

Aggressive Acid Control: Minimizing Progression of Barrett's Esophagus

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Presentation Summary

Barrett's esophagus (BE) is a change in the cellular structure of the lower esophagus believed by many to be caused by frequent acid exposure. The condition is troublesome because of a tendency toward cell proliferation, dysplastic transformation, and cancerous changes within the lesions. It is speculated that the pronounced increase in esophageal adenocarcinoma during the past 25 years may be attributable to acid reflux and associated BE. Strict acid control may cause lesion regression in these patients. However, pH monitoring to confirm adequate acid control is essential, and more than 1 drug may be needed to achieve adequate acid control and manage many patients. More research is needed to determine whether aggressive acid control reduces the dysplasia and cancer risk associated with BE.

can progress over time and as the associated metaplastic epithelium becomes dysplastic, there is a tendency toward more severe dysplasia. In a smaller percentage of cases, cancer may develop.² There is little evidence that any treatment for BE will reduce the risk of cancer associated with the disorder, but recent studies suggest that BE progression can be slowed with appropriate therapy.

Reducing Reflux in BE

One challenge to treating BE is that patients often do not recognize the presence of reflux. In 1 study, only two thirds of BE patients reported heartburn or other symptoms after a Bernstein test, but all patients with reflux esophagitis had a positive reaction. In addition, esophagitis patients experienced symptoms within approximately 2 minutes of starting the acid infusion, whereas BE patients who did react had no symptoms for an average of more than 6 minutes.³ This suggests a decreased acid sensitivity of the metaplastic epithelium in BE, which contributes to patients being unaware of reflux occurring.

Decreased acid sensitivity in these patients makes adequate reflux treatment difficult, based on my experience with pH monitoring. Five consecutive BE patients underwent 24-hour intra-gastric and intraesophageal

The incidence of adenocarcinoma of the esophagus among white males in the United States has risen from 1 case per 100,000 person-years annually in 1975 to almost 5 cases per 100,000 in 1995, while the incidence of esophageal squamous cell carcinoma has decreased slightly.¹ Many experts believe that the adenocarcinoma increase is a result of Barrett's esophagus (BE) secondary to gastroesophageal reflux disease (GERD). There is evidence that BE

pH monitoring to evaluate the effect of the proton pump inhibitor (PPI) omeprazole. To eliminate GERD symptoms, omeprazole was given 20 mg once daily to 3 patients, twice daily to 1 patient, and 3 times daily to 1 patient. Symptoms were eliminated in all; however, 4 of the patients continued to have asymptomatic nocturnal acid exposure (pH decreased to < 4), indicating acid recovery in the stomach and reflux into the esophagus.⁴ These results indicate that BE patients treated with a PPI dose adequate to control symptoms may still have continuing reflux.

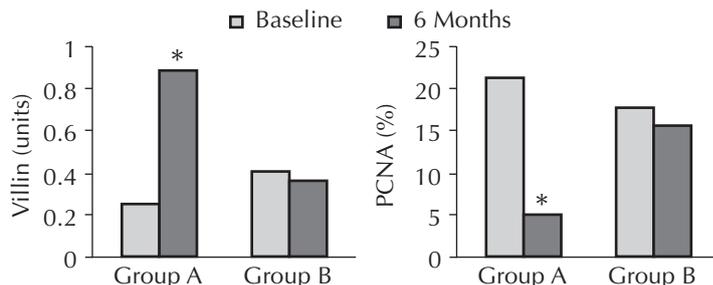
Regression. Additional studies have aimed to determine whether more aggressive PPI treatment could reduce the extent of BE. One study reported on 13 patients with areas of long-segment BE greater than 3 cm who were treated with 60 mg of the PPI lansoprazole daily for 5.7 years.⁵ Using 24-hour pH monitoring to evaluate the resulting degree of acid control and associated changes in the BE area, the study found that all patients showed healing of esophagitis. Eight of the patients with normal pH results showed insignificant changes in

BE length, and 5 patients had no change in BE length and continued to have abnormal reflux despite treatment. The researchers concluded that the control of acid exposure achieved was inadequate to produce BE regression.⁵ However, 9 of the patients showed development of islands of squamous mucosa.

An ex vivo organ cell culture study using endoscopic biopsy specimens from both BE patients and those without BE showed that an acid pulse with a pH of 3.5 introduced into the culture media enhanced BE cell proliferation and delayed cell maturation during the subsequent 24 hours. When culture media pH was maintained at a neutral level, there was no such cell proliferation enhancement in the BE patients. Furthermore, the detrimental effects of the acid pulse were greater than those seen when cultured tissue was subjected to continuous acid exposure. Duodenal and normal esophagus biopsy specimens did not react adversely to acid exposure as did BE tissue. These results imply that acid control in BE patients must be strong enough to produce continuous control and eradicate any acid pulses.⁶

In a more recent study, 42 BE patients with GERD symptoms controlled with 15- to 60-mg lansoprazole daily were divided into 2 groups based on pH monitoring results: 26 with “normalized” acid exposure (group A) and 16 with continued abnormal reflux despite treatment (group B).⁷ Biopsy specimens were evaluated at baseline and after 6 months of treatment for levels of proliferating cell nuclear antigen ([PCNA] as an indicator of cell proliferation) and villin unit expression (as a manifestation of cell differentiation). In group A, where acid was well controlled, a significant decrease from baseline was found in the level of PCNA, and an increase was noted from baseline in villin unit

Figure 1. Effects of Acid Suppression with Lansoprazole in Patients with BE (N = 42)



*P < 0.01. Group A = 26 had “normalized” acid exposure; Group B = 16 had abnormal reflux continued. BE = Barrett’s esophagus; PCNA = proliferating cell nuclear antigen.

Source: Reference 7.

expression. But in group B, without adequate acid control, there was no change (Figure 1). Nocturnal recumbent reflux was present in 18 of the 42 patients (almost all in group B) despite treatment.⁷

Management of BE

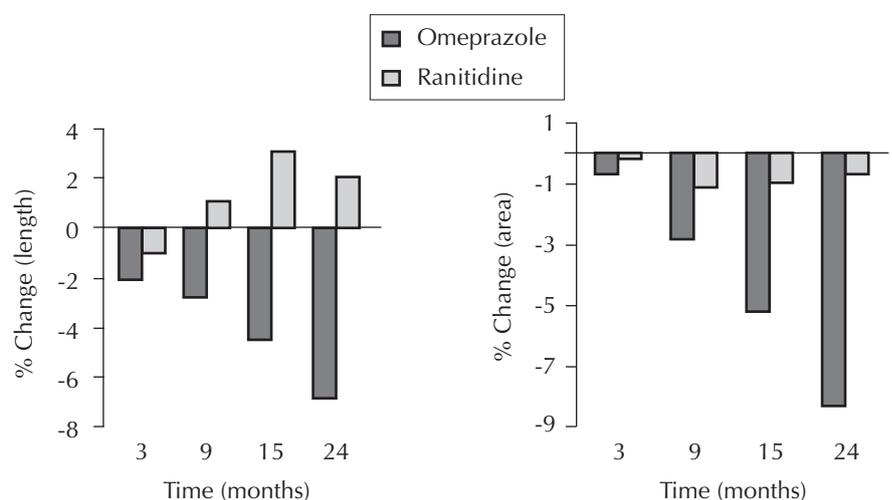
There is now evidence that more aggressive acid control may cause histologic regression of BE lesions. This was observed in a study of 53 BE patients randomized prospectively to receive for 24 months either 150 mg of the histamine₂ receptor antagonist (H₂RA) ranitidine or 40 mg of omeprazole twice daily for symptom control. All patients became asymptomatic with treatment, but 24-hour pH monitoring at 3 months showed that an average reflux rate of 9.4% was still present in patients taking ranitidine compared with a 0.1% average in patients taking omeprazole.⁸ Most importantly, at 24 months, BE length and area were decreased by 7% and 8.5%, respectively, in the patients taking omeprazole, while BE length increased by 2% and BE area decreased by less than 1% in patients taking ranitidine (Figure 2). The decreased lesion size seen with omeprazole therapy started to appear by the first endoscopic evaluation at 3 months after treatment began and improved throughout the 24-month study period. None of the patients showed changes consistent with dysplasia development during aggressive acid control treatment.⁸ These results indicate that if acid is adequately controlled, in this case with very high-dose PPI administration, the result may be a progressive decrease in BE epithelium over time.

Our group has documented a 1- to 3-cm linear regression of BE in 9 study patients after

approximately 3 years of treatment.⁹ Eight patients are male and their ages range from 44 to 72 years. Follow up to date ranges from 13 to almost 48 months and is ongoing. Two of the patients receive a PPI twice daily, and 7 receive the additional treatment of ranitidine once daily at bedtime. Squamous cell islands are present in 5 of the patients, and no dysplasia has developed in these patients during follow up. Total acid control was achieved with titrated PPI doses and confirmed with pH monitoring.

Recommended Approach. Many earlier studies in BE patients used higher than appropriate acid-control rates for patients on treatment and considered the treatment effective if GERD symptoms were eliminated. Patients included in these studies often showed treated upright and supine reflux rates between 4% and 8%.^{3,4} Basing therapy on medication needed to control symptoms is not

Figure 2. Relative Changes in Length and Surface Area of BE



BE = Barrett's esophagus.
Source: Reference 8.

adequate in BE patients. The upper limit of normal reflux for an upright pH study in an untreated patient should be approximately 6% with about 1% recumbent reflux. Patients taking a PPI twice daily should have very little to no upright reflux (< 1.0%) or recumbent reflux (< 0.5%) on 24-hour pH monitoring for treatment to be considered effective. Nocturnal acid reflux is particularly problematic in these patients. Although a PPI dose may be taken at night, reflux pulses occur. This is probably because of regeneration of proton pumps at a fairly active rate. PPIs work best when followed with a meal that will stimulate the parietal cells, and they are not as effective when given at bedtime. Also, nocturnal acid secretion is histamine dependent and, when present, may be better controlled with an H₂RA at night.

Initial therapy in BE patients should be administration of a PPI twice daily to achieve the aforementioned acid control. After 1 month, gastric and esophageal 24-hour pH monitoring should be conducted to determine the effect achieved in terms of acid control. Defining biopsies to identify dysplasia in the presence of healed esophagitis should also be performed at this time. Most patients will require maintenance treatment with a PPI twice daily. However, some may be maintained with a once daily PPI that can be given either in the morning or at night. If pH monitoring indicates incomplete acid control, a PPI twice daily with the addition of an H₂RA at bedtime should be tried to eliminate nocturnal acid secretion. If this strategy fails to produce complete acid control, a PPI 3 times a day with an H₂RA at night may be considered. In all cases, repeated pH monitoring is needed after medication adjustments to confirm acid control.

Conclusion

Although evidence indicates that aggressively treating BE is unlikely to reduce the risk of cancer, studies have noted it may be possible to retard the progression of BE with appropriate therapy. Recent studies suggest that complete acid control is the key to effectively managing these patients and to potentially achieving BE regression. More long-term study is needed to determine whether aggressive acid control can also slow BE progression to dysplasia and cancer.

... REFERENCES ...

1. **Devesa SS, Blot WJ, Fraumeni JF Jr.** Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049-2053.
2. **Hameeteman W, Tytgat G, Houthoff H, van den Tweel J.** Barrett's esophagus: Development of dysplasia and adenocarcinoma. *Gastroenterology* 1989;96:1249-1256.
3. **Johnson DA, Winters C, Spurling TJ, Chobanian SJ, Cattal EL Jr.** Esophageal acid sensitivity in Barrett's esophagus. *J Clin Gastroenterol* 1987;9:23-27.
4. **Katzka DA, Castell DO.** Successful elimination of reflux symptoms does not insure adequate control of acid reflux in patients with Barrett's esophagus. *Am J Gastroenterol* 1994;89:989-991.
5. **Sharma P, Morales TG, Bhawacharyya A, Garewal HS, Sampliner RE.** Dysplasia in short-segment Barrett's esophagus: A prospective 3-year follow up. *Am J Gastroenterol* 1997;92:582-585.
6. **Fitzgerald RC, Omary MB, Triadafilopoulos G.** Dynamic effects of acid on Barrett's esophagus. An ex vivo proliferation and differentiation model. *J Clin Invest* 1996;98:2120-2128.
7. **Ouat-Lascar R, Fitzgerald RC, Triadafilopoulos G.** Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. *Gastroenterology* 1999;117:327-335.
8. **Peters FT, Ganesh S, Kuipers EJ, et al.** Endoscopic regression of Barrett's oesophagus during omeprazole treatment: A randomised double blind study. *Gut* 1999;45:489-494.
9. **Srinivasan R, Katz P, Ramakrishnan A, Castell D.** Effect of maximal acid reflux control on Barrett's esophagus. *Am J Gastroenterol* 1999;94:260.