range, 2.8 to 7.4). Because of rounding, percentages do not all total 100.

($P=0.61$ by McNemar's test). At the initial visit, argyrophil-cell hyperplasia was present in 9 of the 59 infected patients (15 percent). Six of the nine had a regression of preexistent diffuse or linear hyperplasia during follow-up. Sixteen others, however, had progression to micronodular argyrophil-cell hyperplasia (Table 3). Thus, the prevalence of argyrophil-cell hyperplasia increased from 15 to 31 percent ($P=0.08$ by McNemar's test), corresponding to an annual increase of 3.0 percent (95 percent confidence interval, 1.4 to 5.4 percent). The prevalence of micronodular argyrophil-cell hyperplasia increased from 3 to 31 percent ($P<0.001$ by McNemar's test). No argyrophil-cell dysplasia or neoplasia was observed.

The development of atrophic gastritis and that of argyrophil-cell hyperplasia were strongly associated with *H. pylori* infection ($P<0.001$ by Fisher's exact test; odds ratios, 9.9 [95 percent confidence interval, 2.2 to 45] and 35 [2.3 to 606], respectively).

Fundoplication Cohort

At the initial visit, 41 of the 72 patients in the fundoplication cohort were negative for *H. pylori* and 31

Table 2. Corpus Atrophic Gastritis in 105 Patients with Gastroesophageal Reflux Disease Treated with Omeprazole Maintenance Therapy, According to *H. pylori* Status.

CORPUS ATROPHIC GASTRITIS AT BASE-LINE VISIT	CORPUS ATROPHIC GASTRITIS AT LATEST FOLLOW-UP VISIT				TOTAL
	NONE	MILD	MODERATE	SEVERE	
number of patients (percent)					
<i>H. pylori</i> -negative					
None	44	1	1	0	46 (100)
Total	44 (96)	1 (2)	1 (2)	0	46 (100)
<i>H. pylori</i> -positive					
None	41	7	7	4	59 (100)
Total	41 (69)	7 (12)	7 (12)	4 (7)	59 (100)

Table 3. Argyrophil-Cell Hyperplasia in 105 Patients with Gastroesophageal Reflux Disease Treated with Omeprazole Maintenance Therapy, According to *H. pylori* Status.*

HYPERPLASIA AT BASE-LINE VISIT	HYPERPLASIA AT LATEST FOLLOW-UP VISIT				TOTAL
	NONE	DIFFUSE	LINEAR	MICRONODULAR	
number of patients (percent)					
<i>H. pylori</i> -negative					
None	39	2	0	1	42 (91)
Diffuse	2	0	0	0	2 (4)
Micronodular	1	0	0	1	2 (4)
Total	42 (91)	2 (4)	0	2 (4)	46 (100)
<i>H. pylori</i> -positive					
None	35	0	0	15	50 (85)
Diffuse	4	0	0	1	5 (8)
Linear	2	0	0	0	2 (3)
Micronodular	0	0	0	2	2 (3)
Total	41 (69)	0	0	18 (31)	59 (100)

*Because of rounding, percentages do not all total 100.

Table 4. Activity of Corpus Gastritis in 72 Patients with Gastroesophageal Reflux Disease Treated with Fundoplication, According to *H. pylori* Status.*

CORPUS GASTRITIS AT BASE-LINE VISIT	CORPUS GASTRITIS AT LATEST FOLLOW-UP VISIT				TOTAL
	NONE	MILD	MODERATE	SEVERE	
number of patients (percent)					
<i>H. pylori</i> -negative					
None	41	0	0	0	41 (100)
Total	41 (100)	0	0	0	41 (100)
<i>H. pylori</i> -positive					
None	0	5	1	1	7 (23)
Mild	7	7	1	0	15 (48)
Moderate	1	4	0	2	7 (23)
Severe	1	0	1	0	2 (6)
Total	9 (29)	16 (52)	3 (10)	3 (10)	31 (100)

*The mean follow-up time for the *H. pylori*-negative patients was 5.1 years (range, 3.1 to 7.6); for the *H. pylori*-positive patients, it was 5.0 years (range, 2.8 to 7.2). Because of rounding, percentages do not all total 100.

were positive. These two groups did not differ in age. Preoperatively, none of the 41 *H. pylori*-negative patients had histologic signs of active gastritis (Table 4) or atrophic gastritis (Table 5). After an average follow-up of five years, none of these patients had inflammation or atrophy of the gastric mucosa (Tables 4 and 5), and none had become infected with *H. pylori*.

Among the 31 *H. pylori*-positive patients, the baseline scores for corpus gastritis were negative in 7 (23 percent), mild in 15 (48 percent), and moderate to severe in 9 (29 percent) (Table 4). At the last follow-up visit, these scores were negative in 9 (29 percent), mild in 16 (52 percent), and moderate to severe in 6 patients (19 percent). Thus, the prevalence and severity of gastritis in the corpus did not change during follow-up (for prevalence, $P=0.71$ by McNemar's test; for severity, $P=0.72$ by Wilcoxon's rank-sum test). During the postoperative follow-up, the prevalence of atrophic gastritis in these infected patients remained stable at 3 percent, corresponding to an annual increase of 0 percent (97.5 percent confidence interval, 0 to 2.2 percent) (Table 5).

When the two cohorts were compared, no significant increase in the prevalence of atrophic gastritis was found with either treatment in the absence of *H. pylori* infection. However, among the infected patients, atrophic gastritis did not develop after fundoplication but did develop in 18 patients (31 percent) during omeprazole therapy ($P<0.001$ by Fisher's exact test; odds ratio, 28; 95 percent confidence interval, 1.6 to 484) (Fig. 1).

DISCUSSION

In recent years, acid-suppressive therapy has become of pivotal importance in the treatment of gastroesophageal reflux disease. Because of the high relapse rate, patients often receive maintenance therapy. Therefore, the long-term consequences of the treatment are relevant. In the past, attention was specifically given to hypergastrinemia and argyrophil-cell hyperplasia as side effects of treatment with proton-pump inhibitors. However, although elevated fasting serum gastrin levels

Table 5. Corpus Atrophic Gastritis in 72 Patients with Gastroesophageal Reflux Disease Treated with Fundoplication, According to *H. pylori* Status.

CORPUS ATROPHIC GASTRITIS AT BASE-LINE VISIT	CORPUS ATROPHIC GASTRITIS AT LATEST FOLLOW-UP VISIT				TOTAL
	NONE	MILD	MODERATE	SEVERE	
<i>number of patients (percent)</i>					
<i>H. pylori</i> -negative					
None	41	0	0	0	41 (100)
Total	41 (100)	0	0	0	41 (100)
<i>H. pylori</i> -positive					
None	30	0	0	0	30 (97)
Mild	0	1	0	0	1 (3)
Total	30 (97)	1 (3)	0	0	31 (100)

(100 to 400 ng per liter) and focal linear hyperplasia of argyrophil cells occur regularly during treatment,^{13,23} complications, in particular carcinoid formation, have not to our knowledge been observed. Argyrophil-cell hyperplasia occurs predominantly in patients who have atrophic gastritis. Some investigators have regarded this as a normal consequence of aging and have considered the rate of progression to atrophic gastritis during omeprazole therapy to be no different from the rate in controls.^{23,24} However, the control study referred to by these investigators was based on a single cohort of patients with gastric ulcers.^{25,26} Such patients have reduced acid output, and the majority are infected with *H. pylori*. Therefore, these patients are not representative.

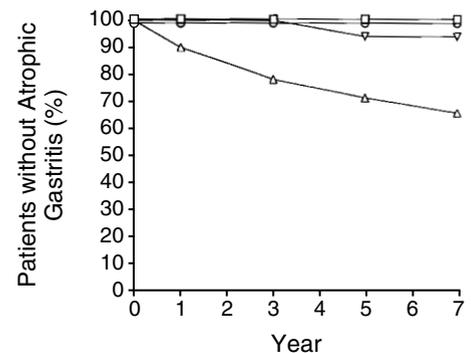
We investigated the role of *H. pylori* in the development of atrophic gastritis during acid-suppressive maintenance therapy. This agent is a frequent cause of chronic active gastritis and has an important role in the development of atrophic gastritis and intestinal metaplasia, conditions that substantially increase the risk of gastric cancer.

Our results demonstrate that gastritis is increased during long-term omeprazole therapy and suggest that this increase may have important clinical consequences. In the fundoplication cohort, the prevalence of atrophic gastritis was not significantly greater among patients with *H. pylori* infection than among those without such infection. The upper limit of the 95 percent confidence interval for the annual increase in the prevalence of atrophic gastritis was approximately 2 percent. In the omeprazole cohort, atrophic gastritis developed among noninfected patients at a similar rate each year (0.8 percent; 95 percent confidence interval, 0.2 to 3 percent). However, among *H. pylori*-infected patients, the annual rate of development of atrophic gastritis was 6.1 percent (95 percent confidence interval, 3.8 to 8.8 percent); signs of atrophy developed in approximately one third of the infected patients after an average of five years of treatment.

The comparison between the cohorts suggests that *H. pylori*-infected patients are at considerably higher risk than uninfected patients for the development of atrophic gastritis during profound acid suppression. We

are aware that aspects of this comparison are problematic and that there may be various confounding variables. This was not a randomized study. The patients in the two cohorts were treated in different hospitals. Nevertheless, the biopsy specimens were obtained according to the same routine. All the specimens were processed at the same laboratory and analyzed by one pathologist. The mean age in the two cohorts differed. The fundoplication group was followed for an average of five years, during which the mean age of the cohort increased from 53 to 58 years. The omeprazole group was followed for five years, during which the mean age of the cohort increased from 62 to 67 years. Atrophic gastritis results from long-lasting gastritis, and the risk of atrophy may increase exponentially at older ages. However, we believe it unlikely that this moderate difference in age completely accounts for the observed discrepancy in the progression of atrophy.

Our results are in accordance with those of other studies. Four cohort studies focused on people without any specific disease or treatment.^{20,27-29} Three did not give separate data for *H. pylori*-positive and *H. pylori*-negative patients.²⁷⁻²⁹ They followed 137 people for 25 years,²⁷ 1422 people for 5 years,²⁸ and 142 people for 6 years²⁹; the annual increase in the prevalence of atrophic gastritis ranged from 1.2 to 3.3 percent. A fourth study, in which 107 people were followed for 11.5 years, specified results according to *H. pylori* status.²⁰ Among 49 people without infection, the prevalence of atrophic gastritis increased by 0.3 percent annually (95 percent confidence interval, 0.04 to 1.2 percent). Among 58 people with *H. pylori* infection, the annual increase was 1.8 percent (95 percent confidence interval, 1.0 to 2.9 percent). Four other studies provided data on people with conditions affecting acid secretion,



No. AT RISK		0	1	3	5	7
Fundoplication						
<i>H. pylori</i> -negative (□)	41	41	41	29	6	
<i>H. pylori</i> -positive (○)	30	30	30	23	4	
Omeprazole						
<i>H. pylori</i> -negative (▽)	46	46	46	34	14	
<i>H. pylori</i> -positive (△)	59	59	52	35	9	

Figure 1. Kaplan-Meier Curves for the Probability of Survival without Atrophic Gastritis, According to Treatment and *H. pylori* Status.

The number of patients at risk for atrophic gastritis is shown for various time points.

reporting on 39 patients with gastric ulcer disease followed for seven years,²⁵ 23 patients with peptic ulcer disease followed for three years after vagotomy,³⁰ 74 patients with peptic ulcer disease followed for five years during omeprazole maintenance treatment,²³ and 195 patients with gastroesophageal reflux disease followed for one to two years during maintenance treatment with omeprazole.³¹ None provided separate results for subjects with and those without *H. pylori* infection. The annual increase in the prevalence of atrophic gastritis ranged from 3.8 to 8.7 percent.

In conclusion, long-term acid-suppressive therapy with omeprazole is not associated with the eradication of *H. pylori* in infected patients. However, such treatment is associated with a persistent increase in inflammation of the corpus and with the development of atrophic gastritis and argyrophil-cell hyperplasia in patients who are positive for *H. pylori*, but not in those who are negative. Future studies of the long-term effects of acid suppression should focus primarily on *H. pylori* rather than on gastrin and argyrophil cells. We suggest that patients with reflux esophagitis who require profound acid-suppressive maintenance therapy should be studied to determine whether they are infected with *H. pylori*. If they are infected, therapy to eradicate *H. pylori* should be considered. It remains to be seen, however, whether such a strategy can prevent atrophy and argyrophil-cell hyperplasia in these patients.

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