REVIEW ARTICLE

Drugs 2005; 65 Suppl. 1: 59–66
0012-6667/05/0001-0059/$39.95/0

Maintenance Therapy in Gastro-oesophageal Reflux Disease

Miguel Bixquert

Department of Medicine, University of Valencia, and Digestive Diseases Service, 'Arnau de Vilanova' Hospital, Valencia, Spain

Abstract

Gastro-oesophageal reflux disease (GORD) is a chronic condition. Symptom control and the maintenance of healing of erosive oesophagitis, if present, are important topics.

In patients responding to a proton pump inhibitor (PPI) and showing no treatment symptoms it is appropriate to consider long-term treatment strategies, whether continuous, intermittent or on demand. Maintenance PPI therapy is well tolerated for up to 10 years of continuous use. Furthermore, tachyphylaxis does not occur during long-term maintenance PPI therapy. Previous concerns about risks of long-term PPI therapy in *Heliobacter pylori*-negative or *H. pylori*-positive patients have not materialized, while no cases of intestinal metaplasia with dysplasia or adeno-carcinoma were found.

The choice between medical and surgical therapy should depend upon informed patient preference. The optimal candidate for antireflux surgery is a young patient, with typical GORD symptoms, with erosive oesophagitis, with previous complete symptom resolution on acid-suppression therapy and unable to undergo continuous therapy, or alternatively in patients with regurgitation predominating over heartburn as long as the surgical procedures are conducted by an expert surgical team.

Endoscopic therapy for erosive GORD should currently be regarded as experimental. The endoscopic procedures are safe, although they remain untested in patients with severe erosive oesophagitis and/or significant hiatal hernia.

1. Introduction

Gastro-oesophageal reflux disease (GORD) is a chronic disease with a trend to recurrence,[1] particularly in patients with lower oesophageal sphincter hypotonia, severe grades of reflux oesophagitis and difficulty in handling their symptoms, and thus with a greater requirement for anti-secretory therapy.[2] The rationale for long-term therapy is given by the disease's natural history itself,[3] as it is not important whether it is erosive (30–50% of the cases) or non-erosive: once the successful initial therapy (endoscopic healing and/or remission of the symptoms) is withdrawn, only 10–25% of the patients with previous oesophagitis and 25–45% of those in the non-erosive group remain in remission after 6 months.

Thus, to withdraw therapy after the acute treatment of GORD has concluded and to wait for events is not the adequate conduct: a long-term

strategy is required. The goals to aim for are: (a) to achieve symptom control, (b) to prevent recurrence of oesophagitis so as to prevent complications, and (c) to preserve the improvement in quality of life achieved with the acute treatment of GORD.[4]

The guiding principle for long-term management is to step down to the treatment that is least costly but is still effective in controlling symptoms;[4] the rationale for this approach is minimisation of cost, without decreasing efficacy. The only patients in whom treatment should not be stepped down are those with severe oesophagitis (Los Angeles grades C and D).[5] Treatment other than a standard dose of proton pump inhibitors (PPIs) is unlikely to prevent relapse of oesophagitis or complication of such stricture in these patients.[5] There are three possible modalities of long-term anti-secretory treatment, with the PPIs being the drugs of first choice: (i) to institute therapy on a daily basis, either with the full doses used in GORD or with half-doses, and to plan whether the duration shall be indefinite or to consider treatment withdrawal after 12 or 24 months and then proceed according to the evolution; (ii) to prescribe intermittent therapy courses (2–4 weeks' duration) with the conventional dosing for symptomatic recurrences; and (iii) to recommend discretional (i.e. 'on-demand' therapy).

In deciding the strategy model of the maintenance therapy to be chosen, a number of premises must be borne in mind: (a) the efficiency of the various possible therapies; (b) the safety of the various possible therapies; and (c) the inherent risk of the disease itself, which is defined by the chronicity of the disorder and the existence of endoscopic lesions. GORD, and particularly the erosive form, is not only able to cause complications — the more the greater the patient's age — but it also is one of the diseases causing the most profound derangement of the patient's quality of life, both in the physical and in the mental contexts, even when it is not accompanied by oesophagitis.[6]

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

2. Efficiency-based Therapy

The best cost-efficiency relationship in GORD is that provided by the PPIs, particularly so when oesophagitis is present.[4,5] Therapy of non-erosive GORD should be based on the same principles as that of the erosive form, with the particularity that in this case restoration of the quality of life is the main objective. However, PPIs are often rather less effective in this concrete form than in the erosive variety.[6]

A small group of patients with non-erosive GORD who were followed for 7–14 years has shown that 75% of them required anti-secretory medication, 40% on a continuous basis and 60% in intermittent or on-demand modalities; furthermore, 62% of the patients in whom endoscopy was repeated evidenced signs of mild-to-moderate oesophagitis. And yet, over that follow-up period the patients stated that their quality of life had improved significantly, in relation to the symptomatic relief achieved[7] (level of evidence 1c; degree of recommendation A).

3. Safety-based Therapy

Currently available evidence suggests that the fear caused by prolonged PPI administration is unfounded, as even under the influence of PPIs the stomach produces enough acid for digesting nutrients, absorbing iron and calcium, and preventing intestinal bacterial overgrowth. There is a certain degree of reduction in vitamin B_{12} absorption, although its clinical consequences are still debated; it might be advisable to monitor the hydroxycobalamine levels in patients receiving long-term daily PPIs, particularly in the elderly or in those following strict vegetarian diets[2] (level of evidence 2c; degree of recommendation B).

The main concern regarding long-term safety has been related to hypergastrinaemia (which is reversible upon withdrawal of the drug) and development of carcinoid tumours in rats, changes that have also been demonstrated after vagotomy or subtotal resection of the gastric fundus (non-reversible) or upon chronic therapy with ranitidine.

Even though hypergastrinaemia has also been demonstrated in humans, in the dog and in the mouse after protracted therapy with PPIs (and also under other circumstances), these species do not evidence the same density of enterochromaffin cells as the rat, nor do they evidence such an exaggerated response to achlorhydria, and in no case has the development of gastric carcinoid tumours been demonstrated.[2,8]

The Maastricht 2-2000 consensus report[9] qualified the indication for *Helicobacter pylori* eradication in patients with GORD requiring long-term profound acid suppression as 'advisable', based on level 3 evidence. This recommendation arose directly from the report by Kuipers et al. in 1996[10] that the prevalence of corpus glandular atrophy increased during chronic omeprazole treatment in HP+ patients, but this work was an uncontrolled descriptive study earning severe criticism.[11] Moreover Lundell et al.,[12] in a randomised controlled trial, found no significant difference in the prevalence of glandular atrophy between the 'chronic omeprazole' group and the 'anti-reflux surgery' group.

Long-term treatment with PPIs changes the pattern of *H. pylori* gastritis from antral predominance to the predominant corpus gastritis, but whether potent anti-secretory therapy accelerates the development of preneoplastic lesions (i.e. glandular atrophy, intestinal metaplasia, dysplasia) in patients infected with *H. pylori* remains unclear.[8] It is not known whether corpus gastritis by itself increases the risk of gastric cancer or whether it is just an epiphenomenon,[13] and the resolution of gastric mucosa inflammation related with *H. pylori* eradication[14] may have no significance with respect to the subsequent risk of *H. pylori*-associated gastric cancer. Additionally, in the patients continuing with the infection and receiving chronic omeprazole, there was no change in antral and corpus gastritis activity or atrophy during 2 years, but inflammation increased.[14]

There are at present also no definitive data available for recommending investigation and eradication of *H. pylori* in patients who are to receive long-term therapy with PPIs with the aim of preventing the development of gastric cancer in the infected patients.[2,8] In the USA, the Food and Drug Administration itself has not considered it necessary to issue a warning regarding such a requirement,[15] and the Canadian Consensus Conference update 2004[16] concludes that routine testing for *H. pylori* infection is unnecessary before starting GORD therapy.

4. GORD Risk-based Therapy

The effects of long-term therapy should be balanced with those of the disease itself, based on current knowledge of the natural history of GORD.[3,10] Generally speaking, patients with non-erosive GORD — who as a group are younger, non-obese, more frequently females and have no hiatus hernia[7] — usually do not progress to the erosive form nor do they develop complications, even over follow-up periods of 11–14 years.[17,18] On the contrary, patients with grades C–D reflux oesophagitis (Los Angeles classification validated;[19] table I) evidence a high risk of mid-term to long-term complications and are those in whom it is easiest to demonstrate the benefit of maintenance anti-secretory therapy. In the case of patients with Los Angeles grades A–B oesophagitis there are insufficient data available for reliably predicting their natural history, although

Table I. The Los Angeles classification of oesophagitis[19]

	Classification
Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of mucosal folds
Grade B	One (or more) mucosal break more than 5 mm that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the circumference
Grade D	One (or more) mucosal break that involves at least 75% of the oesophageal circumference

it has been suggested that one-third of them worsen if they do not receive sustained treatment[6] (level of evidence 2c; degree of recommendation B).

5. Selection of a Long-term Treatment Strategy

The most important gastroenterologic textbooks[2,8] and all the revision-in-depth, clinical guidelines and expert panel recommendations[5,15,16] underscore two incontrovertible aspects: that PPIs represent the optimum long-term medical, or drug, therapy; and that the most effective therapy is usually the most efficient one. Actually, the US Food and Drug Administration has approved all five marketed PPIs for maintenance therapy and, with the exception of omeprazole, even at one-half the standard doses.[2,4,5] The study of Klinkenberg-Knol et al.[17] has demonstrated, in a group of 230 patients with reflux oesophagitis initially healed under omeprazole therapy (40 mg/day) and then maintained in remission for an average of 11 years, that 62% of them could be maintained asymptomatic with 20 mg/day doses and that only in 11% of the cases did it become necessary to increase the dose to 60 mg/day; these results demonstrate that the PPIs do not present long-term tolerance/tachyphylaxis phenomena. Furthermore, and from the endoscopic point of view, only one case of oesophagitis recurrence was recorded per 9.4 years of follow-up, and there were no peptic stenoses, Barrett's oesophagus did not progress, and there were no significant changes in the gastric mucosa in these patients[17] (level of evidence 2a; degree of recommendation B).

There are three strategic possibilities for the long-term treatment of GORD: medical (drug) therapy, surgical therapy, and endoscopic therapy.

5.1 Medical (Drug) Therapy

There are, in turn, three 'real' options for medical therapy, as the so-called 'weekend' therapy did not prove effective.

5.1.1 Daily Maintenance Therapy

After the acute therapy phase has been completed, maintenance therapy with the same PPI is given continuously. Again, two possibilities exist: with daily administration of the conventional standard dose (20 mg for omeprazole and rabeprazole, 30 mg for lansoprazole, and 40 mg for pantoprazole and esomeprazole), or with daily administration of one-half the conventional dose (10 mg for rabeprazole, 15 mg for lansoprazole, and 20 mg for pantoprazole and esomeprazole). This approach, the so-called 'step-down' approach — starting with the full dose or even double doses (40 mg/day for omeprazole) during the acute therapy phase — which seeks to use a lower than standard dose for maintenance, is not always successful, and many patients (particularly younger ones) have to turn back to full dosage for control of their symptoms.[20] Figure 1 illustrates the results achieved with half-dose esomeprazole *versus* half-dose lansoprazole in maintenance therapy in already-healed oesophagitis.[21]

5.1.2 Intermittent Therapy

This consists of the administration of brief courses (some 2 weeks) of therapy with conventional doses of the PPI when symptoms recur.[22] This maintenance modality, which has shown itself to be efficient and yield positive results in terms of quality of life,[23,24] may be considered for young adults with non-erosive GORD or with grades A–B oesophagitis, as the close correlation between presence of clinical manifestations of GORD and presence of lesions does not hold for the elderly. Maintenance therapy in the aged population, which furthermore usually takes other drugs that may and do worsen abnormal reflux, should be carried out with daily and life-long full doses of the PPI[25] (level of evidence 3b; degree of recommendation B).

5.1.3 'On-demand' or Discretional Therapy

This is given only when GORD manifestations occur, and not on a daily basis. This is actually quite often what the patient does while in the phase of maintenance therapy. This strategy has been

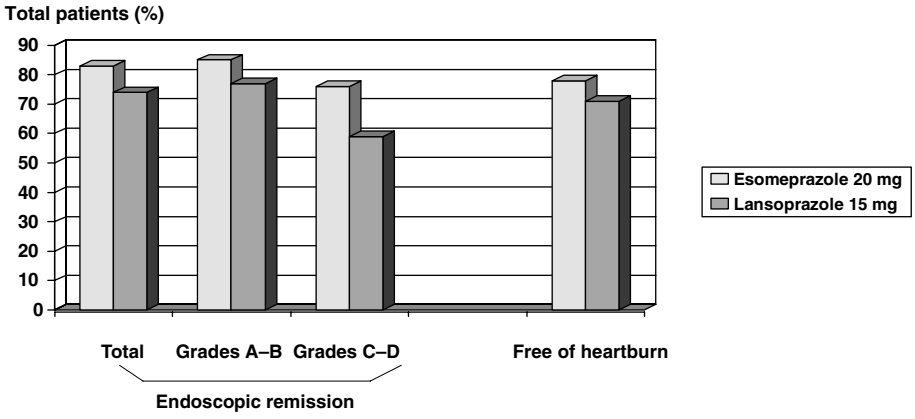

Fig. 1. Maintenance therapy in patients with healed reflux oesophagitis. Comparison of omeprazole 20 mg/day and lansoprazole 15 mg/day over 6 months.

recommended especially for GORD without oesophagitis.

The first trial of this therapy model was carried out with omeprazole,[26] with satisfactory results. It is perhaps the preferable trial with the more recent PPIs, which have a better pharmacokinetic profile (greater rapidity of onset, potency and duration of effects). Talley et al.[27] compared two doses of esomeprazole (20 mg and 40 mg) in on-demand therapy (not more than one dose per day) *versus* placebo in 721 patients with non-erosive GORD over 6 months, after having achieved complete resolution of the symptoms with omeprazole or esomeprazole. With either dose, at least 90% of the patients remained free of complaints. In this type of patient, esomeprazole 20 mg suffices; no added benefit accrues from esomeprazole 40 mg (level of evidence 1b; degree of recommendation A).

Although the 'on-demand' strategy has been typically designed for patients with non-erosive GORD, and it is so stated in the recommended clinical guidelines, a very interesting Spanish study[28] has shown very good long-term results with this strategy in a group of 55 patients (17 patients with non-erosive GORD and 38 patients with grades A–B oesophagitis) successfully treated initially with rabeprazole 20 mg/day for 4 weeks (non-erosive GORD) to 8 weeks (erosive GORD) and then followed for 6 months, while they were being instructed and trained to take on-demand therapy (only when symptoms occurred) with the same PPI at the same dosage. Symptomatic control was achieved in 95% of the patients with one dose every 3–4 days; the average degree of satisfaction was 90/100 and the quality of life levels achieved during the acute phase therapy were maintained during the 6 months of follow-up (level of evidence 1b; degree of recommendation A).

A possible general approach to long-term therapy is illustrated in figure 2. A number of clinical trials have demonstrated that the various PPIs are similarly effective in long-term therapy[29,30] (level of evidence 1c; degree of recommendation A).

5.2 Surgical Therapy

The guidelines and recommendations of the various societies, beginning with those of the Genval conference,[4] consider anti-reflux surgery as a maintenance therapy option in the case of fully documented GORD, particularly when erosive, for younger patients who respond to drug therapy but do not wish to take medication continuously, or in those patients in whom regurgitation predominates over heartburn, but always provided that the surgical procedure is carried out by an expert surgical team and after extensive discussion with

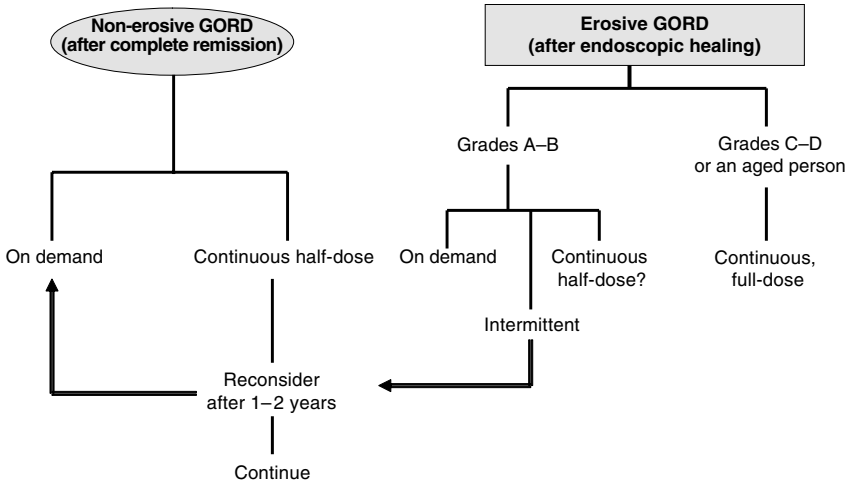

Fig. 2. Possible general maintenance therapy approach in gastro-oesophageal reflux disease (GORD).

the patient[31] (level of evidence 1c; degree of recommendation A).

A significant study by Spechler et al.,[29] in which 160 patients were followed for 9.1–10.6 years, compared the evolution of those remaining under medical therapy with that of those undergoing surgery (but not laparoscopic surgery). Ninety-two per cent of the patients under drug therapy, and 62% of the surgical patients, used anti-secretory medication on a continuous basis. In both groups, patients with Barrett's oesophagus developed adenocarcinoma at a yearly rate of 0.4%, while in those without Barrett's oesophagus the yearly rate was only 0.07%. The authors concluded that surgery cannot be offered either for prevention of the risk of adenocarcinoma development or for indefinitely avoiding the need to continue taking anti-secretory medication. Furthermore, failure of medical therapy is not a good reason for choosing surgery, as refractoriness to medical therapy may be due to an incorrect diagnosis of GORD[30,31] (level of evidence 1b; degree of recommendation A).

At present, anti-reflux surgery is no longer performed via laparotomy, as in the aforementioned study, but via laparoscopy (in the USA, since 1991). The cost-effectiveness and cost-utility ratios of this type of surgery are superior to those of the open modality (even though the efficacy and safety of both modalities are similar), mainly because of an earlier recovery and an earlier return to activity in the laparoscopic group.[31] Neither of the two options is devoid of failure, which occurs at a rate of 9–30% at 5 or 10 years in 'open' fundoplication and at a rate of 2–9% at 5 years in laparoscopic fundoplication. Furthermore, in patients undergoing laparoscopic surgery a number of morpho-functional problems arise 5–8 years after surgery;[32] these problems are summarised in table II.

A recent study has compared the results of open *versus* laparoscopic anti-reflux surgery in a group of 60 patients 1 month, 6 months and 5 years after

Table II. Evolution after 5–8 years of a group of 200 patients with gastro-oesophageal reflux disease undergoing laparoscopic anti-reflux surgery[32]

	Proportion (%)
Functional complaints	
Abdominal distension	66
Impossibility to eructate	28
Dysphagia	20
Heartburn	40 (27% mild)
Oesophageal dilation required	5
Surgical re-intervention required	13
Continuous proton pump inhibitor medication required	11

surgery. There were no differences in the results as regards diet, quality of nocturnal rest, requirement for medication, patient satisfaction and GORD symptoms at the end of the 5 years, and neither in the endoscopic, manometric or pH-metric examinations. One out of every four of the patients having undergone open surgery complained about the abdominal scar. After either procedure, the quality of life returned to nearly-normal levels from 6 months after surgery onwards[33] (level of evidence 1b; degree of recommendation A).

5.3 Endoscopic Therapy

Therapeutic endoscopy has developed anti-reflux techniques and procedures that place it about half-way between pharmacologic and surgical therapy;[34] thus, endoscopic therapy may be considered for patients who do not wish to be continuously dependent on PPIs. Even though the initial results are encouraging — as the patients' quality of life improves, the need to take PPIs is reduced to one out of every three or four patients, and the abnormal pH-metry improves — no evidence is available beyond 12–18 months. The safety of the procedure is good, but the manometric changes at the lower oesophageal sphincter are slight and clinically irrelevant. The inclusion criteria would be the same as for open surgery, and four exclusion criteria are recognised: refractory GORD, GORD with grades C–D oesophagitis, presence of hiatus hernia greater than 3 cm, and presence of Barrett's oesophagus.

Evaluable, but uncontrolled, data are available for three endoscopic procedures. One of them uses endoscopically applied radiofrequencies in the lower oesophageal sphincter area in order to achieve a thickening of the regional smooth muscle and achieve a 'reinforcement' of the sphincter; another one uses endoscopic suturing to perform a cardioplasty, and the third implants inert biopolymers as a reinforcement in the submucosal area of the lower oesophageal sphincter. The main questions to bear in mind and consider before clinically applying any of the endoscopic anti-reflux therapies are: Are they (is it) effective as compared with present pharmacological or surgical therapy? Are they equivalent among and between themselves? Are their (its) effects long-lasting? Are they (is it) safe? Do they (does it) have a good cost-effectiveness ratio? There are at present no comparative studies available between the various endoscopic procedures, nor between the endoscopic procedures and the pharmacological or surgical strategies, nor randomised control studies *versus* placebo.[35] Thus, and although it has been stressed that the majority of patients feel satisfied with therapy and their quality of life improves, morbidity rates have been reported of up to 2.5% with the radiofrequency procedure and recurrence rates of up to 25% with endoscopic suture, and the cost-effectiveness ratio has not been determined for any of them.

Thus, these procedures cannot be indiscriminately applied in assistential practice, and they should be reserved for very concrete and definite cases fulfilling all the inclusion criteria – no hiatus hernia, erosive oesophagitis B-C, positive response to antisecretory therapy, pathological intraoesophagic pH monitoring – and none of the exclusion criteria – significant hiatus hernia, reflux oesophogitis D, peptic stenosis, oesophagic peptic ulcer, Barrett oesophagus, previous oesophagic surgery[34,35] – furthermore having available experienced endoscopists who have already mastered the required learning curve. Endoscopic procedures should be carried out only within the framework of controlled studies unless they demonstrate similar efficacy and safety as the established options (level of evidence 2b; degree of recommendation B).

References

1. Eissele R, Arnold R. Long-term management of GERD. In: Misiewicz JJ, editor. Management Issues in Gastroesophageal Reflux Disease. London: Life Science Communications, 1999: 24-33
2. Richter JE. Gastroesophageal reflux disease. In: Yamada T, editor. Textbook of Gastroenterology 4th ed. Philadelphia: Lippincott, Williams and Wilkins, 2003: 1196-224
3. Bixquert M. Lo primero es conocer la historia natural. In: Dominguez JE, Sobrino M, editors. Enfermedad por reflujo gastroesofágico. Pautas diagnóstico-terapéuticas para la práctica clínica. Barcelona: Prous Science, 2003: 1-10
4. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management — The Genval Workshop Report. Gut 1999; 44 Suppl 2: S1-S16

5. Dent J, Jones R, Kahrilas P, et al. Management of gastro-oesophageal reflux disease in general practice. BMJ 2001; 322: 344-7
6. Galmiche JP, Bruley des Varannes S. Endoscopy-negative reflux disease. Curr Gastroenterol Rep 2001; 3: 206-14
7. Pace F, Bollani S, Molteni P, et al. Natural history of gastro-esophageal reflux disease without esophagitis (NERD) — a reappraisal 10 years on. Dig Liver Dis 2004; 36: 111-5
8. Kahrilas PJ, Pandolfino JE. Gastroesophageal reflux disease and its complications, including Barrett's metaplasia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 7th ed. Philadelphia: Saunders, 2002: 599–622.
9. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of H. pylori infection — The Maastricht 2-2000 consensus report. Aliment Pharmacol Ther 2002; 16: 167-80
10. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, et al. Atrophic gastritis and H. pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med 1996; 334: 1018-22
11. Freston JW. Should we eradicate H. pylori before long term antireflux therapy? Gut 2001; 49: 616-7
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. McColl KEL. H. pylori infection and long term proton pump inhibitor therapy. Gut 2004; 53: 5-7
14. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of H. pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut 2004; 53: 12-20
15. Freston JW. Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective. Am J Gastroenterol 1997; 92 Suppl 5: 1S-7S
16. Armstrong D, Marshall JK, Chiba N, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults — update 2004. Can J Gastroenterol 2005; 19: 15-35
17. 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: 661-4
18. Ramakrishnan A, Katz PO. Pharmacologic management of gastroesophageal reflux disease. Curr Gastroenterol Rep 2002; 4: 218-24
19. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45: 172-80
20. Marzo M, Alonso P, Bonfill X, et al. Centro Cochrane Iberomaericano. Clinical practice guideline on the management of patients with gastroesophageal reflux disease (GERD). Gastroenterol Hepatol 2002; 25: 85-110
21. Lauritsen K, Deviere J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux esophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17: 333-41
22. Bardhan KD, Muller-Lissner S, Bigard MA, et al. Symptomatic gastro-esophageal reflux disease: double-blind controlled study of intermittent treatment with omeprazole or ranitidine. Br Med J 1999; 318: 502-7
23. Stalhammar N-O, Carlsson J, Peacock R, et al. Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-esophageal reflux disease. Pharmacoeconomics 1999; 16: 483-7
24. Wiklund I, Bardhan KD, Müller-Lissner S, et al. Quality of life during acute and intermittent treatment of gastro-esophageal reflux disease with omeprazole compared with ranitidine. Results from a multi-center clinical trial. Ital J Gastroenterol Hepatol 1998; 30: 19-27
25. Richter JE. Gastroesophageal reflux disease in the older patient: presentation, treatment and complications. Am J Gastronterol 2000; 95: 368-72
26. Lind T, Havelund T, Lundell L, et al. On-demand therapy with omeprazole for the long-term management of patients with heartburn without esophagitis — a placebo-controlled randomized trial. Aliment Pharmacol Ther 1999; 13: 907-14
27. Talley NJ, Venables TL, Green JRB, et al. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-esophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. Eur J Gastroenterol Hepatol 2002; 14: 857-63
28. Ponce J, Argüello L, Bastida G, Ponce M, Ortiz V, Garrigues V. On-demand therapy with rabeprazole in nonerosive and erosive gastroesophageal reflux disease in clinical practice: effectiveness, health-related quality of life, and patient satisfaction. Dig Dis Sci 2004; 49: 931-6
29. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease. JAMA 2001; 285: 2331-8
30. Peterson WL, Kharilas PJ, Berardi RR, et al. Improving the management of GERD: evidence-based therapeutic strategies, in Freston JW (ed), Acid Related Diseases Am Gastroenterol Assoc, Self Study Program 2003; 15-40
31. Carballo F. Tratamiento a largo plazo de la ERGE. Análisis coste-efectividad del tratamiento farmacológico (a demanda y continuo) y el tratamiento quirúrgico. Gastroenterol Hepatol 2001; 24 Suppl 2: 54-60
32. Bammer T, Hinder RA, Klaus A, et al. Five-to-eight year outcome of the first laparoscopic Nissen fundoplications. J Gastrointestinal Surg 2001; 5: 43-8
33. Nilsson G, Wenner J, Larsson S, Jonson F. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-esophageal reflux. Br J Surg 2004; 91: 552-9
34. Johnson DA. Endoscopic therapy for GERD — baking, sewing or stuffing: an evidence-based perspective. Rev Gastroenterol Disord 2003; 3: 142-9
35. Hogan WJ. Endoscopic therapy for gastroesophageal reflux disease. Curr Gastroenterol Rep 2003; 5: 206-12

Correspondence and offprints: *Miguel Bixquert Jiménez*, Calle Isabel la Católica 62, E-46183 La Eliana, Valencia, Spain.
E-mail: miguel.bixquert@uv.es