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ORIGINAL ARTICLE

Lansoprazole for Long-Term Maintenance Therapy of Erosive Esophagitis: Double-Blind Comparison with Ranitidine

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Abstract In a study evaluating the efficacy and safety of lansoprazole to prevent the relapse of erosive esophagitis (EE), 206 of 241 patients (85%) healed after open-label treatment with lansoprazole 30 mg once daily for 8 weeks and received double-blind maintenance treatment with lansoprazole 15 mg once daily or ranitidine 150 mg twice daily for up to 1 year. At 1 year, 67% of lansoprazole-treated and 13% of ranitidine-treated patients remained healed ($P < 0.001$). Lansoprazole-treated patients experienced significantly greater symptom relief ($P < 0.001$), and, if asymptomatic at entry into the maintenance phase, remained asymptomatic for significantly longer than ranitidine-treated patients ($P < 0.001$). Symptom status correlated with healing ($P = 0.001$), supporting the symptom-directed management of EE. Both treatments were well tolerated and no unexpected events occurred. Daily therapy with lansoprazole to prevent the relapse of EE is effective, well tolerated, and superior to ranitidine in the maintenance of healing and symptom relief.

Keywords Erosive esophagitis · Gastroesophageal reflux disease · Maintenance therapy · Lansoprazole · Heartburn · Ranitidine

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Introduction

Erosive esophagitis (EE), a chronic relapsing manifestation of gastroesophageal reflux disease (GERD), is estimated to affect 2% of the population in the United States [1]. Morbidity associated with EE includes heartburn, diminished quality of life, and increased risk of serious esophageal complications, such as esophageal ulcer, stricture, Barrett's esophagus, or esophageal cancer [2, 3]. Extraesophageal manifestations such as respiratory problems, chest pain, laryngeal symptoms, and increased mortality may also be associated with GERD [4].

Acid suppression with proton pump inhibitors (PPIs) is now the preferred treatment option for the initial treatment of GERD [5]. Although short-term, acid-suppressive treatment is effective, the majority of patients with EE relapse unless therapy is continued [6–8]. PPIs are also the preferred agents for the maintenance treatment of EE in patients with healed disease [5, 8–10]; a recent Cochrane review found that both healing and maintenance doses of PPIs were more effective than all of the other therapies (histamine-2 receptor antagonists [H_2RAs], prokinetics, sucralfate) for the long-term management of patients with EE [8].

A study to evaluate the long-term efficacy and safety of the PPI lansoprazole for relapse prevention in patients with healed EE was started almost a decade ago. At that time, H_2RAs were the main alternatives to PPIs for both short- and

long-term acid suppression. Thus, ranitidine was chosen as the comparator for the maintenance phase of the study. Today, H_2RAs are not considered as first-line treatment for EE; however, they remain useful in patients who are intolerant to PPIs. The study consisted of a short-term (8-week) acute healing phase with lansoprazole alone; a 1-year blinded maintenance phase in which the Food and Drug Administration (FDA)-approved maintenance doses of lansoprazole and ranitidine were compared; and a 6-year open-label maintenance phase with lansoprazole alone. This paper presents the results of the 8-week acute treatment period and the 1-year double-blind maintenance phase. The results of the 6-year open-label maintenance phase are reported elsewhere [11].

Methods

Study Design

The M94-140 study (sponsored by Takeda Global Research & Development Center, Inc.) was a Phase III, randomized, parallel-group, positive-controlled, multicenter study consisting of a screening period, an 8-week open-label acute treatment period, a double-blind maintenance treatment period that lasted until the recurrence of EE or for up to 1 year, and a titrated open-label treatment period that lasted for up to 6 years (Fig. 1). This paper focuses on the 8-week acute treatment period and the 1-year double-blind maintenance treatment period of the study.

Ethical Approval/Patient Consent

The study was conducted in accordance with FDA and good clinical practice regulations, and all applicable local regulations. Each investigator underwent a review by an institutional review board, which also approved the protocol with all amendments, the informed consent form, and all other patient information forms related to the study. Each patient was required to sign the informed consent form prior to the initiation of study-specific procedures.

Patients

Male or female patients who were at least 18 years of age with endoscopically proven EE (Grade $\geq$2 using the modified Hetzel–Dent grading scale summarized in Table 1) without coexisting duodenal ulcer and/or gastric ulcer $\geq$3 mm in diameter were eligible for participation in the acute treatment period of this study. To qualify for the double-blind maintenance treatment period, patients had to have endoscopically proven healed EE (Grade 0 or 1) at the end of the 8-week acute treatment period. However, patients could still be symptomatic and be considered for the maintenance phase. Patients were excluded from enrollment if they required more than occasional use ($\leq$10 days/month) of non-steroidal inflammatory drugs (NSAIDs). However, aspirin for cardiovascular indications ($\leq$325 mg/day) was allowed. The use of Gelusil® as needed for the relief of discomfort was also permitted throughout the study. Patients who received a PPI within 4 weeks prior to starting the acute phase of the study were not permitted to enroll. Use of other acid-reducing medications prior to the screening visit was allowed, although these medications (except antacids) had to be discontinued at least 7 days prior to screening. Patients who did not heal (Grade 0 or 1) at the end of the 8-week acute treatment period were not eligible for entry into the double-blind maintenance phase.

Treatment (Acute and Double-Blind)

During the acute treatment period, all patients received open-label oral lansoprazole 30 mg once daily for 8 weeks; this dose is approved by the FDA for the healing of EE. Patients qualifying for the double-blind maintenance treatment period were randomized in an equal ratio to one of the following treatment groups: oral lansoprazole 15 mg once daily or oral ranitidine 150 mg twice daily, for up to 1 year. These doses are currently approved by the FDA for the maintenance of healing of EE.

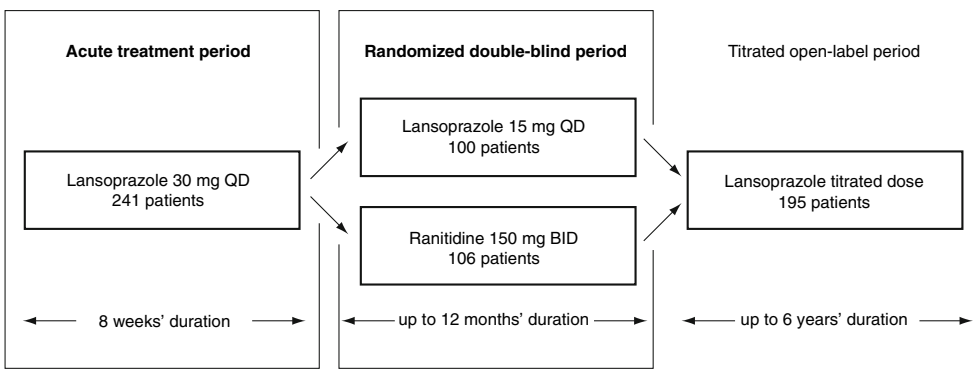

Fig. 1 Overview of the study design. This paper focuses on the highlighted acute open-label treatment and randomized double-blind treatment periods of the study. BID = twice daily; QD = daily

Table 1 The modified Hetzel–Dent esophagitis grading scale [12] developed for Takeda Global Research & Development Center, Inc. for use in lansoprazole studies [13]

Grade	Description
0	Normal-appearing mucosa by endoscopy
1	Mucosal edema, hyperemia, and/or friability of mucosa
2	One or more erosion(s)[a]/ulceration(s)[b] involving <10% of the distal 5 cm of the esophagus
3	Erosions[a]/ulcerations[b] involving 10–50% of the distal 5 cm of the esophagus or an ulcer measuring 3–5 mm in diameter
4	Multiple erosions[a]/ulcerations[b] involving >50% of the distal 5 cm of the esophagus or a single large ulcer >5 mm in diameter

[a] Erosion: superficial break in the esophageal mucosa which is less than 3 mm in width, with or without exudate. Red spots or streaks without breaks in the mucosa are not considered to be erosions

[b] Ulcer: a discrete lesion with appreciable depth and >3 mm in diameter

Study Procedures

During the screening period, patients underwent endoscopy, and gastric biopsy specimens were obtained for endocrine cell evaluation and the appraisal of acute and chronic inflammation, intestinal metaplasia, atrophy, and *Helicobacter pylori* (*H. pylori*) status. A Warthin-Starry silver-stained section along with a positive-control stained slide was assessed to determine the presence of *H. pylori*. Symptom assessments based on investigator interviews and complete physical examinations were also performed. At the end of the 8-week acute treatment period, patients returned to the study center for endoscopy, gastric biopsy, and symptom assessment based on investigator interview. During the double-blind treatment period, patients returned to the study center at months 1, 3, 6, 9, and 12, or in the event of symptom recurrence, for endoscopy, gastric biopsy, and symptom assessment based on investigator interview. The number of Gelusil® tablets (rescue medication) taken since the previous visit was also documented.

Symptoms of heartburn during the day and night were graded according to a 4-point scale (none: no symptoms; mild: did not last long and were easily tolerated; moderate: caused discomfort and interrupted usual activities; severe: caused great interference with usual activities and may have been incapacitating). Symptomatic recurrence was defined as a failure of the study drug to effectively control moderate or severe day and/or night heartburn. A quality of life questionnaire was completed at screening, at the end of the 8-week acute treatment period, and at months 1, 3, 6, 9, and 12 of the double-blind treatment period.

During both the acute and double-blind treatment periods, the safety of the study medications was monitored through adverse events, the use of concurrent medications, brief physical examinations, vital signs assessments, gastric biopsies, and laboratory evaluations, including serum gastrin, a pregnancy test (for women of childbearing potential), and the measurement of digoxin and/or theophylline levels, if applicable. A detailed description of the histological procedures performed on [14] and the classifications of findings from the biopsies are presented elsewhere [15].

Endpoints/Outcomes

The primary aim of the study was to compare the endoscopic recurrence rates of EE, defined as EE Grade ≥ 2 (using the modified Hetzel–Dent grading scale, summarized in Table 1) during maintenance treatment with ranitidine or lansoprazole at FDA-approved doses. The primary efficacy variable was the time to recurrence of esophagitis. Secondary efficacy variables included changes in the severity of symptoms, time to recurrence of day and night heartburn, the average number of Gelusil® tablets used per day, and improvements in the quality of life during the double-blind treatment period. The main safety outcome was the occurrence of adverse events. In addition, laboratory values and gastric biopsy findings during the double-blind treatment period were compared with those obtained at baseline.

Statistical Methods

It was planned that approximately 180 patients (90 patients/group) would enter the double-blind treatment period of the study. This sample size had a 92% probability of detecting significant treatment differences if the true recurrence rates were 25% and 50% for lansoprazole and ranitidine by the end of the double-blind treatment period, respectively ($P < 0.05$, two-sided test).

Efficacy analyses were performed on the intent-to-treat (ITT) and evaluable populations. The ITT population included all patients who entered the double-blind treatment period and who received at least one dose of the study medication. The evaluable population was considered as the primary analysis population and included only patients with evaluable data during the double-blind treatment period. The exclusion of subjects from the evaluable population was determined by adherence to protocol and the availability of per-protocol endoscopy results. All patients

who received at least one dose of the study medication were included in the safety analyses.

The primary efficacy variable, time to recurrence of EE, was estimated using life-table methodology. The results were also displayed as the percentage of patients who remained healed (maintenance rates). Treatment group comparisons were made using Cochran-Mantel-Haenszel methodology, with time as the stratification factor.

Life-table analysis of between-treatment differences in the time to return of heartburn symptoms was performed using Cochran-Mantel-Haenszel methodology for ordered response categories using the baseline value as the stratification factor. Between-treatment comparisons for the subjects' average number of Gelusil® tablets used per day were performed using the Wilcoxon two-sample test. The medians of the average number of tablets were presented. For the quality of life, comparison between treatment groups for change from double-blind baseline to each visit for item and scale scores were analyzed by either the Cochran-Mantel-Haenszel test (for single items with ordered scores) or analysis of variance (ANOVA).

Retrospective analyses were performed to evaluate the relationship between symptom status and the presence of EE (McNemar's test), and to determine the predictors of recurrence (logistic regression analysis). The demographic and baseline variables evaluated as possible predictors of recurrence included age, gender, race, body mass index, tobacco use, alcohol consumption, grade of EE, symptom severity, *H. pylori* status at acute baseline, and double-blind treatment group.

For the safety analyses, all treatment-emergent and treatment-related adverse events during the acute and double-blind periods were summarized, and the proportion of patients reporting adverse events in each treatment group during the double-blind period was compared using Fisher's exact test.

Statistical tests used in the analysis of data were two-tailed, and a type I error rate (alpha level) of 0.05 was used. All analyses were performed using SAS® 6.12 (SAS Institute Inc., SAS, Cary, NC).

Results

Patient Disposition

A total of 241 patients with EE received acute treatment with lansoprazole 30 mg once daily for 8 weeks. At the end of the acute treatment period, 206 (85%) patients showed healed EE (Grade 0 or 1) as determined by endoscopy and entered the double-blind treatment period, 13 (5%) withdrew from acute open-label treatment prematurely (six patients because of adverse events), and 22 (9%) remained unhealed and were, thus, not eligible for entry into the double-blind treatment period. A total of 195 patients (95%) completed the double-blind period (experienced recurrence or completed 1 year of therapy).

All 206 patients who entered the double-blind treatment period received at least one dose of study medication and were included in the ITT analyses. Of these patients, 100 were randomized to receive lansoprazole 15 mg once daily and 106 to receive ranitidine 150 mg twice daily for a maximum of 1 year or until recurrence (EE Grade $\geq$2). Within the ITT population, there were no statistically significant differences between treatment groups with respect to demographic variables or the severity of esophagitis at acute baseline (Table 2). The severity of day or night heartburn at acute baseline did not differ significantly between treatment groups. The majority (68–77%) of patients in each treatment group reported mild to moderate day heartburn within the 2 weeks prior to acute baseline, and approximately half (43–56%) reported mild to moderate night heartburn within the same time period.

A total of 177 patients (86%) were considered to be evaluable and were included in the evaluable efficacy analyses (89 patients who received lansoprazole and 88 who received ranitidine). The remaining 29 patients were excluded from the evaluable analyses for various deviations from the protocol, the most common reasons being: less than 14 total days of prescribed study medication (nine patients, 4%); no available per-protocol endoscopy after the start of double-blind treatment (eight patients, 4%); and chronic pre-study use of NSAIDs (seven patients, 3%).

Recurrence Rates

Evaluable patients receiving lansoprazole 15 mg once daily remained healed of EE (primary endpoint) significantly longer ($P < 0.001$) than those receiving ranitidine 150 mg twice daily. By the end of the 1-year double-blind treatment period, 67% (95% confidence interval: 56.4–77.6) of the lansoprazole-treated patients remained healed of EE compared to only 13% (95% confidence interval: 4.4–22.5) of ranitidine-treated patients (Fig. 2). Among subjects with the recurrence of EE, the median time to recurrence was three times longer in the lansoprazole group compared to the ranitidine group (92 and 36 days, respectively). Results in the ITT population were almost identical to those in the evaluable population.

Symptom Assessment

The majority of patients (91%) were asymptomatic (free of moderate or severe day and/or night heartburn) at double-blind baseline. Patients remained asymptomatic for

Table 2 Demographic and baseline characteristics of patients who received double-blind treatment with ranitidine ($n = 106$) or lansoprazole ($n = 100$) for the maintenance therapy of erosive esophagitis (EE; intent-to-treat [ITT] population)

Treatment group ITT population (*N*) ITT population (*N*)	Ranitidine 150 mg BID *N* = 106, % (*n*)	Lansoprazole 15 mg QD *N* = 100, % (*n*)
Gender		
Female	37% (39)	28% (28)
Male	63% (67)	72% (72)
Age (years)[a]		
Mean (SD)	50.3 (14.3)	49.6 (13.4)
Range	19–82	19–77
Race		
White	89% (94)	91% (91)
Black	7% (7)	7% (7)
Other	5% (5)	2% (2)
Tobacco use		
Tobacco nonuser[b]	79% (84)	72% (72)
Tobacco user	21% (22)	28% (28)
Alcohol use		
Nondrinker[c]	51% (54)	48% (48)
Drinker	49% (52)	52% (52)
Caffeine use		
No	12% (13)	18% (18)
Yes	88% (93)	82% (82)
H. pylori status[d]	*N* = 105	*N* = 99
Positive	18% (19)	17% (17)
Negative	82% (86)	83% (82)
Body mass index[a]		
Mean (SD)	29.5 (4.8)	28.5 (4.5)
Range	17–41	20–47
Grade of esophagitis at acute baseline		
Grade 2	59% (63)	58% (58)
Grade 3	30% (32)	36% (36)
Grade 4	10% (11)	6% (6)

BID = twice daily; QD = daily; SD = standard deviation

[a] At acute baseline

[b] Includes ex-tobacco users

[c] Includes ex-drinkers

[d] Assessed by histology (Warthin-Starry silver stain) during the screening period; results not available for all patients

significantly ($P < 0.001$) longer when treated with lansoprazole as compared with ranitidine (Fig. 3). By the end of the 1-year double-blind treatment period, 56% of the lansoprazole-treated patients remained asymptomatic compared with only 15% of ranitidine-treated patients. Ranitidine-treated patients used eight times more Gelusil® (average of 0.90 tablets/day) compared to the lansoprazole-treated patients (0.11 tablets/day) ($P < 0.001$). As with recurrence rates, symptom results in the ITT population were almost identical to those in evaluable patients.

Relationship Between Symptoms and Healing

Ranitidine-treated patients were more likely to be symptomatic (moderate or severe day and/or night heartburn) at the time of recurrence of EE than lansoprazole-treated patients. This relationship was analyzed in 91 evaluable patients who underwent symptom assessment at the time of endoscopy when the recurrence of EE was identified. Of these patients, 45 of 65 treated with ranitidine (69%) were symptomatic compared with 10 of 26 treated with lansoprazole (38%).

During maintenance treatment, it was unusual for study participants who were asymptomatic to have relapse of EE. This relationship was summarized from 511 visits when patients underwent symptom assessment at the time of endoscopy. For patient visits without heartburn symptoms present, EE was observed in 10% (39/376) of the visits overall (25% [20/79] of visits for ranitidine patients and 6% [19/297] of visits for lansoprazole patients). When heartburn symptoms were present during a visit, EE was observed in 44% (60/135) of visits overall (53% [48/90] of visits for ranitidine patients and 27% [12/45] of visits for lansoprazole patients). This suggests a relationship between the presence of EE and symptom status during maintenance treatment (McNemar's test: $P = 0.001$ overall, $P = 0.005$ for ranitidine, and $P = 0.052$ for lansoprazole). The majority of recurrences of EE (66/99) were observed early during the

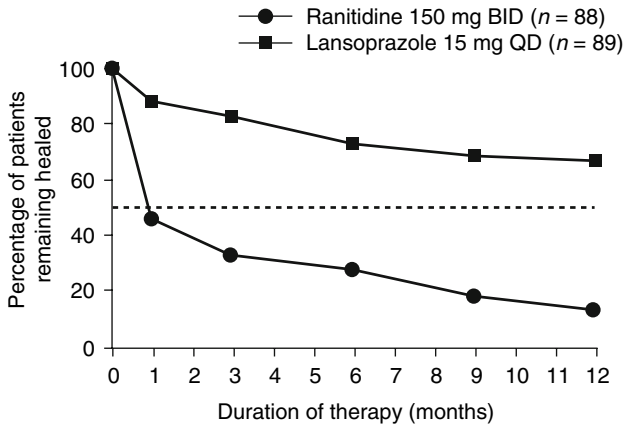

Fig. 2 Percentage of patients remaining healed of erosive esophagitis (EE) during maintenance therapy with ranitidine 150 mg twice daily or lansoprazole 15 mg once daily as calculated by life-table methods (evaluable patients); $P < 0.001$ for the between-treatment difference in the time to recurrence. BID = twice daily; QD = daily

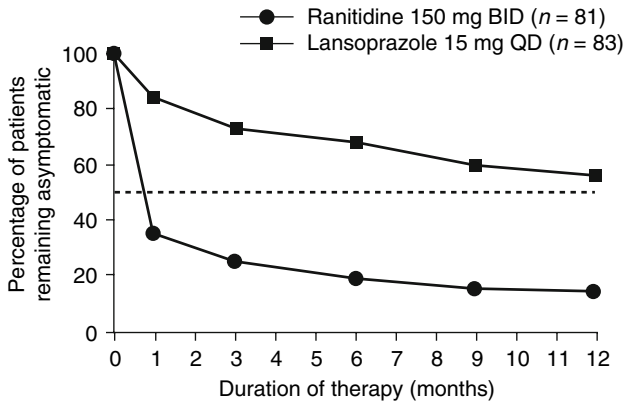

Fig. 3 Percentage of patients remaining asymptomatic (free of moderate or severe day and/or night heartburn) during therapy with ranitidine 150 mg twice daily or lansoprazole 15 mg once daily calculated by life-table methods (evaluable patients); $P < 0.001$ for the between-treatment difference in the time to recurrence. BID = twice daily; QD = daily

course of treatment: during the first 3 months of treatment, EE was observed in 54% (45/84) of visits with symptoms present and in 18% (21/119) of visits without symptoms present.

Predictors of Recurrence

In logistic regression analysis, the treatment group was the most important variable predicting recurrence (odds ratio = 0.15 [95% CI = 0.08–0.30]) during the double-blind maintenance phase of the study, with ranitidine patients being seven times as likely to recur as lansoprazole patients. The number of patients who needed to be treated with lansoprazole instead of ranitidine in order to prevent one recurrence of EE was three. Subjects over the age of 65 years and subjects with a higher baseline EE grade were also more likely to recur (model coefficients statistically significant at $P = 0.01$ and $P = 0.02$, respectively). No other demographic variables (gender, race, body mass index, tobacco use, alcohol consumption, symptom status, *H. pylori* status) predicted recurrence.

Quality of Life

Throughout the maintenance phase of the study, lansoprazole-treated patients showed significantly ($P \leq 0.05$) greater improvements than ranitidine-treated patients in several quality of life parameters. Specifically, lansoprazole-treated patients showed significantly greater improvements in the frequency of heartburn, severity of heartburn, symptom index, problems of activity limitation, eating and drinking problems, symptom problems, health distress, and social functioning. Quality of life findings from the study are presented elsewhere [16].

Safety Evaluation

Extent of Exposure

Patients treated with lansoprazole remained on maintenance therapy for significantly longer (mean 236.9 days) than patients treated with ranitidine (mean 88.7 days; $P \leq 0.05$).

Adverse Events

During the acute treatment period, lansoprazole was well tolerated, with 37 out of 241 patients (15%) reporting at least one adverse event that was considered to be possibly or probably related to treatment. The only such event reported by more than 5% of patients was diarrhea (reported in 6% of patients). Seven patients discontinued treatment due to adverse events: abdominal pain (two patients); myalgia; abdominal pain and chest pain; abdominal pain and flatulence; anorexia and nausea; and headache.

During the double-blind maintenance phase, there were significantly ($P = 0.02$) more subjects with treatment-emergent adverse events among lansoprazole subjects (71%) than among ranitidine subjects (55%), who had nearly a 3-fold shorter treatment exposure than subjects receiving lansoprazole. No significant difference between lansoprazole and ranitidine was observed in the overall incidence of adverse events considered to be possibly or probably related to treatment (20% vs. 12%, respectively), or the overall incidence of any specific adverse event considered to be possibly or probably related to treatment. In addition, no unexpected events occurred. The most

frequently reported adverse events were abdominal pain (5%) and headache (5%) for lansoprazole, and headache (6%) for ranitidine. Nine lansoprazole-treated patients and one ranitidine-treated patient experienced at least one serious adverse event. None of these were considered to be related to the study medication. Two lansoprazole-treated patients and no ranitidine-treated patients discontinued treatment due to adverse events, both considered by the investigator not to be related to the study drug. One subject discontinued treatment due to inflammation at the injection site due to intravenous drug use, and the other subject due to bloody diarrhea, duodenal ulcer, and kidney failure.

Laboratory and Biopsy Findings

No clinically significant trends were observed in any laboratory parameters. Changes in fasting serum gastrin levels were as expected in these patients, and any increases seen in lansoprazole-treated patients usually occurred early during the course of therapy and then stabilized. During the acute-treatment period, 12 patients had serum gastrin levels >200 pg/ml and five patients had levels >400 pg/ml. During the double-blind phase, two ranitidine and 13 lansoprazole patients had levels >200 pg/ml, and one ranitidine and three lansoprazole patients had levels >400 pg/ml. At the end of the double-blind treatment period, the median fasting serum gastrin level was 69.5 pg/ml in the lansoprazole group and 53.0 pg/ml in the ranitidine group. Gastric biopsy findings were generally unremarkable and were as expected in this population of patients [15].

Discussion

Clinical trials have shown that the majority of patients with healed EE who received maintenance therapy with placebo will relapse within 1 month of such a treatment [17, 18]. In the current study, lansoprazole 15 mg once daily maintained endoscopically confirmed remission for a significantly longer period of time than ranitidine 150 mg twice daily, with 67% of lansoprazole-treated patients and 13% of ranitidine-treated patients remaining healed at 1 year. Of note, less than half of the ranitidine-treated patients (46%) remained in remission after 1 month of therapy, compared with 88% of lansoprazole-treated patients.

Another study compared lansoprazole and ranitidine in the maintenance of the healing of EE using a healing (rather than maintenance) dose of ranitidine (300 mg twice daily) [19]. This study showed that lansoprazole at daily doses of 30 or 15 mg was more effective than ranitidine 300 mg twice daily with respect to the time to endoscopic relapse ($P \leq 0.001$). Relapse had occurred in 20.0%, 31.4%, and 67.6% of the patients treated with lansoprazole 30 mg, 15 mg, and ranitidine, respectively, after 12 months. In addition, lansoprazole prevents the recurrence of esophagitis in most patients, regardless of the degree of erosion prior to healing [20]. Other PPIs have also been compared with ranitidine as a long-term maintenance therapy for EE and, as in the current study, when administered at FDA-approved doses for maintenance therapy, they have produced significantly higher remission rates than ranitidine [21, 22].

The current study also showed that lansoprazole provided superior control of the symptoms of EE over ranitidine when administered at FDA-approved doses. Both the extent and duration of symptomatic relief and the requirement for rescue Gelusil® were significantly better with lansoprazole than ranitidine. Similarly, another study comparing lansoprazole and ranitidine for the maintenance of the healing of EE showed that lansoprazole-treated patients experienced significantly less heartburn and episodes of regurgitation than ranitidine-treated patients [19]. Studies comparing other PPIs and ranitidine for the symptomatic control of EE have also found superior symptom control with PPIs compared to H_2RAs [21–23].

In this study, symptom status appeared to correlate with the presence or recurrence of EE during maintenance treatment. Ranitidine-treated patients were more likely to be symptomatic at the time of recurrence of EE than lansoprazole-treated patients. Furthermore, for patients who were asymptomatic, the relapse of EE was unusual during the study. During the maintenance phase, only 39 out of 376 patient visits (10%) showed positive results for EE without symptoms of heartburn. These results provide support for the symptom-based treatment of EE patients, in that symptoms may indicate the presence or recurrence of EE and the need to consider treatment modification. However, in view of the high likelihood of recurrence without effective maintenance therapy, treatment decisions should *not* be made solely on the basis of symptoms.

A high correlation between the absence of symptoms and the maintenance of the healing of EE was also found in a study of maintenance treatment with once daily esomeprazole for 6 months [24]. Among patients who reported no heartburn, healing was maintained in more than 98% of patients treated with esomeprazole 40 or 20 mg, 95% of patients treated with esomeprazole 10 mg, and 92% of patients receiving placebo. Few patients with the recurrence of EE were heartburn-free. However, the recurrence of symptoms did not predict the recurrence of EE: only 4.2%, 15.2%, and 38.5% of patients who had heartburn and received esomeprazole 40, 20, and 10 mg, respectively, experienced the recurrence of EE. In a study of maintenance treatment with pantoprazole 20 mg daily for 6 months in elderly (>65 years of age) patients with healed EE, the

presence of any reflux symptom (heartburn, acid regurgitation, or chest pain) was found to significantly predict the relapse of EE (odds ratio 26.7; $P = 0.0001$) [25].

Despite these correlations between symptoms and the maintenance of the healing of EE, several studies have shown that symptoms are not a good predictor of the presence or absence of EE when patients are off acid-suppressing medications. A study using the data from five double-blind trials of acute healing treatment (8 weeks) with PPIs in 11,945 patients with EE showed that, at baseline, the severity of heartburn did not correlate with esophagitis severity [26]. Another analysis of the same patient population showed that, while the presence of persistent dysphagia correlated with unhealed EE, it was not a reliable predictor of EE severity [27]. Taking into account the fact that symptoms are not a good predictor of the presence or absence of EE at baseline, the data from the current study suggest that, once a diagnosis of EE has been confirmed, symptom status provides a reasonable basis for choosing the most appropriate management strategy.

Age and EE grade prior to initial healing (acute treatment baseline) were found to predict recurrence during the maintenance phase of this study. The elderly often have more severe grades of esophagitis, despite having less prominent symptoms than younger GERD patients [28]. A recent analysis by DeVault et al. [29] showed no effect of age on EE healing with PPIs or H_2RAs; however, the maintenance of healing was not addressed. The severity of EE grade has been previously shown to negatively impact the initial healing and maintenance of EE healing with PPIs and H_2RAs [18, 30]. However, we found that treatment was the most important predictor of recurrence; patients receiving ranitidine maintenance treatment had seven times the likelihood of recurrence as compared to patients receiving lansoprazole (odds ratio of 0.15). A study of maintenance treatment with esomeprazole 20 mg or lansoprazole 15 mg once daily for 6 months in patients with EE also showed that the recurrence of EE was more likely with higher baseline grades of the disease [31]. After 6 months, the endoscopic/symptomatic relapse rate was 19.5% for lansoprazole and 11.6% for esomeprazole in patients with lower baseline grades of disease (Los Angeles grades A and B), and 30.5% and 20.7%, respectively, in patients with higher baseline grades of disease (Los Angeles grades C and D). In the current study, life-table analysis estimated that 17% of ranitidine subjects with Grade 2 and 10% of ranitidine subjects with Grades 3 or 4 EE remained healed compared to 70% (Grade 2) and 63% (Grades 3 or 4) of lansoprazole subjects at the end of the 12-month treatment period.

The current study showed that maintenance treatment with lansoprazole was significantly better than ranitidine in improving patients' quality of life. Other studies have also shown a greater improvement in the quality of life during maintenance treatment with PPIs than with H_2RAs [32, 33]. However, some studies have found no difference between PPIs and H_2RAs in terms of the improvement in the quality of life during maintenance therapy [34, 35]. All of these studies, however, showed that treatment is associated with the improved quality of life of patients with GERD.

Overall, in this study, lansoprazole 15 mg once daily was well tolerated over a 1-year period. There were no clinically important differences between lansoprazole and ranitidine with respect to adverse events, laboratory abnormalities, and gastric biopsy results, and no serious adverse events were considered to be treatment-related. The results of this study, therefore, add to the extensive body of clinical data supporting the safety and tolerability of lansoprazole for short- or long-term use in patients with acid-related disorders [36]. Overwhelming evidence from this study and others [8, 20] indicates that maintenance therapy with a PPI should be considered for all patients with healed EE.

In conclusion, maintenance therapy with lansoprazole 15 mg once daily in patients with EE is effective and well tolerated, and is superior to ranitidine 150 mg twice daily in terms of the maintenance of healing and symptom relief. Importantly, symptom status appears to correlate with the maintenance of healing, thus, providing support for the symptom-directed management of EE.

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References

1. Spechler SJ. Epidemiology and natural history of gastro-oesophageal reflux disease. *Digestion*. 1992;51(suppl 1):24–29.
2. McDougall NI, Johnston BT, Kee F, Collins JSA, McFarland RJ, Love AHG. Natural history of reflux oesophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. *Gut*. 1996;38:481–486. doi:10.1136/gut.38.4.481.
3. Heading RC. Review article: diagnosis and clinical investigation of gastro-oesophageal reflux disease. A European view. *Aliment Pharmacol Ther*. 2004;20(suppl 8):9–13. doi:10.1111/j.1365-2036.2004.02221.x.
4. Ruigomez A, Garcia Rodriguez LA, Wallander MA. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther*. 2004;20:751–760. doi:10.1111/j.1365-2036.2004.02169.x.
5. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice

Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol*. 1999;94:1434–1442. doi:10.1111/j.1572-0241.1999.1123_a.x.
6. Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2004;20(suppl 8):2–4. doi:10.1111/j.1365-2036.2004.02219.x.
7. Holtmann G, Adam B, Liebregts T. Review article: the patient with gastro-oesophageal reflux disease—lifestyle advice and medication. *Aliment Pharmacol Ther*. 2004;20(suppl 8):24–27. doi:10.1111/j.1365-2036.2004.02224.x.
8. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database Syst Rev*. 2004;4:CD003245. doi:10.1002/14651858.CD003245.pub2.
9. Crawley JA, Schmitt CM. How satisfied are chronic heartburn sufferers with their prescription medications? Results of the patient unmet needs survey. *J Clin Outcomes Manag*. 2000;7:29–34.
10. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet*. 2006;367:2086–2100. doi:10.1016/S0140-6736(06)68932-0.
11. Peura DA, Lee C, Siepman N, Kovacs TO. Long-term efficacy of symptom-based, titrated dose lansoprazole in preventing relapse of erosive reflux esophagitis in subjects with a recent history of erosive reflux esophagitis. *Gastroenterology*. 2005;128(suppl 2):A527–A528.
12. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology*. 1988;95:903–912.
13. Kovacs TO, Lee CQ, Chiu YL, Pilmer BL, Metz DC. Intravenous and oral lansoprazole are equivalent in suppressing stimulated acid output in patient volunteers with erosive oesophagitis. *Aliment Pharmacol Ther*. 2004;20(8):883–889. doi:10.1111/j.1365-2036.2004.02188.x.
14. Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of non-antral gastric endocrine growth in man. *Digestion*. 1988;41:185–200.
15. Haber M, Amer F, Peura D, Qin Q. Chronic gastritis and erosive esophagitis: prevalence and effect of long-term lansoprazole treatment. *Gastroenterology*. 2005;128:A527.
16. Kovacs TOG, Atkinson S, Spalding J, Hunt B. Long-term GERD symptoms and quality-of-life improvement in subjects with healed erosive esophagitis treated for up to 7 years with titrated-dose lansoprazole. *Gastroenterology*. 2006;130(suppl 2):A454. abstract.
17. Johnson DA, Benjamin SB, Vakil NB, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol*. 2001;96:27–34. doi:10.1111/j.1572-0241.2001.03443.x.
18. Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. *Ann Intern Med*. 1996;124:859–867.
19. Gough AL, Long RG, Cooper BT, Fosters CS, Garrett AD, Langworthy CH. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. *Aliment Pharmacol Ther*. 1996;10:529–539. doi:10.1046/j.1365-2036.1996.14156000.x.
20. Freston JW, Jackson RL, Huang B, Ballard ED. Lansoprazole for maintenance of remission of erosive oesophagitis. *Drugs*. 2002;62:1173–1184. doi:10.2165/00003495-200262080-00004.
21. Adamek RJ, Behrendt J, Wenzel C. Relapse prevention in reflux oesophagitis with regard to *Helicobacter pylori* status: a double-blind, randomized, multicentre trial to compare the efficacy of pantoprazole versus ranitidine. *Eur J Gastroenterol Hepatol*. 2001;13:811–817. doi:10.1097/00042737-200107000-00009.
22. Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. *Aliment Pharmacol Ther*. 2004;20:567–575. doi:10.1111/j.1365-2036.2004.02121.x.
23. Festen HP, Schenk E, Tan G, Snel P, Nelis F. Omeprazole versus high-dose ranitidine in mild gastroesophageal reflux disease: short- and long-term treatment. The Dutch Reflux Study Group. *Am J Gastroenterol*. 1999;94:931–936. doi:10.1111/j.1572-0241.1999.989_1.x.
24. Vakil NB, Shaker R, Johnson DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. *Aliment Pharmacol Ther*. 2001;15:927–935. doi:10.1046/j.1365-2036.2001.01024.x.
25. Pilotto A, Leandro G, Franceschi M, Ageing and Acid-Related Disease Study Group. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. *Aliment Pharmacol Ther*. 2003;17:1399–1406. doi:10.1046/j.1365-2036.2003.01593.x.
26. Fennerty MB, Johnson DA. Heartburn severity does not predict disease severity in patients with erosive esophagitis. *MedGenMed*. 2006;8(2):6.
27. Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: prevalence, severity, and response to proton pump inhibitor treatment. *Clin Gastroenterol Hepatol*. 2004;2(8):665–668. doi:10.1016/S1542-3565(04)00289-7.
28. Pilotto A, Franceschi M, Leandro G, et al. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *J Am Geriatr Soc*. 2006;54(10):1537–1542. doi:10.1111/j.1532-5415.2006.00899.x.
29. DeVault KR, Morgenstern DM, Lynn RB, Metz DC. Effect of pantoprazole in older patients with erosive esophagitis. *Dis Esophagus*. 2007;20:411–415. doi:10.1111/j.1442-2050.2007.00642.x.
30. Annibale B, Franceschi M, Fusillo M, Beni M, Cesana B, Delle Fave G. Omeprazole in patients with mild or moderate reflux esophagitis induces lower relapse rates than ranitidine during maintenance treatment. *Hepatogastroenterology*. 1998;45(21):742–751.
31. DeVault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. *Clin Gastroenterol Hepatol*. 2006;4:852–859. doi:10.1016/j.cgh.2006.03.006.
32. Wiklund I, Bardhan KD, Müller-Lissner S, et al. Quality of life during acute and intermittent treatment of gastro-oesophageal reflux disease with omperazole compared with ranitidine. Results from a multicentre clinical trial. The European Study Group. *Ital J Gastroenterol Hepatol*. 1998;30(1):19–27.
33. Hansen AN, Bergheim R, Ageratums H, Lund H, Wiklund I, Moum B. Long-term management of patients with symptoms of gastro-oesophageal reflux disease—a Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. *Int J Clin Pract*. 2006;60(1):15–22. doi:10.1111/j.1368-5031.2006.00768.x.
34. Oster G, Thompson D, Katz S, et al. The GORD outcomes trial: a randomized study to assess outcomes and costs in primary care practice. *Gastroenterology*. 1998;114:A32. doi:10.1016/S0016-5085(98)80130-3. abstract.
35. Kaplan-Machlis B, Spiegler GE, Zodet MW, Revicki DA. Effectiveness and costs of omeprazole vs. ranitidine for treatment of symptomatic gastroesophageal reflux disease in primary care clinics in West Virginia. *Arch Fam Med*. 2000;9(7):624–630. doi:10.1001/archfami.9.7.624.
36. Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. *Drugs*. 2001;61:1801–1833. doi:10.2165/00003495-200161120-00011.