PROTAGONIST

Should we eradicate *Helicobacter pylori* before long term antireflux therapy?

J Labenz

Helicobacter pylori infection invariably induces chronic active gastritis which can give rise to serious consequences such as peptic ulcer and gastric malignancies. Generally accepted indications for treatment are *H pylori* associated peptic ulcer disease and early stages of low grade mucosa associated lymphoid tissue lymphoma of the stomach. In contrast, treatment of *H pylori* in patients with gastro-oesophageal reflux disease (GORD) requiring long term treatment with a proton pump inhibitor (PPI) has not yet been put on a scientific footing. In support of this indication in patients with GORD and no associated ulcer disease, the following theoretical arguments might be advanced.

In contrast, treatment of *H pylori* in patients with gastro-oesophageal reflux disease (GORD) requiring long term treatment with a proton pump inhibitor (PPI) has not yet been put on a scientific footing. In support of this indication in patients with GORD and no associated ulcer disease, the following theoretical arguments might be advanced.

(1) *H pylori* is involved in the pathogenesis of GORD so that eradication of this organism would lead to an improvement in, or even elimination of, GORD.

(2) Eradication of *H pylori* infection is associated with an improvement in the effectiveness of treatment with PPI in patients with GORD.

(3) PPI treatment of GORD carries a higher risk in patients with *H pylori* infection than in *H pylori* negative patients, and this risk can be eliminated by eradication of the infection.

(1) *H pylori* is involved in the pathogenesis of GORD so that eradication of this organism would lead to an improvement in, or even elimination of, GORD

H pylori infection interferes with the regulation of gastric acid secretion. The effect of eradication therapy on acid secretion is closely linked to the type of gastritis before treatment. In the case of duodenal ulcer patients with antrum dominant gastritis, acid hypersecretion normalises within some months, while in the case of gastric ulcer patients with more severe corpus gastritis, acid hyposecretion disappears within a few weeks.¹ It is conceivable, although not yet unequivocally proved in patients with confirmed GORD, that treatment of *H pylori* can lead to an improvement in, or the healing of, GORD (at least in individual cases). To date, the literature contains two well

designed clinical studies on the treatment of *H pylori* in patients with GORD; one study was unable to show any influence of eradication on the natural course of GORD over a period of one year and the other study suggested a benefit of eradication therapy.^{2,3} In addition, patients with peptic ulcer frequently experience an improvement or even resolution of heartburn with eradication of *H pylori* and healing of ulceration.⁴ Nevertheless, a major role of *H pylori* infection in the pathogenesis of GORD is unlikely.⁵ This evaluation is based on epidemiological time trends, case control studies, and some but not all eradication studies, suggesting a protective rather than an aggravating effect of the infection with respect to GORD.

(2) Eradication of *H pylori* infection is associated with an improvement in the effectiveness of treatment with PPIs in patients with GORD

H pylori increases the pH elevating effect of PPIs.⁶ The ammonia generated by *H pylori*,⁷ and probably also aggravation of corpus gastritis under PPIs, play a decisive role in this phenomenon.⁸ Presumably due to this effect, short term studies suggested that PPIs work better in patients with GORD and *H pylori* infection than in uninfected GORD patients.⁹ In a multivariate analysis of long term omeprazole studies, *H pylori* proved to be a predictor of the success of treatment¹⁰ while long term cohort studies argue against a clinically relevant effect of *H pylori* with respect to the required maintenance dose of omeprazole.^{11,12}

(3) PPI treatment of GORD carries a higher risk in patients with *H pylori* infection than in *H pylori* negative patients, and this risk can be eliminated by eradication of the infection

Numerous studies have, without exception, shown that in *H pylori* infected patients receiving PPI treatment, the severity of corpus gastritis in terms of chronicity and activity increases, while in the antrum gastritis improves.¹³ It may be assumed that the increase in gastritis severity also leads to an increase in mutagenic risk. The extent to which the shift in gastritis per se actually leads to an increase in the risk of gastric cancer remains unclear. Interestingly, the resulting corpus dominant type of gastritis is found disproportionately more frequently in patients with early gastric cancer—as has been shown in a large case control study¹⁴—and in relatives of gastric carcinoma

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patients.¹⁵ Also, many patients with early gastric cancer, in particular of the diffuse type, do not have atrophy or intestinal metaplasia, and Hattori did not find precursor lesions in the margins of gastric microcarcinomas.¹⁶ Deterioration of corpus gastritis also facilitates the development of atrophy.¹¹ In a proportion of those infected, *H pylori* gastritis itself led to the development of atrophy and intestinal metaplasia, lesions that are recognised precursors of gastric cancer.¹⁷ The important question whether PPI treatment accelerates the development of atrophy cannot be answered definitively. The annual incidence of atrophy appears to be increased from 1–3% to 4–8% whenever a state of reduced acid secretion is present.¹⁸ In 1996, Kuipers *et al* published a report in which they compared two cohorts of GORD patients.¹⁹ One of these cohorts, in the Netherlands, received long term treatment with omeprazole while the other cohort, in Sweden, underwent antireflux surgery. During follow up, the annual incidence of atrophy was 6.1% of *H pylori* positive patients receiving omeprazole while atrophy rarely developed in *H pylori* positive patients after surgery and in *H pylori* negative patients of both cohorts. The study has been criticised on methodological grounds. However, in other long term studies of PPI treatment, the incidence of atrophy in *H pylori* infected patients was consistent with Kuiper's study.^{11–20} In 1999, Lundell *et al* reported the eagerly awaited results of a randomised study comparing omeprazole maintenance therapy with antireflux surgery in patients with GORD.²¹ During the three year follow up, they did not find a significant excess of atrophy development in *H pylori* positive patients receiving omeprazole. However, this study too had several methodological flaws and reanalysing the data adds support to Kuipers' study rather than disproving it.^{21–23} At this point in time, we do not know whether eradicating *H pylori* infection before long term treatment with a PPI actually reduces the risk of atrophy development. We do however know from a randomised controlled study that cure of infection prevents deterioration of the corpus gastritis.²⁶

In conclusion, treatment of *H pylori* infection can, in individual cases, lead to improvement in reflux symptoms although a clinically relevant effect on the natural history of GORD has not been proved with certainty. It is conceivable that in individual cases the dose of PPI needs to be adjusted following eradication of the organism. Simply ignoring the *H pylori* infection in patients with GORD and on long term PPI treatment inevitably leads to aggravation of corpus gastritis and probably also to acceleration of the development of atrophy. Both a more severe corpus gastritis and atrophy are indicators of an elevated risk of gastric cancer. Treatment with omeprazole can be used without risk for at least 10 years, in patients with *H pylori* infection also. However, whether this also applies to longer periods of treatment is as yet unclear. Presumably, a randomised controlled study investigating this long term safety aspect will never be carried out.

Reasons for eradicating *H pylori* before long term antireflux therapy

- Eradication of *H pylori* may lead to improvement of reflux symptoms.
- Eradication of *H pylori* may help to prolong the disease free interval in patients with GORD.
- PPIs aggravate *H pylori* gastritis in the corpus and promote the development of atrophy.
- *H pylori* eradication before initiating PPI long term treatment cures *H pylori* gastritis.
- *H pylori* eradication should be offered to patients who will probably require PPI treatment for more than 10 years.

As our current knowledge suggests that apart from the side effects of treatment no clinically relevant disadvantages are to be expected by eradicating infection in patients with GORD, the cautious physician will search for and eradicate *H pylori*, in particular in younger GORD patients requiring long term PPI treatment. Although this approach heals antral and corpus gastritis, this recommendation is not evidence based. It should however be pointed out that in other areas, chronic infections (for example, hepatitis C) associated with only a potential for fatal outcome are currently being treated with side effects associated expensive drugs despite a lack of evidence based proof of a long term beneficial effect of the treatment on the prognosis of the disease.

- 1 Iijima K, Ohara S, Sekine H, *et al*. Changes in gastric acid secretion assayed by endoscopic gastrin test before and after *Helicobacter pylori* eradication. *Gut* 2000;**46**:20–6.
- 2 Axon ATR, Bardhan K, Moayyedi P, *et al*. Does eradication of *Helicobacter pylori* influence the recurrence of symptoms in patients with symptomatic gastro-oesophageal reflux disease?—A randomised double blind study. *Gastroenterology* 1999;**116**:A117.
- 3 Schwizer W, Thumshirn M, Dent J, *et al*. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001;**357**:1738–42.
- 4 Malfertheiner P, Veldhuyzen van Zanten S, Dent J, *et al*. Does cure of *Helicobacter pylori* infection induce heartburn? *Gastroenterology* 1998;**114**:A212.
- 5 Labenz J, Malfertheiner P. *Helicobacter pylori* in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997;**41**:277–80.
- 6 Pantoflickowa D, Blum AL, Bercik P. Omeprazole: *Helicobacter pylori* makes thee greater yet. *Gut* 1999;**44**:448–9.
- 7 Bercik P, Verdú E, Armstrong D, *et al*. The effect of ammonia on omeprazole-induced reduction of gastric acidity in subjects with *Helicobacter pylori* infection. *Am J Gastroenterol* 2000;**95**:947–55.
- 8 Gillen D, Wirz A, Neithercut WD, *et al*. *Helicobacter pylori* infection potentiates the inhibition of gastric acid secretion by omeprazole. *Gut* 1999;**44**:468–75.
- 9 Holtmann G, Cain CR, Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999;**117**:11–16.
- 10 Carlsson R, Bate C, Dent J, *et al*. Does *H. pylori* infection influence the response to treatment with acid inhibition in patients with gastroesophageal reflux disease (GERD)? *Scand J Gastroenterol* 1997;**32**(suppl 224):56.
- 11 Klinkenberg-Knol EC, Nelis F, Dent J, *et al*. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;**118**:661–9.

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- 12 Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, *et al.* *Helicobacter pylori* and the efficacy of omeprazole for gastroesophageal reflux disease. *Am J Gastroenterol* 1999;**94**:884–7.
- 13 Stolte M, Meining A, Schmitz JM, *et al.* Changes in *Helicobacter pylori*-induced gastritis in the antrum and corpus during 12 months of treatment with omeprazole and lansoprazole in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998;**12**:247–53.
- 14 Meining A, Bayerdörffer E, Müller P, *et al.* Gastric carcinoma risk index in patients infected with *Helicobacter pylori*. *Virchows Arch* 1998;**432**:311–14.
- 15 Meining A, Bayerdörffer E, Stolte M. *Helicobacter pylori* gastritis of the gastric cancer phenotype in relatives of gastric carcinoma patients. *Eur J Gastroenterol Hepatol* 1999;**11**:717–20.
- 16 Hattori. Development of adenocarcinoma of the stomach. *Cancer* 1996;**57**:1528–34.
- 17 Kuipers EJ, Uytterlinde AM, Pena AS, *et al.* Long-term sequelae of *Helicobacter pylori* gastritis. *Lancet* 1995;**345**:1525–8.
- 18 Kuipers EJ, Lee A, Klinkenberg-Knol EC, *et al.* Review article: the development of atrophic gastritis—*Helicobacter pylori* and the effects of acid suppressive therapy. *Aliment Pharmacol Ther* 1995;**9**:331–40.
- 19 Kuipers EJ, Lundell L, Klinkenberg-Knol EC, *et al.* Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;**334**:1018–22.
- 20 Eissele R, Brunner G, Simon B, *et al.* Gastric mucosa during treatment with lansoprazole: *Helicobacter pylori* is a risk factor for argyrophil-cell hyperplasia. *Gastroenterology* 1997;**112**:707–17.
- 21 Lundell L, Miettinen P, Myrvold HE, *et al.* Lack of effect of acid suppression therapy on gastric atrophy. *Gastroenterology* 1999;**117**:319–26.
- 22 Kuipers EJ, Klinkenberg-Knol EC, Meuwissen SGM. Omeprazole and accelerated onset of atrophic gastritis. *Gastroenterology* 2000;**118**:239–40.
- 23 McColl KEL, Murray L, Gillen D. Omeprazole and accelerated onset of atrophic gastritis. *Gastroenterology* 2000;**118**:239.
- 24 Pounder RE, Williams MP. Omeprazole and accelerated onset of atrophic gastritis. *Gastroenterology* 2000;**118**:238–9.
- 25 Stolte M, Meining A. Omeprazole and accelerated onset of atrophic gastritis. *Gastroenterology* 2000;**118**:242–3.
- 26 Schenk BE, Kuipers EJ, Nelis F, *et al.* Effect of *Helicobacter pylori* eradication on chronic gastritis during omeprazole therapy. *Gut* 2000;**46**:615–21.

ANTAGONIST

Should we eradicate *Helicobacter pylori* before long term antireflux therapy?

J W Freston

Patient management recommendations that might become health care policy should be based on the highest level of evidence. The evidence supporting the recommendation to “test and treat” for *Helicobacter pylori* infection before starting long term antireflux treatment falls well short of this standard. This recommendation arose directly from the report by Kuipers and colleagues¹ in 1996 that the prevalence of corpus glandular atrophy increased during chronic omeprazole treatment in patients infected with *H pylori*. We were pleased to have another reason to eradicate *H pylori*; the prevailing wisdom was that no *H pylori* should go unpunished. This aggressive approach has been challenged, particularly in the case of patients with gastro-oesophageal reflux disease (GORD). Approximately 42% of adults in the USA suffer from GORD.² Nearly 7% experience heartburn on a daily basis,³ making them potential candidates for proton pump inhibitor (PPI) therapy and, therefore, testing for *H pylori* infection. Apart from the obvious economic and antimicrobial resistance implications, growing evidence indicates that *H pylori* infection protects against the complications of GORD, including Barrett’s oesophagus, dysplasia, and oesophageal adenocarcinoma.⁴ The death rate for oesophageal cancer now exceeds that of gastric cancer in males in the USA.⁵ Given these considerations, the evidence supporting the test

and treat approach should be substantial. Instead, it is weak

Uncontrolled studies

The study of Kuipers *et al* is often misrepresented as a controlled trial. It began as an uncontrolled descriptive study of corpus biopsy changes during chronic omeprazole treatment in *H pylori* infected GORD patients living in the Netherlands. After the fact, the authors identified a group of Swedish patients treated with antireflux surgery and used their gastric biopsy data for comparison. Lack of randomisation to an appropriate control group introduced bias. Omeprazole treated patients were older than surgery patients by an average of nine years. Glandular atrophy increases with age: its prevalence is twice as high in *H pylori* infected subjects aged 57–68 years than in those aged 46–56 years.⁶ A comparison of glandular atrophy in two different populations may also be significant because of the influence genetic, socioeconomic, nutritional, and dietary factors have on the development of atrophy. The most troubling aspect of Kuipers’ study was a total absence of atrophy at baseline in the omeprazole cohort combined with the absence of any increase in atrophy over a period of five years in the surgery cohort. These findings differ from all other studies that show at least some atrophy in populations

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with *H pylori* gastritis and at least some progression over time if the infection is untreated (see below). This combination of unusual findings was responsible for the difference reaching statistical significance.

Other uncontrolled studies have yielded conflicting results: some reported an increase in atrophy in infected GORD patients treated with PPIs⁷⁻⁹ while others did not.¹⁰⁻¹¹ The recent study of Geboes and colleagues¹¹ from the Netherlands was particularly revealing because they found no increase in the prevalence of atrophy after five years of PPI therapy in a Dutch population that was similar to the PPI cohort in Kuipers' study. This issue clearly cannot be resolved on the basis of uncontrolled studies.

Controlled trials

Lundell and colleagues¹² randomised GORD patients to either chronic omeprazole treatment or antireflux surgery. They found no significant difference between the groups in the prevalence of glandular atrophy. The US FDA reviewed the data linking PPI therapy to glandular atrophy. The review included the studies of Kuipers *et al* and Lundell *et al*, as well as the unpublished randomised controlled trials of PPI maintenance therapy for 12–60 months. The comparator groups were placebo, ranitidine, and antireflux surgery. The prevalence of atrophy did not differ significantly between the groups. The FDA concluded that PPIs did not accelerate the development of gastric atrophy, intestinal metaplasia, or cancer.¹³ The FDA also concluded that PPI labels should not contain a recommendation to test and treat before undertaking PPI therapy.

Commentary on quality of evidence

Among their myriad shortcomings, uncontrolled trials are particularly limited in their ability to discern causes of time dependent changes, such as glandular atrophy. Only the study of Lundell *et al* and those analysed by the FDA were controlled. They must be given more credence, despite their shortcomings, which are dwarfed by those of uncontrolled trials. Kuipers' study framed a hypothesis which has now been tested and rejected on the basis of controlled trials. The effect of PPIs on glandular atrophy is either non-existent or so trivial that it does not deserve the attention the issue continues to receive. In any case, the evidence hardly justifies a broad recommendation to test and treat the huge pool of GORD patients who will benefit from long term PPI therapy.

Reasons for not eradicating *H pylori* before long term antireflux therapy

- Patient management recommendations, especially those that might become health care policy, should be based on the highest level of evidence.
- The recommendation to eradicate *H pylori* infection before embarking on long term antireflux therapy is based on an uncontrolled observation that corpus glandular atrophy appeared to increase during PPI therapy. Evidence from controlled trials does not support the observation. As the effect is either non-existent or so small as to be clinically meaningless, the recommendation is inappropriate.

- 1 Kuipers EJ, Lundell L, Klinkenberg-Knol EC, *et al*. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;**334**:1018–22.
- 2 Szarka LA, Locke GR. Practical pointers for grappling with GORD. Heartburn gnaws at quality of life for many patients. *Postgrad Med* 1999;**105**:1–11.
- 3 Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: Incidence and precipitating factors. *Dig Dis* 1976;**21**:953–6.
- 4 Vicari JJ, Peek RM, Falk GW, *et al*. The seroprevalence of *cagA*-positive *Helicobacter pylori* strains in the spectrum of gastroesophageal reflux disease. *Gastroenterology* 1998;**115**:50–7.
- 5 Greenlee RT, Hill-Harmon MB, Murray T, *et al*. Cancer Statistics, 2001. *CA Cancer J Clin* 2001;**51**:51–6.
- 6 Hackelsberger A, Günther T, Schultze V, *et al*. Role of aging in the expression of *Helicobacter pylori* gastritis in the antrum, corpus, and cardia. *Scand J Gastroenterol* 1999;**34**:138–43.
- 7 Eissele R, Brunner G, Simon B, *et al*. Gastric mucosa during treatment with lansoprazole: *Helicobacter pylori* is a risk factor for argyrophil cell hyperplasia. *Gastroenterology* 1997;**112**:707–17.
- 8 Berstad AE, Hatlebakk JG, Maartmann-Moe H, *et al*. *Helicobacter pylori* gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. *Gut* 1997;**41**:740–7.
- 9 Klinkenberg-Knol EC, Nelis F, Dent J, *et al*. Long-term omeprazole treatment in resistant gastroesophageal reflux diseases: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;**118**:661–9.
- 10 Freston JW, Rose PA, Heller CA, *et al*. Safety profile of lansoprazole: The US clinical trial experience. *Drug Safety* 1999;**20**:195–205.
- 11 Geboes K, Dekker W, Mulder CJJ, *et al*. Long-term lansoprazole treatment for GORD: Clinical efficacy and influence on gastric mucosa. *Aliment Pharmacol Ther* 2001 (in press).
- 12 Lundell L, Miettinen P, Myrvold HE, *et al*. Lack of effect of acid suppression therapy on gastric atrophy. *Gastroenterology* 1999;**117**:319–26.
- 13 Freston JW. Long-term acid control and proton pump inhibitors: Interactions and safety issues in perspective. *Am J Gastroenterol* 1997;**92**(suppl):51S–7S.

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