REVIEW ARTICLE

Drugs 2002; 62 (8): 1173-1184
0012-6667/02/0008-1173/$30.00/0

Lansoprazole for Maintenance of Remission of Erosive Oesophagitis

James W. Freston,[1] *Robert L. Jackson,*[2] *Bidan Huang*[3] and *E. David Ballard II*[2]

1 University of Connecticut Health Center, Farmington, Connecticut, USA
2 TAP Pharmaceutical Products, Inc., Lake Forest, Illinois, USA
3 Abbott Laboratories, Abbott Park, Illinois, USA

Contents

Abstract

Gastro-oesophageal reflux disease, which is experienced daily by a significant proportion of individuals, may result in serious sequelae such as erosive oesophagitis. Short-term treatment with acid antisecretory therapy (a proton pump inhibitor or a histamine H_2 receptor antagonist) is highly effective in healing the erosive oesophagitis lesion. However, numerous studies confirm that unless maintenance therapy is initiated virtually all patients will experience oesophagitis relapse within 1 year, as well as an increasing severity of oesophagitis and risk for complications such as Barrett's oesophagus and adenocarcinoma.

Studies evaluating the efficacy of proton pump inhibitor and H_2 antagonist maintenance therapy have found that only the proton pump inhibitors significantly reduce the incidence of oesophagitis relapse. Pharmacoeconomic studies have also confirmed that proton pump inhibitor maintenance therapy is cost effective, by virtue of the ability of these agents to reduce the incidence of relapse as well as prolong the time to relapse and increase the number of weeks per year that patients are without symptoms.

Lansoprazole, a member of the proton pump inhibitor class of agents, has been extensively studied in the treatment of patients with a variety of acid-related disorders. Among those with erosive oesophagitis, maintenance therapy with lansoprazole 15 or 30mg once daily is highly effective in preventing relapse. Studies have documented that lansoprazole 15 and 30mg once daily for six months prevents oesophagitis relapse in up to 81 and 93% of patients, respectively, with comparable percentages of patients remaining in remission after 1 year of treatment. These high rates of remission have also been observed in studies

of patients with lesions that were difficult to heal at baseline (resistant to healing with at least 3 months of H_2 antagonist therapy). Moreover, lansoprazole produces high remission rates regardless of the grade of erosive oesophagitis before acute healing. Among symptomatic patients with heartburn, lansoprazole provides rapid and effective relief of daytime and night-time heartburn and prevents relapse of symptoms. Lansoprazole has a wide margin of safety and is well tolerated when administered as monotherapy in short- and long-term clinical trials.

Taken together these data suggest that proton pump inhibitor therapy represents the preferred and ideal long-term management strategy for the patient with erosive oesophagitis. Lansoprazole is a well-established member of this class of agents and, as such, has an extensive body of literature that supports its safety, tolerability and clinical efficacy in preventing relapse in these patients.

Erosive oesophagitis is one of several severe complications that may arise from the pathological reflux of gastric or duodenal contents into the distal oesophagus, a condition commonly known as gastro-oesophageal reflux disease or GORD.[1,2] It is estimated that 2% of the US population have erosive oesophagitis, a disease characterised by a chronic relapsing nature that produces significant decrements in the quality of life of affected patients.[3-6]

Short-term treatment with a proton pump inhibitor is highly effective in healing erosive oesophagitis, as confirmed by the results of two recently published clinical trials.[7,8] Numerous other comparative studies performed with lansoprazole 30mg once daily for 8 weeks have confirmed erosive oesophagitis healing rates of greater than 90%.[9-12] The effectiveness of proton pump inhibitors in healing erosive oesophagitis lesions is underscored by their ability to produce high rates of healing in patients whose oesophagitis failed to heal following a course of histamine H_2 receptor antagonist therapy. Studies have confirmed healing rates of greater than 84% with lansoprazole 30 or 60mg once daily in these patients.[10,13,14] Proton pump inhibitors are also highly effective in rapidly relieving the symptoms associated with erosive oesophagitis and improving the quality of life of patients.[15,16]

Following acute erosive oesophagitis healing and symptom relief, virtually all patients will experience oesophagitis relapse within 1 year unless continuous maintenance therapy is initiated.[17-21] In addition, prospective as well as retrospective analyses suggest that up to 23% of patients with erosive oesophagitis progress to more severe grades of the disease upon relapse.[22-25]

Lansoprazole, a member of the proton pump inhibitor class of agents, has been extensively studied in a wide variety of acid-related diseases. This article describes the rationale for long-term treatment of oesophagitis and reviews the body of clinical trials that confirm the high degree of efficacy and benign safety profile of lansoprazole in preventing relapse of erosive oesophagitis and providing continuous relief of symptoms during long-term therapy. Alternative approaches to long-term medical therapy, such as alternate-day and 'on-demand' therapy, have not been compared with continuous maintenance therapy in clinical trials. They are therefore not addressed in this review.

1. Rationale for Long-Term Maintenance Therapy of Healed Erosive Oesophagitis

Among those with healed erosive oesophagitis not given maintenance therapy, approximately 70% will experience relapse within 6 months and up to 90% will relapse within 1 year.[17-21] Although the proton pump inhibitors and the H_2 antagonists are widely used and effective in the acute healing of erosive oesophagitis, numerous studies have confirmed that only the proton pump inhibitors significantly reduce the incidence of oesophagitis relapse.[24-29] Less than 30% of patients prescribed proton pump inhibitor maintenance

therapy experience relapse of erosive oesophagitis within 1 year.[20,21,29-33] In contrast, among those prescribed maintenance H_2 antagonist therapy, between 68 and 88% experience oesophagitis recurrence within 1 year.[17,25] These relapse rates seen with H_2 antagonist therapy are only slightly lower than those observed (up to 90%) in placebo-treated patients.[17,25]

Patients with erosive oesophagitis are also at risk for the development of complications such as stricture (4 to 20% prevalence), ulceration (2 to 7% prevalence) and haemorrhage (<2% prevalence).[23] Among patients with erosive oesophagitis with stricture, recurrence following dilatation is common unless acid reflux is well controlled.[34] Results from several studies suggest that maintaining acid suppression with a proton pump inhibitor prevents or delays the occurrence of erosive oesophagitis-related stricture[23] and reduces the frequency of repeated dilatation in patients with oesophageal stricture.[35-40] In a comparative study with ranitidine 600mg twice daily, lansoprazole 30mg once daily prolonged the time to first repeat dilatation and increased the probability of not requiring further dilatation.[40] After 6 months of continuous treatment, 77% of the lansoprazole-treated patients reported no dysphagia compared with 55% of the ranitidine-treated patients ($p = 0.0086$).[40]

Daily heartburn is experienced by approximately one-third of patients with a previous diagnosis of erosive oesophagitis.[6] While this symptom may be trivialised, it has serious implications in the risk for developing Barrett's oesophagus (10 to 15% prevalence among those with erosive oesophagitis) and its progression to adenocarcinoma, two diseases that have substantially increased in prevalence during the last decade,[41,42] as well as quality of life of patients.[6] Among those with heartburn studied by McDougall and colleagues,[6] 49% of patients considered the symptom to be of moderate or major severity and 4% considered it to be unbearable. Moreover, in a case-controlled study by Lagergren and colleagues,[43] the frequency and intensity of heartburn symptoms and their chronicity were found to have a significant effect on the risk of developing oesophageal adenocarcinoma. More than three episodes of heartburn per week increased the risk of oesophageal adenocarcinoma by more than 16-fold.[43] Similarly, those who experienced heartburn for more than 20 years also had a greater than 16-fold increased risk for oesophageal adenocarcinoma.[43] Numerous studies have confirmed that proton pump inhibitor therapy reduces the incidence, frequency and severity of heartburn,[15,44-46] and studies have found an association between treatment with lansoprazole or omeprazole and the formation of 'islands' of squamous mucosa within the area of columnar epithelium.[47,48] Nevertheless, there is no evidence that the long-term use of proton pump inhibitors for erosive oesophagitis reduces the risk of developing Barrett's oesophagus or reduces the rate of progression to dysplasia or adenocarcinoma.

In addition to numerous clinical benefits, several pharmacoeconomic evaluations have documented the cost effectiveness of proton pump inhibitor therapy in the maintenance of healed erosive oesophagitis. The cost effectiveness of these agents is primarily due to the reduction in the number of relapses, prolonged time to relapse, and more weeks per year without reflux symptoms in those treated with a proton pump inhibitor compare with a H_2 antagonist or a prokinetic agent.[18,49-53] These effects, in turn, reduce the utilisation of healthcare resources such as physician office visits, repeat procedures and the need for hospitalisation.[18,49-53]

These data have resulted in most clinicians recognising the need for continuous maintenance treatment with a proton pump inhibitor in order to prevent erosive oesophagitis relapse as well as keeping patients symptom-free and at decreased risk for complications. On the basis of their high rate of clinical efficacy (i.e. low incidence of relapse), effective and prompt control of patient symptoms, and reduction in the occurrence of complications, the proton pump inhibitor class of

agents represents an ideal long-term maintenance regimen.

2. Results with Lansoprazole

2.1 Long-Term Maintenance Therapy to Prevent Relapse of Erosive Oesophagitis

The results of eight trials that studied lansoprazole for healed erosive oesophagitis maintenance therapy are summarised in table I.[20,21,27,54-59] Differences in study design, population characteristics, and erosive oesophagitis grading scale often limit the ability to compare and contrast results across studies, however, several consistencies are apparent. Daily dosages of lansoprazole 15 or 30mg are associated with low rates of oesophagitis relapse at the end of 6 months as well as at the end of 1 year.[20,21,27,54-59]

Robinson and colleagues[20] in a double-blind study of patients who had healed erosive oesophagitis after a course of antisecretory therapy (lansoprazole or ranitidine) were randomised to lansoprazole 15mg, lansoprazole 30mg or placebo, each administered once daily. After 6 months, healing was maintained in 81% of those receiving lansoprazole 15mg and 93% of those receiving lansoprazole 30mg compared with only 27% of those receiving placebo.[20] These results after 6 months are similar to those found in an active treatment comparator trial of lansoprazole and omeprazole by Baldi and associates.[56] Healed erosive oesophagitis was maintained in 83% of those treated with lansoprazole 15mg and 95% of those treated with lansoprazole 30mg once daily, respectively, compared with 93% of those treated with omeprazole 20mg once daily.

Compared with H_2 antagonist treatment, significantly higher percentages of patients treated with lansoprazole remained in remission. After 6 months in the study by Hirshowitz et al.,[58] 71% of those treated with lansoprazole 15mg continued to have healed erosive oesophagitis compared to 29% of those treated with ranitidine 150mg twice daily. Gough and colleagues[27] treated patients with lansoprazole 15 or 30mg once daily or ranitidine 300mg twice daily, which is twice the approved US Food and Drug Administration (FDA) dosage for this indication, and found 6-month remission rates of 81% with lansoprazole 15mg, 86% with lansoprazole 30mg and 39% with ranitidine. The reasons for the superiority of proton pump inhibitors over H_2 antagonists in maintaining remissions may be due to more prolonged control of intragast-

Table I. Remission rates during long-term lansoprazole therapy of erosive oesophagitis in patients enrolled in randomised, double-blind, parallel group studies

Reference	Drug regimen (no. of evaluable patients)	Remission rate (%)	
		6 mo	12 mo
Lansoprazole dosage versus placebo comparisons[a]			
Hatlebakk et al.; 1997[54]	Lansoprazole 15mg (50)	76[b]	72
	Lansoprazole 30mg (53)	90[b]	85
Poynard et al.; 1995[55]	Lansoprazole 15mg (99)		87
	Lansoprazole 30mg (85)		89
Robinson; 1996[20]	Lansoprazole 15mg[c] (59)	81	79
	Lansoprazole 30mg[c] (56)	93	90
	Placebo (55)	27	24
Lansoprazole dosage versus active treatment comparisons[a]			
Baldi et al.; 1996[56][d]	Lansoprazole 15mg (295)	83	73
	Lansoprazole 30mg (309)	95	86
	Omeprazole 20mg (302)	93	87
Carling et al.; 1996[57][d]	Lansoprazole 30mg (124)		90
	Omeprazole 20mg (120)		91
Hirschowitz et al.; 1999[58][d,e]	Lansoprazole 15mg[c] (100)	71	65
	Ranitidine 300mg (106)	29	15
Gough et al.; 1996[27]	Lansoprazole 15mg[c] (86)	81	66
	Lansoprazole 30mg[c] (75)	86	79
	Ranitidine 600mg (74)	39	31
Lauritsen et al.; 2002[59][d]	Lansoprazole 15mg[c,f]	74	
	Esomeprazole 20mg[f]	83	
Lansoprazole dosage versus placebo in patients not responding to H_2 antagonist therapy[a]			
Sontag et al.; 1996[21]	Lansoprazole 15mg[c] (50)	72	67
	Lansoprazole 30mg[c] (49)	72	55
	Placebo (47)	13	13

a Patients enrolled in maintenance trials demonstrated healing of erosive oesophagitis in short-term treatment studies or in non-blind lead-in phases.

b Personal communication from investigator.

c $p < 0.001$ lansoprazole *vs* ranitidine or placebo; esomeprazole *vs* lansoprazole.

d Presented as an abstract.

e Results of intent-to-treat population analysis.

f A total of 1236 patients were randomised in the study.

ric pH above 4 by the proton pump inhibitors[60] and the development of tolerance to H_2 antagonists.[61,62]

Given the chronic nature of erosive oesophagitis requiring long-term treatment as well as factors that may increase the risk for relapse (i.e. decreasing patient compliance with long-term therapy), studies that follow patients for longer periods of time (i.e. 1 year) may provide more accurate measures of maintenance therapy efficacy. Several studies have confirmed that the oesophagitis remission rates observed with lansoprazole after 1 year of therapy were comparable to those observed after 6 months.

In the trial by Robinson and colleagues,[20] 79 and 90% of patients treated with lansoprazole 15 or 30mg, respectively, remained in remission after 1 year of treatment compared with 24% of placebo-treated patients. This disparity in remission rates favouring lansoprazole therapy was also observed in comparative trials of ranitidine, even when ranitidine was administered at 300mg twice daily. Gough and colleagues[27] and Hirschowitz and associates[58] reported 1-year remission rates in ranitidine-treated patients of 31 and 15%, respectively, compared with 66 and 65% with lansoprazole 15mg and 79% with lansoprazole 30mg.

In the studies comparing lansoprazole with omeprazole, the high 1-year remission rates observed in the treatment groups were comparable: 73% with lansoprazole 15mg, 86 to 90% with lansoprazole 30mg, and 87 to 91% with omeprazole 20mg.[56,57] Although the reason for the low remission rate data in the study by Hirschowitz and colleagues[58] is unknown, it is noteworthy that the therapeutic gain in those treated with lansoprazole over those treated with ranitidine was 42% after 6 months and 50% after 1 year. These therapeutic gains are comparable to those of the trial by Gough and colleagues[27] in which the study populations had higher remission rates.

In a recent abstract presented by Lauritsen and colleagues,[59] a 6-month remission rate of 83% was reported with esomeprazole 20mg. This 6-month remission rate is identical to that observed with lansoprazole 15mg in the abstract by Baldi and colleagues,[56] and comparable to that observed with lansoprazole 15mg in studies by Robinson[20] and Gough[27] (81% remission rate noted in both studies). Of note, as compared to the esomeprazole results in this study, higher 6-month remission rates have consistently been observed in studies of lansoprazole 30mg (≥86%).[20,27,56] In the study by Lauritson,[59] a 6-month remission rate of 73% was observed with lansoprazole 15mg. Like the findings of Hirschowitz and colleagues,[58] clinical or patient population factors that may have contributed to this observation are unknown. Furthermore, this study only followed patients for 6 months in contrast to several lansoprazole trials that have confirmed high remission rates after 12 months of treatment.[20,54-57]

Treatment with lansoprazole is significantly more effective in preventing oesophagitis relapse as well as reducing the number of recurrences during maintenance therapy than placebo. In the study by Robinson and colleagues,[20] 75% (41/55) of placebo recipients experienced one or more recurrences of erosive oesophagitis during the 1-year maintenance period compared with 20% (12/59) of those treated with lansoprazole 15mg once daily and 9% (5/56) of those receiving lansoprazole 30mg once daily (table II). Multiple relapses of erosive oesophagitis were common among those receiving placebo, with 45% (25/55) of placebo

Table II. Frequency of recurrences: distribution of patients by number of recurrences during the 1-year maintenance period and by treatment group. Reproduced with permission[20]

Treatment group (no. pts)	Number of recurrences (% pts)[a]					
	0[b]	1	2	3	4	5
Placebo (55)	25.5	29.1	10.9	12.7	14.6	7.3
Lansoprazole 15mg (59)	79.7	11.9	6.8	1.7	0	0
Lansoprazole 30mg (56)	91.1	3.6	3.6	1.8	0	0

a Numbers total slightly more than 100% because of rounding.

b Patients who remained healed throughout the maintenance period.

recipients experiencing two or more relapses compared with 8% (5/59) of those receiving lansoprazole 15mg and 5% (3/56) of those receiving lansoprazole 30mg.[20]

The results of the majority of placebo- and active-control treatment trials confirm that long-term maintenance therapy with lansoprazole, at a dosage of 15 or 30mg once daily, is highly effective in sustaining erosive oesophagitis remission. Six-month and 1-year remission rates among patients treated with lansoprazole were generally 80% or greater at both evaluation endpoints. Numeric differences in remission rates that favoured the 30mg dose of lansoprazole over the 15mg dose were observed, however, these differences were not statistically significant.[20,27,54-56] Oesophagitis remission rates observed with lansoprazole were comparable to those found with omeprazole and significantly higher than those with placebo or ranitidine, even when the latter was used at dosages that exceed those recommended by the US FDA. The low remission rates observed with H_2 antagonist maintenance therapy (<40% at 6 months and <31% at 1 year) were comparable to those found with placebo. This suggests that both of these maintenance strategies represent less than optimal management of the patient with healed erosive oesophagitis.

2.2 Lesions Resistant to Healing with Histamine H_2 Receptor Antagonist Treatment

Approximately 50% of patients with erosive oesophagitis treated with standard doses of H_2 antagonists fail to exhibit mucosal healing after 8 weeks of treatment.[14,63-65] In studies of patients with healed erosive reflux oesophagitis that had been resistant to healing with a course of H_2 antagonist therapy, results have confirmed that lansoprazole is highly effective in acute lesion healing. Three studies performed with lansoprazole 30mg once daily found healing rates of between 84 and 96% after 8 weeks[10,13,14] and up to 100% after 12 weeks of treatment.[10]

Proton pump inhibitor therapy is highly effective in maintaining oesophagitis remission, even in patients with difficult to heal erosive oesophagitis.[21] In a study of patients with healed erosive oesophagitis that had been resistant to healing after at least 3 months of H_2 antagonist therapy, Sontag and colleagues[21] observed that at the end of 6 months a significantly ($p < 0.001$) greater percentage of patients treated with either lansoprazole 15 or 30mg remained in remission compared with those receiving placebo, 72% in both lansoprazole treatment groups versus 13% in the placebo treatment group. This significantly higher 6-month remission rate observed in those treated with lansoprazole 15 and 30mg compared with placebo persisted during the remainder of the study period with 1-year remission rates of 67 and 55% versus 13%, respectively.[21]

The data observed in the maintenance trial by Sontag and colleagues[21] support the use of lansoprazole maintenance therapy even in patients with difficult to heal erosive oesophagitis lesions. The remission rates observed were comparable to those observed in other studies involving patients with lesions that were not previously resistant to healing with H_2 antagonist therapy.[20,27,56-58] Overall, given the high remission rates observed with lansoprazole in this trial[21] and the low remission rates observed with H_2 antagonist therapy in other trials, these data suggest a clear preference for proton pump inhibitor maintenance therapy, regardless of the acute healing regimen of the patient.

2.3 Effect of Baseline Oesophagitis Grade

The results of studies that analysed the 6-month and 1-year efficacy of lansoprazole in sustaining oesophagitis remission by baseline grade of mucosal damage before healing are presented in figure 1 and figure 2. Lansoprazole maintenance therapy at a dosage of 15 or 30mg once daily produced 6-month remission rates of 85 and 96%, respectively, in patients with grade 2 erosive oesophagitis at baseline before healing (figure 1).[20] Remission rates observed in those with more severe disease at baseline (grade 3 or 4 erosive oesophagitis) were 77 and 90% at 6 months in those receiving

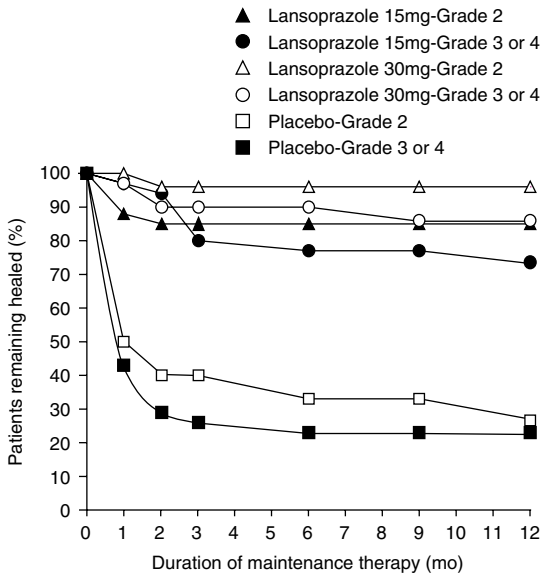

Fig. 1. Patients enrolled in maintenance trials demonstrating healing of erosive oesophagitis in short-term treatment studies or in non-blind lead-in phases were randomised to maintenance therapy with lansoprazole 15mg, lansoprazole 30mg or placebo. The figure shows the proportion of patients who remained healed (no erosions seen on endoscopy) during the 1-year maintenance period, by treatment group and baseline oesophagitis grade 2 versus 3 or 4 before healing. Significantly higher percentages of those treated with lansoprazole remained healed throughout the one-year maintenance treatment period, even when remission rates were stratified by baseline oesophagitis grade. Percentages were calculated by life-table methods.[20]

lansoprazole 15 and 30mg once daily, respectively. These rates are just slightly lower than those observed in patients with grade 2 disease at baseline.[20] Remission rates by grade of oesophagitis at baseline observed after 1 year of lansoprazole treatment were similar to those noted at 6 months. Placebo-treated patients with grade 2 disease at baseline were found to have remission rates that were significantly lower than those observed with lansoprazole: only 33 and 27% of placebo recipients with grade 2 disease remained in remission at 6 months and 1 year, respectively. Among placebo recipients with more severe disease (grade 3 or 4) only 26 and 23% remained in remission at 6 months and 1 year, respectively.

In patients with erosive oesophagitis resistant to healing after at least 3 months of H_2 antagonist therapy, the 6-month and 1-year remission rates in those receiving lansoprazole 15 or 30mg once daily were generally higher among those with grade 2 disease at baseline compared with those with grade 3 or 4 disease (figure 2).[21] Among those with grade 2 disease, 6-month remission rates of 85 and 68% were observed with lansoprazole 15 and 30mg once daily, respectively. Six-month remission rates of 58 and 77% were observed in patients with grade 3 or 4 disease receiving lansoprazole 15 and 30mg once daily, respectively. After 1 year, healing was maintained in over 80% of those with grade 2 disease receiving lansoprazole 15mg. Among placebo recipients, healing was maintained in only 21% of those with grade 2 disease at baseline after 6 months and 1 year. Of note, all of the placebo recipients with grade 3 or 4 erosive oesophagitis at baseline relapsed within 1 month.

The clinical interpretation of the lower remission rates observed with lansoprazole in patients with grades 3 or 4 erosive oesophagitis at baseline compared with those with grade 2 is limited by the small number of patients with these more severe forms of erosive oesophagitis who were enrolled in these trials – a reflection of low overall prevalence of grade 3 and 4 disease (approximately 25 and 7%, respectively) among those with erosive oesophagitis.[15] At least 50% of patients receiving placebo experienced oesophagitis relapse within 1 month of initiation of maintenance therapy, regardless of oesophagitis grade at baseline or history with H_2 antagonists. The clinical importance of the prompt initiation of effective remission maintenance therapy is underscored by the results of Sontag and colleagues.[21] All the patients with healed grade 3 or 4 erosive oesophagitis at baseline who had been resistant to healing with at least 3 months of H_2 antagonist therapy and had been administered placebo maintenance therapy experienced relapse within 1 month.

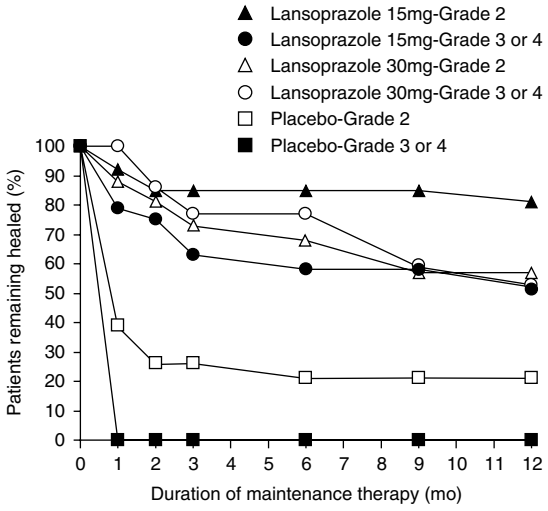

Fig. 2. Patients who demonstrated erosive oesophagitis healing and who had lesions that had been resistant to healing after at least 3 months of H_2 antagonist therapy were randomised to treatment with lansoprazole 15mg, lansoprazole 30mg or placebo. The figure shows the proportion of patients who remained healed (no erosions seen on endoscopy) during the 1-year maintenance period, by treatment group and by baseline oesophagitis grade 2 versus grade 3 or 4 before healing. Significantly higher percentages of those receiving lansoprazole remained healed throughout the 1-year maintenance treatment period, even when remission rates were stratified by baseline oesophagitis grade. All patients with grade 3 or 4 and 39% of those with grade 2 erosive oesophagitis at baseline randomised to placebo experienced relapse within 1 month. Percentages were calculated by life-table methods.[21]

2.4 Symptom Relief

Heartburn severity and chronicity are strongly associated with an increased risk for adenocarcinoma (16-fold greater risk).[43] This has significantly increased our appreciation of the need to control this symptom in patients with gastro-oesophageal reflux disease and erosive oesophagitis. Numerous clinical studies have confirmed that treatment with lansoprazole produces rapid and effect relief of heartburn.[15,44-46]

A double-blind, randomised study of lansoprazole 15 and 30mg once daily found that greater percentages of patients with erosive oesophagitis were asymptomatic (no moderate or severe daytime or night-time heartburn) significantly longer than placebo recipients (figure 3).[20] During the first 6 months of treatment over 80% of patients receiving lansoprazole 15 or 30mg once daily remained asymptomatic compared with approximately 50% of those receiving placebo. After 12 months of treatment, 72% of those receiving lansoprazole 15mg and 67% of those receiving lansoprazole 30mg remained asymptomatic compared with 35% of placebo recipients. Lansoprazole was significantly more effective compared with placebo in controlling symptoms of daytime and night-time heartburn ($p < 0.001$).

Sontag and colleagues[21] observed a more disparate difference in heartburn relief between lansoprazole and placebo in the study of patients with erosive oesophagitis lesions that were resistant to healing with H_2 antagonist therapy. After 6 months, 81 and 76% of those receiving lansoprazole 30 or 15mg, respectively, were asymptomatic compared with 21% of those receiving placebo. At the end of the 1-year study period, all placebo recipients were symptomatic or withdrew from the study, whereas 66 and 64% of those treated with lansoprazole 30 or 15mg once daily, respectively, remained asymptomatic.

2.5 Long-Term Safety

Lansoprazole has been shown to have a wide margin of safety and was well tolerated when used as monotherapy in short- and long-term clinical trials for a variety of indications. During long-term treatment the most commonly reported adverse event was diarrhoea, which was reported by between 1.9 and 5.0% of patients in these studies.[20,21,27,54,56] Other commonly reported adverse events in the studies by Sontag and colleagues [21] and Gough and associates [27] were headache, abdominal pain, dizziness and vomiting. All other events were reported by <1% of lansoprazole recipients. In long-term trials, no significant differences in the incidence or severity of adverse events were noted with lansoprazole 15 or 30mg once daily, and omeprazole 20mg once daily, ranitidine 300mg twice daily or placebo.[20,21,27,56,57] In a recent review of 702 patients enrolled in lansoprazole

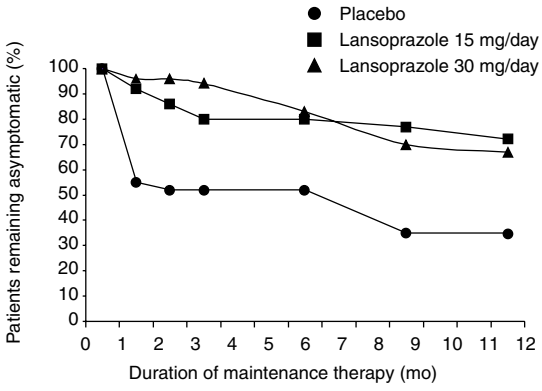

Fig. 3. Patients enrolled in maintenance trials demonstrating healing of erosive oesophagitis in short-term treatment studies or in non-blind lead-in phases were randomised to maintenance therapy with lansoprazole 15mg, lansoprazole 30mg or placebo. The figure shows the proportion of patients who remained asymptomatic during the 1-year maintenance period. Lansoprazole was significantly superior to placebo in controlling symptoms of daytime and night-time heartburn ($p < 0.001$). At 12 months, 72% of patients receiving lansoprazole 15mg and 67% of those receiving lansoprazole 30mg were asymptomatic compared with 35% of those receiving placebo. Percentages were calculated by life-table methods; patient data were considered to be censored at the time of the first erosive recurrence. An asymptomatic state was defined as no moderate or severe daytime or night-time heartburn. Reproduced with permission.[20]

long-term comparator trials, diarrhoea was the only event considered treatment-related and reported by over 2% of patients in any treatment group with 3.2% of lansoprazole recipients and 2.0% of placebo recipients reporting this adverse event.[66] The percentage of patients discontinuing a long-term clinical trial because of an adverse event was also similar between placebo-treated (8%, 16/201) and lansoprazole-treated (6%, 19/315) patients.[66]

The effects of long-term administration of lansoprazole on serum gastrin levels are not generally considered clinically significant or result in a need to change drug therapy.[66,67] Long-term treatment with a proton pump inhibitor may result in an increase in median serum gastrin levels; however, these levels generally remain within the normal range throughout the course of treatment and return to baseline levels within 1 month of treatment discontinuation.[67]

3. Conclusion

Gastro-oesophageal reflux disease is a chronic relapsing condition that often results in serious sequelae such as erosive oesophagitis. Because reflux of gastric acid is essential for the development of oesophagitis, and its associated symptoms and complications, the use of effective acid inhibitory therapy represents the most rational strategy for acute healing and symptom relief as well as for maintaining the healed oesophageal mucosa. Patients with poorly managed erosive oesophagitis have an increased risk for complications and a substantially diminished quality of life.[6,17]

Proton pump inhibitors represent a significant breakthrough in the acute treatment and chronic maintenance of healed erosive oesophagitis, and are considered the "gold standard" for the management of patients with these conditions.[68] Taken together, clinical data strongly suggest that maintenance therapy with a proton pump inhibitor prevents oesophagitis relapse in greater percentages of patients than placebo as well as H_2 antagonist therapy, even in patients who do not respond to initial H_2 antagonist therapy for acute healing. Results suggest that proton pump inhibitor therapy also reduces the risk of oesophagitis-related complications such as stricture and need for repeat dilatation. Moreover, emerging data suggest that more aggressive gastric acid control may reduce the risk of Barrett's oesophagus and adenocarcinoma, which are a growing burden. However, this hypothesis remains to be tested.

Maintenance therapy with a proton pump inhibitor is cost effective in patients with healed erosive oesophagitis based on the prevention of oesophagitis relapse, the reduction in patient symptoms, and improvement in quality of life. Patients who experience erosive oesophagitis relapse impart an increased load on the healthcare system through their need for additional office visits, upper gastrointestinal endoscopies and hospitalisation. The prevention of oesophagitis relapse in these individuals, in

turn, results in reductions in the utilisation of these healthcare resources.

Lansoprazole is a well-established member of the proton pump inhibitor class of agents and, as such, has an extensive body of literature supporting its clinical efficacy and patient tolerability, as well as safety with short- and long-term use in patients with a variety of acid-related disorders. Among those with erosive oesophagitis, lansoprazole significantly alters the natural course of the disease, freeing patients from the inevitable relapse that occurs in untreated patients and those prescribed H_2 antagonists. A number of clinical trials performed in different patient populations have confirmed that up to 93 and 81% of those receiving lansoprazole 30 or 15mg, respectively, continue to have healed oesophageal mucosa after 6 months, with comparable percentages after 1 year (up to 90% with either lansoprazole 15 or 30 mg).

The high rates of erosive oesophagitis remission observed with lansoprazole have also been observed in patients with difficult to heal disease (i.e., patients with healed erosive oesophagitis that was resistant to healing after at least 3 months of H_2 antagonist therapy). Lansoprazole prevents oesophagitis relapse in most patients, regardless of grade of erosive oesophagitis before healing.

Although numeric differences in remission rates slightly favouring erosive oesophagitis maintenance therapy with lansoprazole 30mg compared with lansoprazole 15mg have been observed in several studies, these differences were not statistically significant. Given the lack of a price difference between the two doses of lansoprazole, increasing the dose from 15mg to 30mg is a clinically and economically viable option in patients who continue to have symptoms or experience a relapse on the lower dose. Treatment with lansoprazole 15 or 30mg is well tolerated with a very low percentage of patients reporting adverse events and no statistically significant differences observed in either the incidence or severity of adverse events between the two doses.

Acknowledgements

Dr Freston is a consultant for the following pharmaceutical companies: Johnson and Johnson-Merck; TAP Pharmaceutical Products; Inc.; AstraZeneca; and Pfizer.

References

1. Galmich J-P, Bruley des Varannes S. Symptoms and disease severity in gastro-esophageal reflux disease. Scand J Gastroenterol 1994; 29 Suppl. 201: 62-8
2. Klinkenberg-Knol EC, Feston HPM, Meuwissen SGM. Pharmacological management of gastro-esophageal reflux disease. Drugs 1995; 49: 695-710
3. Locke GR, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterol 1997; 112: 1448-56
4. Richter JE. Long-term management of gastroesophageal reflux disease and its complications. Am J Gastroenterol 1997; 92 (4): 30S-4S
5. Spechler SJ. Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 1992; 51 Suppl. 1: 24-9
6. McDougall NI, Johnston BT, Kee F, et al. Natural history of reflux esophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. Gut 1996; 38: 481-6
7. Howden CW, Ballard D, Robieson W. Evidence of therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive oesophagitis. Clin Drug Invest 2002; 22 (2): 99-109
8. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97: 575-83
9. Earnest DL, Dorsch E, Jones J, et al. A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis. Am J Gastroenterol 1998; 93: 238-43
10. Robinson M, Sahba B, Avner D, et al. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Aliment Pharmacol Ther 1995; 9: 25-31
11. Castell DO, Richter JE, Robinson M, et al. Effacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. Am J Gastroenterol 1996; 91: 1749-57
12. Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30mg vesus omeprazole 40mg in the treatment of reflux oesophagitis grade II, III, and Iva (a Dutch multicentre trial). Eur J Gastroenterol Hepatol 1996; 8: 1101-6
13. Sontag SJ, Kogut DG, Fleischmann R, et al. Lansoprazole heals erosive reflux esophagitis resistant to histamine H2-receptor antagonist therapy. Am J Gastroenterol 1997; 92: 429-37
14. Feldman M, Harford WV, Fisher RS, et al. Treatment of reflux esophagitis resistant to H2-receptor antagonists with lansoprazole, a new H+/K+-ATPase inhibitor: a controlled, double-blind study. Am J Gastroenterol 1993; 88: 1212-7
15. Richter JE, Kahrilas PJ, Sontag S, et al. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol 2001; 96: 3089-98
16. Mathias SD, Castell DO, Elkin E, et al. Health-related quality of life of patients with acute erosive reflux esophagitis. Dig Dis Sci 1996; 41: 11: 2123-9
17. Fennerty MB, Castell D, Fendrick AM, et al. The diagnosis and treatment of gastroesophageal reflux disease in a managed care environment: suggested disease management guidelines. Arch Int Med 1996; 156: 477-84

18. Harris RA, Kuppermann M, Richter JE. Proton pump inhibitors or histamine-2 receptor antagonists for the prevention of recurrences of erosive reflux esophagitis: a cost-effectiveness analysis. Am J Gastroenterol 1997; 92: 2179-87
19. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988; 95: 903-12
20. Robinson MG, Lanza F, Avner D. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 24: 859-67
21. Sontag SJ, Kogut DG, Fleischmann R, et al. Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H2-RA therapy. Am J Gastroenterol 1996; 91: 1758-65
22. Ollyo J-B, Monnier P, Fontolliet C, et al. The natural history, prevalence and incidence of reflux oesophagitis. Gullet 1993; 3 Suppl.: 3-10
23. Howden CW, Castell DO, Cohen S, et al. The rationale for continuous maintenance treatment of reflux esophagitis. Arch Intern Med 1995; 155: 1465-71
24. Robinson M, Lanza F, Lansoprazole Study Group. Lansoprazole for one year prevents recurrence of erosive reflux esophagitis [abstract]. Gastroenterology 1994; 106: 166
25. Sontag SJ, Richter J, Campbell D, et al. Lansoprazole (Lan) for one year prevents recurrence of erosive reflux esophagitis (ERE) [abstract]. Am J Gastroenterol 1993; 88: 1499
26. Chiba N. Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: a systematic overview. Can J Gastroenterol 1997; 11 Suppl. B: 66B-73B
27. Gough AL, Long RG, Cooper BT, et al. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. Aliment Pharmacol Ther 1996; 10: 529-39
28. Vigneri S, Termini R, Leandro G, et al. A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med 1995; 333: 1106-10
29. Klinkenberg-Knol EC, Festen HP, Jansen JB, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. Ann Intern Med 1994; 121: 161-7
30. Lundell L, Backman L, Ekstrom P, et al. Prevention of relapse of reflux esophagitis after endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine. Scand J Gastroenterol 1991; 26: 248-56
31. Fiasse R, Druez P, Coppens JP, et al. Omeprazole in the treatment of patients with severe reflux oesophagitis not responding to H2-receptor antagonists and ineligible for surgery. Acta Gastroenterol Belg 1990; 53: 573-84
32. Dent J, Yeomans ND, Mackinnon M, et al. Omeprazole versus ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. Gut 1994; 35: 590-8
33. Hallerback B, Unge P, Carling L, et al. Omeprazole or ranitidine in long-term treatment of reflux esophagitis: the Scandinavian Clinics for United Research Group. Gastroenterology 1994; 107: 1305-11
34. Marks RD, Richter JE. Peptic strictures of the esophagus. Am J Gastroenterol 1993; 88: 1160-73
35. Miller LS, Vinayek R, Frucht H, et al. Reflux esophagitis in patients with Zollinger-Ellison syndrome. Gastroenterology 1990; 98: 341-6
36. Koop H, Arnold R. Long-term maintenance treatment of reflux esophagitis with omeprazole: prospective study in patients with H2-blocker resistant esophagitis. Dig Dis Sci 1991; 36: 552-7
37. Carr SJ, Wicks AC. Omeprazole and oesophageal stricture. Lancet 1992; 339: 316
38. Ching CK, Shaheen MZ, Holmes GKT. Is omeprazole more effective in the treatment of resistant reflux esophagitis and associated peptic stricture?. [abstract]. Gastroenterology 1990; 98: 30
39. Marks RD, Richter JE, Rizzo J, et al. Omeprazole versus H2-receptor antagonists in treating patients with peptic stricture and esophagitis. Gastroenterology 1994; 106: 907-15
40. Swarbrick ET, Gough AL, Christian J, et al. Prevention of recurrence of oesophageal stricture, a comparative study of lansoprazole and high dose ranitidine [abstract]. Gastroenterology 1994; 106: 189
41. Bytzer P, Christensen PB, Damkier P, et al. Adenocarcinoma of the esophagus and Barrett's esophagus: a population based study. Am J Gastroenterol 1999; 94: 86-91
42. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83: 2050-3
43. Lagergren J, Bergstrom R, Lindgrena A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-31
44. Richter JE, Kovacs TOG, Greski-Rose PA, et al. Lansoprazole in the treatment of heartburn in patients without erosive esophagitis. Aliment Pharmacol Ther 1999; 13: 795-804
45. Howden CW, Henning JM, Huang B, et al. Management of heartburn in a large, randomized, community-based study: comparison for four therapeutic strategies. Am J Gastroenterol 2001; 96: 1704-10
46. Richter JE, Campbell DR, Kahrilas PJ, et al. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. Arch Intern Med 2000; 160: 1803-9
47. Gore S, Healey CJ, Suton R, et al. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Aliment Pharmacol Ther 1993; 7: 623-8
48. Sampliner RE, Romero R, LaFleur L. Effect of up to 3 years of high dose lansoprazole on Barrett's esophagus. Gastroenterology 1994; 89: 1844-8
49. Goeree R, O'Brien B, Blackhouse G, et al. Economic evaluation of long term management strategies for erosive esophagitis [abstract]. Annu Meet Int Soc Technol Assess Health Care 1998; 14: 74
50. Harris RA, Kuppermann M, Richter JE. Prevention of recurrences of erosive reflux esophagitis: a cost-effectiveness analysis of maintenance proton pump inhibition. Am J Med 1997; 102: 78-88
51. Bate CM, Richardson PDI. A one year model for the cost-effectiveness of treating reflux esophagitis. Br J Med Econ 1992; 2: 5-11
52. Jonsson B, Stalhammar NO. The cost effectiveness of omeprazole and ranitidine in intermittent and maintenance treatment of reflux esophagitis-the case for Sweden. Br J Med Econ 1993; 6: 111-26
53. Zagari M, Villa KF, Freston JW. Proton pump inhibitors versus H2 receptor antagonists for treatment of erosive gastroesophageal reflux disease: a cost-comparative study. Am J Manag Care 1995; 1: 247-55
54. Hatlebakk JG, Berstad A. Lanosprazole 15mg and 30mg daily in maintaining healing and symptom relief in patients with reflux oesophagitis. Aliment Pharmacol Ther 1997; 11: 365-72
55. Poynard T, Staub JL, Lemerez M, et al. Efficacy and safety of lansoprazole 15mg OAD or 30mg OAD as one year maintenance treatment for erosive reflux esophagitis: a randomized

trial [abstract]. Gastroenterology 1995 Apr; 108 (4 Suppl.): A195
56. Baldi F, Bardhan KD, Borman BC, et al. Lansoprazole maintains healing in patients with reflux esophagitis [abstract]. Gastroenterology 1996 Apr; 110 (4 Suppl.): A55
57. Carling L, Axelsson C, Forsell H, et al. Lansoprazole versus omeprazole in long term maintenance treatment of reflux oesophagitis: a Scandinavian multicentre trial [abstract 1036]. Gut 1996; 39 Suppl. 3: 182
58. Hirschowitz BI, Greski-Rose P, Huang B, et al. Lansoprazole is superior to ranitidine in the maintenance of healed erosive esophagitis [abstract]. Gastroenterology 1999; 116: A187
59. Lauritsen K, Junghard O, Eklund S. Esomeprazole 20 mg compared with lansoprazole 15 mg for maintenance therapy in patients with healed reflux esophagitis. J Gastroenterol Hepatol 2002; 17 Suppl.: A1007
60. Bell NJV, Burget D, Howden CW, et al. Appropriate acid suppression for management of gastro-oesophageal reflux disease. Digestion 1992; 51 Suppl. 1: 59-67
61. Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. Am J Gastroenterol 2000; 95: 57-61
62. Wilder-Smith CH, Merki HS. Tolerance during dosing with H2-receptor antagonists: an overview. Scand J Gastroenterol 1992; 27 Suppl. 193: 14-9
63. Sontag SJ. Rolling review: gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1993; 7: 293-312
64. Feldman M, Burton ME. Histamine-2 receptor antagonists: standard therapy for acid-peptic diseases (second of two parts). N Engl J Med 1990; 323: 1749-55
65. Koelz HR. Treatment of reflux esophagitis with H2-blockers, antacids and prokinetic drugs: an analysis of randomized clinical trials. Scand J Gastroenterol 1989; 24 Suppl. 156: 25-36
66. Freston JW, Rose PA, Heller CA, et al. Safety profile of lansoprazole. Drug Saf 1999; 20 (2): 195-205
67. Freston JW. Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective. Am J Gastroenterol 1997; 92 (4): 51S-7S
68. Howden CW, Freston JW. Setting the 'Gold Standards' in the management of gastroesophageal reflux disease. Gastroenterol Today 1996; 6: 1-3

Correspondence and offprints: Dr *James W. Freston*, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, IL 06030-1111, USA.
E-mail: freston@nso.uchc.edu