REVIEW ARTICLE

Drugs 2005; 65 Suppl. 1: 75–82
0012-6667/05/0001-0075/$39.95/0

Potent Gastric Acid Inhibition in the Management of Barrett's Oesophagus

Ángel Lanas

Gastroenterology Service, Clinical University Hospital, Zaragoza, Spain

Abstract

Barrett's oesophagus is the consequence of excessive and prolonged gastro-oesophageal reflux. The therapeutic objectives in Barrett's oesophagus include the reduction of gastro-oesophageal reflux in order to relieve symptoms and the prevention of the biologic progression to adenocarcinoma. The first objective may be achieved with standard proton pump inhibitor (PPI) therapy, which is the base of the medical therapy in this type of patients, but this therapy has been found not to be associated with normalization of the intraluminal pH of the oesophagus in many patients with Barrett's oesophagus. This condition seems to be necessary in order to reduce mucosal cell proliferation in some studies. Therefore, it has been proposed that patients with Barrett's oesophagus need profound acid inhibition with high-dose PPI. This therapeutic approach provides symptom relief, but there is no direct evidence that it is associated with Barrett's oesophagus regression or progression to adenocarcinoma. Nevertheless, recent and preliminary data suggest that long-term PPI therapy may reduce the risk of developing disease progression. Profound acid inhibition is also combined with endoscopy ablative or resection therapy in patients with Barrett's oesophagus. This therapeutic approach should be still regarded as experimental and more data are needed before its therapeutic role in patients with Barrett's oesophagus is established.

1. The Problem: Definition and Magnitude

The transformation of the normal squamous epithelium of the oesophagus into a columnar epithelium with intestinal metaplasia (histologic evidence of goblet cells) as a consequence of chronic gastro-oesophageal reflux is known as Barrett's oesophagus (BE).[1] The metaplastic epithelium usually begins at the oesophago-gastric union and extends proximally to varying lengths, which give rise to the denominations of 'ultra-short' BE (some millimetres), 'short' BE (up to 3 cm) and 'long' BE (longer than 3 cm from the beginning of the gastric mucosal folds).[1]

Up to 6–14% of the patients with gastro-oesophageal reflux disease develop BE.[1] The prevalence of the diagnosis of BE has increased quite considerably in past years. A recent Spanish study[2] shows that the raw incidence of this diagnosis has increased 19-fold, from 1.5/100 000 individuals per year in the period 1976–1978 to 28.5/100 000 in 1999–2001. Over that period, the age-adjusted and gender-adjusted rate increased by a factor of 15.7, while the number of fibrogastroscopies only increased by a factor of 1.9. The raw prevalence of BE diagnoses increased from 12/100 000 individuals per year in 1985 to 155/100 000 in 2001. The prevalence of short-segment BE (<3 cm) was 99/100 000 in

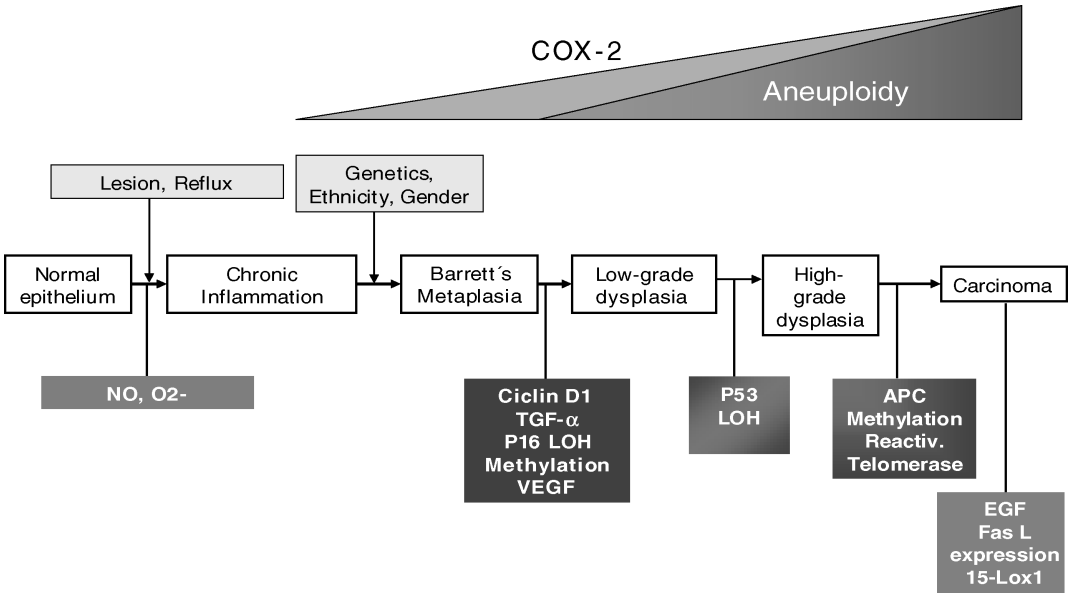

Fig. 1. Diagram of the morphologic sequence and molecular changes associated with the progression of gastro-oesophageal reflux disease that lead to the development of Barrett's oesophagus and carcinoma. Details presented in the text and in reference.[3] **APC** = activated protein C; **COX-2** = cyclooxygenase-2; **EGF** = epidermal growth factor; **LOH** = loss of heterozygosity; **TGF** = transforming growth factor; **VEGF** = vascular endothelial growth factor.

2001.[2] The dramatic increase in the diagnosis of BE observed in recent years can be ascribed to a number of factors, among them the better identification of cases with a short metaplastic segment and possibly an increase in gastro-oesophageal reflux disease (GORD) among the population.

Besides the need to provide relief and therapy for the reflux-derived symptoms that the patients have, the greatest problem the gastroenterologists are faced with is the pre-malignant quality of this lesion. The incidence of oesophagus adenocarcinoma has increased quite considerably in the Western world since 1970. The cause of this increase is believed to be directly related to the increased incidence of GORD and of BE, as 0.5–1% of the latter develop adenocarcinoma.[1,2] The sequence includes the presence of long-lasting gastro-oesophageal reflux that induces the transformation of the squamous epithelium into a columnar one with intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma and finally invasive carcinoma.[3] This progression is accompanied by a series of genetic changes that may condition the irreversibility of the process and that includes the inactivation of tumour-suppressor genes through loss of heterozygosity, mutation and/or hypermethylation of the gene promoters.[3] Among the early phenomena occurring, mutation of the *p16* gene and overexpression of cyclooxygenase-2 have been described, the latter correlating in frequency and intensity with the neoplastic progression, together with cellular hyperproliferation and apoptosis inhibition. Figure 1 summarises some of the molecular and biologic events observed in the course of the progression from a normal oesophagus to BE and adenocarcinoma.

Degrees of evidence and recommendation are rated according to the criteria established in the Introduction of this issue.

2. Therapeutic Objectives in BE

As the aforementioned sequential progression is initiated by gastro-oesophageal reflux, therapy in BE is aimed at two fundamental aspects.

2.1 Reducing Gastro-oesophageal Reflux in Order to Relieve Symptoms

The means for achieving this objective do not differ from those used in GORD, although the presence of the metaplastic lesion (and particularly of long-segment BE) is considered to represent a severe complication and to require a more potent control of reflux and a more exhaustive follow-up of the patient.

2.2 Preventing the Biologic Progression to Adenocarcinoma

In preventing the progression of BE to adenocarcinoma a number of measures and interventions are applied, both pharmacological and endoscopic or surgical. However, the assessment of this objective is more difficult, as the natural history of the disease is not well understood and the proportion of patients with BE who eventually develop a carcinoma is small.

3. Therapeutic Interventions

The present-day management of the patient with BE constitutes a progressive sequence of therapeutic interventions based on pharmacological therapy (table I). As the presence of BE is considered to represent an important and severe complication of GORD, it is assumed that treatment with proton pump inhibitors (PPIs) is the therapy of first choice in the pharmacological management. Its efficacy in symptom control is unquestioned.[4] There is, however, a number of important issues that may restrict PPI therapy in this disease, which shall now be addressed (table II).

3.1 Is Symptomatic Control in the Patient with BE Associated with Normalisation of the Intra-oesophageal pH?

Recent data show that the suppression of symptoms is frequently not accompanied by normalisation of the intra-oesophageal pH (level of evidence 1a). This fact reinforces the idea of the necessity to monitor the intra-oesophageal pH in BE patients taking PPIs in order to optimise therapy to the most adequate doses, without relying solely on the presence or absence of symptoms (degree of recommendation B).

A study of a small series of 50 patients with GORD but without BE has shown that 50% of the patients taking standard doses of PPIs continued to present an abnormal intra-oesophageal acid reflux despite total control of the symptoms derived from the gastro-oesophageal reflux.[5] In another study on patients with long-segment BE it was demonstrated that 50% of them were taking PPI doses that were lower than the standard recommended ones (omeprazole 20 mg/day) for symptom control, and this correlated well with an inadequate normalisation of intragastric pH. An increase in the omeprazole dose to 20 mg b.i.d., or even t.i.d., normalised the symptoms and the pH-metry profile in most patients, but not in all (30% of the patients still had abnormal reflux using the standard dosage). Furthermore, symptomatic control also did not guarantee the normalisation of the intragastric pH.[6] Similar conclusions were arrived at in another study, in which only 35% of the patients in a short series of long-segment BE evidenced complete normalisation of the acid or bile reflux under PPI therapy despite having achieved symptomatic control.[7] Finally, in another study of a short series of patients with BE it was shown that most of them did not achieve normalisation of the intra-oesophageal pH despite being asymptomatic under therapy with omeprazole 40 mg/day or 80 mg/day. The fundamental cause was night-time reflux, and a good correlation was demonstrated between intragastric pH and reflux.[8]

3.2 Is Therapy with PPIs or Anti-reflux Surgery Associated with a Reduction in the Length of the BE Segment and/or with Progressive Normalisation of BE?

The more classical studies pointed out that neither PPI therapy nor anti-reflux surgery were associated with regression of the length of the BE

Table I. Current therapeutic management of Barrett's oesophagus

1. Basal therapy — reduction of gastro-oesophageal reflux
   - (a) Pharmacologic — high doses of PPIs; in general the dose of the PPI should be increased to the standard dose b.i.d. It may be advisable to perform 24-h pH monitoring if appropriate control of oesophageal intraluminal acid is to be confirmed
   - (b) Anti-reflux surgery — in younger patients or in those with good *ad vitam* prognosis. Nissen's fundoplication, or Collins' technique if the oesophagus is short
2. Follow-up — early detection of dysplasia or adenocarcinoma
   - (a) Multiple biopsies (every 1–2 cm, four quadrants)
   - (b) If no dysplasia is detected, endoscopic revision at 3-year intervals (at 5-year intervals in some recommendations)
   - (c) If low-grade dysplasia is present, repeat endoscopy and biopsies after 6 months; if still present, repeat after 1 year. If no longer present, return to standard follow-up at 3-year intervals
   - (d) If high-grade dysplasia is present
     - (i) Confirmation by two pathologists
     - (ii) If necessary, repeat endoscopy and perform new biopsies
     - (iii) If no surgical contraindication, exeresis of the oesophagus
     - (iv) If there is a contraindication, endoscopic ablative therapy
3. Endoscopic therapies — elimination of metaplastic or dysplastic tissue
   - (a) Basis therapy — high doses of PPIs (pH-metry monitorisation advisable)
   - (b) Types of therapy
     - (i) Thermal:
       Multipolar electrocoagulation
       Argon coagulation
       Laser therapy — Nd-YAG, argon, potassium titanile phosphate
       Thermal probe
     - (ii) Mechanical:
       Endoscopic mucosal resection
       Biopsy with Jumbo forceps
     - (iii) Photodynamic:
       5-Aminolevulinic acid
       Haematoporfirin derivates
       Sodium porphymers
     - (iv) Other:
       Cryotherapy, ultrasound
4. Drug therapies in chemoprevention — prevention of oesophageal cancer
   - (a) Basis therapy — high doses of PPIs (pH-metry monitorisation advisable)
   - (b) Chemoprevention (experimental)
     - (i) Non-steroidal anti-inflammatory drugs and aspirin
     - (ii) Selective cyclooxygenase-2 inhibitors (Coxibs)
     - (iii) Anti-oestrogens
     - (iv) Free radical scavengers (superoxide dismutase)

PPI = proton pump inhibitor.

segment.[9,10] This concept has been recently questioned by some surgical teams but it must presently be assumed that, although partial results are achieved, BE does not regress or disappear with these measures (level of evidence 2b).

A recent follow-up study of 91 patients shows that over one-third of the BE patients evidence regression/histologic improvement after anti-reflux surgery, and that this fact depends on factors such as the extent of the BE segment and the duration of follow-up after surgery.[11,12] Finally, some studies have shown that intensive PPI therapy is associated with partial regression of the intestinal metaplasia.[13,14] It is in fact not infrequent in clinical practise to observe the development of smaller or larger islands of squamous epithelium in the area of columnar epithelium after PPI therapy.

Table II. Summary of the levels of evidence and degrees of recommendation in the pharmacologic management of Barrett's oesophagus (BE) in answering the questions posed.

Question 1: Is symptomatic control in the patient with BE associated with normalisation of the intra-oesophageal pH?
Answer: Symptomatic control with anti-secretory drug therapy does not guarantee normalisation of intra-oesophageal pH (level of evidence 1a)
Recommendation: It is advisable to give double doses and/or monitor intra-oesophageal pH in order to assess the therapeutic efficacy (degree of recommendation B)
Question 2: Is therapy with PPIs or anti-reflux surgery associated with a reduction in the length of the BE segment and/or with progressive normalisation of BE?
Answer: Therapy with PPIs or anti-reflux surgery does not achieve elimination of BE. Intensive PPI therapy or effective surgery achieve partial regression of uncertain significance (level of evidence 2b)
Question 3: Is therapy with potent acid inhibition associated with prevention of the development of adenocarcinoma in BE?
Answer: Potent acid inhibition or reduction of gastro-oesophageal reflux do not avoid the need for endoscopic surveillance, when indicated, in the patient with BE (level of evidence 2b)
Recommendation: Potent acid inhibition therapy or anti-reflux surgery do not avoid the need for endoscopic surveillance, when indicated, in the patient with BE (degree of recommendation B)
Question 4: Is profound acid inhibition a necessity in the management of patients with BE undergoing endoscopic ablation of the metaplastic segment?
Answer: Potent acid inhibition in association with ablative therapy seems to reduce/delay the recurrence rate of BE after ablation or resection of the metaplastic tissue (level of evidence 2b)
Recommendation: Ablative therapy in BE has not yet demonstrated long-term efficacy and should be performed at specialised centres. It requires maintaining the patients under effective anti-reflux therapy and strict periodic follow-up surveillance (degree of recommendation B)
Question 5: Which is the medical (drug) therapy of first choice for patients with BE?
Answer: The drug therapy of first choice for patients with BE is PPI therapy at effective doses (level of evidence 1a)
Recommendation: It is advisable for the patient with BE to receive therapy with double doses of the selected PPI. It is advisable to monitor the therapeutic efficacy with pH-metry (degree of recommendation B)

PPI = proton pump inhibitor.

3.3 Is Therapy with Potent Acid Inhibition Associated with Prevention of the Development of Adenocarcinoma in BE?

Profound acid inhibition or reduction of gastro-oesophageal reflux do not prevent the progression of BE, but may reduce the risk of its development (level of evidence 2b).

Oesophageal exposure to acid is associated with increased proliferation and reduction of apoptosis in the cells of BE.[15,16] The degree of cell proliferation in biopsy specimens of BE decreases after adequate PPI therapy, a phenomenon not observed in oesophageal specimens from patients without adequate control of intragastric acidity.[17,18] The clinical significance of these observations is uncertain, but they do lend support to the idea of the necessity for profound acid inhibition in the patient with BE.

Some authors have suggested a greater efficacy of anti-reflux surgery as compared with anti-secretory therapy in the prevention of cancer deaths in patients with BE,[19,20] but this has not been confirmed in other studies.[8,21] A recent Australian study points out that the risk of high-grade or low-grade dysplasia development correlates with the delay in initiating PPI therapy after the diagnosis of BE.[22]

3.4 Is Profound Acid Inhibition a Necessity in the Management of Patients with BE Undergoing Endoscopic Ablation of the Metaplastic Segment?

As the bulk of the available evidence shows that gastro-oesophageal reflux control through medical therapy or anti-reflux surgery does not prevent the possibility of progression to cancer in the BE epithelium, new preventive therapeutic strategies have been developed over the past few years, the main one among them being endoscopic ablative therapy.[23] The possibilities of chemoprophylaxis with cyclooxygenase-2 inhibitors, acetylsalicylic acid, non-steroidal anti-inflammatory drugs or

oestrogens are also being explored.[23] All the therapeutic modalities mentioned have as a common denominator the association of potent acid inhibition with PPIs, as the probability of recurrence of Barrett's oesophagus increases with persistence of reflux (level of evidence 2b).

Endoscopic therapy is at present the most and best developed therapeutic modality, its aim being the elimination or ablation of the metaplastic mucosa, with later re-epithelisation with the squamous epithelium in an acid-free environment. Its major indication is the patient with dysplasia, especially severe dysplasia confirmed at follow-up, with contraindications for elective surgery.[23] The progress and improvement of the endoscopic techniques may in the future lead to changes in this clinical approach, so that the endoscopic therapy might expand its indications, in part displacing surgery for the management of severe dysplasia and intramucosal cancer, or even intervening before these situations do appear. Pride of place among the various modalities of endoscopic therapy corresponds to mucosal resection, which allows a better histologic assessment besides removing all the suspect tissue. One of the problems arising with the other ablative endoscopic therapies (thermal or photodynamic) is that columnar epithelium remnants may persist beneath the squamous epithelium that covers the exposed surface after therapy.[23] Finally, the long-term results of these therapies are still to be seen, and it should be stressed that they are also associated with complications such as stenosis, bleeding or perforation. In any case, the available studies underscore the fact that potent acid inhibition is a requisite during and after ablative therapy in order to provide an acid-free — or at least 'low-acid' — environment for the process of re-epithelisation of the oesophageal mucosa with squamous epithelium (degree of recommendation B). These studies have shown that the persistence of reflux and the length of the BE segment are the determinant factors for the frequency of post-ablation BE recurrence,[24–26] although not all studies consider that complete normalisation of intra-oesophageal acid exposure is necessary.[27]

3.5 Which is the Medical (Drug) therapy of First Choice for Patients with BE?

The medical therapy chosen must aim at achieving the two objectives originally mentioned. Symptomatic control appears to be easy to achieve even though it is not equivalent to normalisation of intragastric pH or to normalisation of gastro-oesophageal reflux. The second objective (to interrupt/delay/reduce the progression to adenocarcinoma) appears to be more difficult to achieve with the current therapies, or at least there is no evidence that this occurs. Nevertheless, some indirect evidences underscore the need for profound acid inhibition and for monitorisation of the degree of inhibition achieved.[28] In this context, it has been observed that potent and adequate antisecretory therapy reduces cell proliferation in the metaplastic mucosa of BE, and that the risk of dysplasia and/or adenocarcinoma may decrease. Thus, and in spite of the existing uncertainties, current recommendations suggest that double the standard PPI dose, with morning and evening administration, is the most adequate attitude in this condition (degree of recommendation B). In any case, these recommendations are not based on robust data, nor do they take into account the differences in acid-inhibition potency between the various PPIs in the market (with the addition of generic presentations of omeprazole). Furthermore, there are no cost-utility studies assessing the value of high-dose PPI therapy. Studies comparing the efficacy of the various PPIs are frequent for patients with GORD or oesophagitis (*q.v.*) but are much more scarce and limited for patients with BE who, as already pointed out, are believed to be more refractory to acid inhibition. A recent Australian study, reported in abstract form,[29] points out that esomeprazole 40 mg b.i.d. was superior to standard PPI therapy in the control of gastric acidity and in the normalisation of intra-oesophageal pH, a finding noted in practically all the patients treated with esomeprazole at the doses described but only in 50% of the patients under standard therapy with other PPIs. More recent data, also reported in abstract form, suggest that the optimum dosage of

esomeprazole in patients with BE is 40 mg b.i.d., as with this dosage the intra-oesophageal pH was above 4.0 for a mean of 23 ± 1.1 h daily.[30]

In conclusion, standard PPI therapy has been found not to be associated with normalisation of the intraluminal pH of the oesophagus in many patients with BE. Therefore, it has been proposed that patients with BE need profound acid inhibition with high-dose PPI, which is the basis of the medical therapy in this type of patient. This therapeutic approach provides symptom relief, but there is no evidence that it is associated with BE regression. Nevertheless, recent and preliminary data suggest that long-term PPI therapy may reduce the risk of developing disease progression. Profound acid inhibition with PPI is also combined with endoscopy ablative or resection therapy in patients with BE. This therapeutic approach should still be regarded as experimental, and further data are needed before its therapeutic role in patients with BE is established.

Acknowledgement

This manuscript was made possible by a grant from Astra Zeneca, Spain and grant C03/02 from the Instituto de Investigación Carlos III.

References

1. Spechler SJ. Barrett's esophagus. N Engl J Med 2002; 346: 836-42
2. Alcedo J, Lanas A, Ferrandez A, et al. Trends in the epidemiology and outcome of Barrett's esophagus in Spain. Gut 2002; 51 Suppl 3: A27
3. Morales C, Souza RF, Spechler SJ. Hallmarks of cancer progression in Barrett's oesophagus. Lancet 2002; 360: 1587-9
4. Sampliner RE. Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2002; 97: 1888-95
5. Milkes D, Gerson LB, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalization of intraesophageal and intragastric pH in patients with gastroesophageal reflux disease (GERD). Am J Gastroenterol 2004; 99: 991-6
6. Basu KK, Bale R, West KP, et al. Persistent acid reflux and symptoms in patients with Barrett's oesophagus on proton-pump inhibitor therapy. Eur J Gastroenterol Hepatol 2002; 14: 1187-92
7. Sarela AI, Hick DG, Verbeke CS, et al. Persistent acid and bile reflux in asymptomatic patients with Barrett esophagus receiving proton pump inhibitor therapy. Arch Surg 2004; 139: 547-51
8. Yeh RW, Gerson LB, Triadafilopoulos G. Efficacy of esomeprazole in controlling reflux symptoms, intraesophageal, and intragastric pH in patients with Barrett's esophagus. Dis Esophagus 2003; 16: 193-8
9. Sharma P, Sampliner RE, Camargo E. Normalization of esophageal pH with high-dose proton pump inhibitor therapy does not result in regression of Barrett's esophagus. Am J Gastroenterol 1997; 92: 582-5
10. Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinoma of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology 2001; 121: 1286-93
11. Csendes A. Surgical treatment of Barrett's esophagus: 1980–2003. World J Surg 2004; 28: 225-31
12. Parrilla P, Martinez de Haro LF, Ortiz A, et al. Standard antireflux operations in patients who have Barrett's esophagus. Current results. Chest Surg Clin N Am 2002; 12: 113-26
13. 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: 489-94
14. Neumann CS, Iqbal TH, Cooper BT. Long term continuous omeprazole treatment of patients with Barrett's oesophagus. Aliment Pharmacol Ther 1995; 9: 451-4
15. 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: 2120-8
16. Souza RF, Shewmake K, Terada LS, et al. Acid exposure activates the mitogen-activated protein kinase pathways in Barrett's esophagus. Gastroenterology 2002; 122: 299-307
17. Ouatu-Lascar R, Fitzgerald RC, Triadafilopoulos G. Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. Gastroenterology 1999; 117: 327-35
18. Peters FT, Ganesh S, Kuipers EJ, et al. Effect of elimination of acid reflux on epithelial cell proliferative activity of Barrett esophagus. Scand J Gastroenterol 2000; 35: 1238-44
19. Gurski RR, Peters JH, DeMeester SR, et al. Barrett's esophagus can and does regress after antireflux surgery: a study of prevalence and predictive features. J Am Coll Surg 2003; 196: 706-12; discussion 712–13
20. Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. Br J Surg 1996; 83: 274-8
21. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA 2001; 285: 2331-8
22. Hillman LC, Chiragakis L, Shadbolt B, et al. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004; 180: 375-6

23. Lanas A. Nuevas perspectivas terapeuticas en el esófago de Barrett. Gastroenterol Hepatol 2003; 27: 21-9
24. Kahaleh M, Van Laethem JL, Nagy N, et al. Long-term follow-up and factors predictive of recurrence in Barrett's esophagus treated by argon plasma coagulation and acid suppression. Endoscopy 2002; 34: 950-5
25. Basu KK, Pick B, Bale R, et al. Efficacy and one year follow up of argon plasma coagulation therapy for ablation of Barrett's oesophagus: factors determining persistence and recurrence of Barrett's epithelium. Gut 2002; 51: 776-80
26. Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of factors predictive of complete regression of Barrett's esophagus. Am J Gastroenterol 1999; 94: 3420-6
27. Van Laethem JL, Cremer M, Peny MO, et al. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. Gut 1998; 43: 747-51
28. Wurm P, de Caestecker J. Pharmacotherapy for chronic gastro-oesophageal reflux disease and Barrett's oesophagus. Expert Opin Pharmacother 2003; 4: 1049-61
29. Sneineh AA, Tam W, Schoeman M, et al. Magnitude of gastric and oesophageal acid control with Esomeprazole 40 mg bd in comparison with standard ppi in patients with Barrett's oesophagus. Gut 2004; 53 Suppl VI: A102
30. Spechler S, Sharma P, Traxler B, et al. Effect of esomeprazole on intragastric and intraesophageal ph in patients with Barrett's esophagus. Gastroenterology 2004; 126 Suppl 2: S1245

Correspondence and offprints: *Ángel Lanas*, Gastroenterology Service, Clinical University Hospital, 50009 Zaragoza, Spain.
E-mail: alanas@unizar.es