J Gastroenterol (2011) 46:724–735
DOI 10.1007/s00535-011-0397-7

ORIGINAL ARTICLE—ALIMENTARY TRACT

Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial

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Received: 16 December 2010 / Accepted: 28 February 2011 / Published online: 16 April 2011

Abstract
Background The efficacy of low-dose lansoprazole has not been established for the prevention of recurrent gastric or duodenal ulcers in those receiving long-term low-dose aspirin (LDA) for cardiovascular and cerebrovascular protection. This study sought to examine the efficacy of low-dose lansoprazole (15 mg once daily) for the secondary prevention of LDA-associated gastric or duodenal ulcers.

Methods Patients were randomized to receive lansoprazole 15 mg daily ($n = 226$) or gefarnate 50 mg twice daily ($n = 235$) for 12 months or longer in a prospective, multicenter, double-blind, randomized active-controlled trial, followed by a 6-month follow-up study with open-label lansoprazole treatment. The study utilized 94 sites in Japan and 461 Japanese patients with a history of gastric or duodenal ulcers who required long-term LDA therapy for cardiovascular and cerebrovascular disease.
Results The primary endpoint was the development of gastric or duodenal ulcers. The cumulative incidence of gastric or duodenal ulcers on days 91, 181, and 361 from the start of the study was calculated by the Kaplan–Meier method as 1.5, 2.1, and 3.7%, respectively, in the lansoprazole group versus 15.2, 24.0, and 31.7%, respectively, in the gefarnate group. The risk of ulcer development was

For the Lansoprazole Ulcer Prevention Study Group (Low-Dose Aspirin Therapy).

Electronic supplementary material The online version of this article (doi:10.1007/s00535-011-0397-7) contains supplementary material, which is available to authorized users.

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significantly (log-rank test, $P < 0.001$) lower in the lansoprazole group than in the gefarnate group, with the hazard ratio being 0.099 (95% confidence interval [CI] 0.042–0.230).

Conclusion Lansoprazole was superior to gefarnate in reducing the risk of gastric or duodenal ulcer recurrence in patients with a definite history of gastric or duodenal ulcers who required long-term LDA therapy.

Keywords Low-dose aspirin · Gastric or duodenal ulcers · Lansoprazole · Cardiovascular diseases · Cerebrovascular diseases

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin (LDA), are known to disrupt the mucosal resistance to gastric acid through mechanisms including the decreased production of endogenous prostaglandin in the gastric mucosa, and are thus associated with adverse events such as gastric or duodenal ulcers. In one Japanese study of patients presenting with a bleeding ulcer, 7.6% were taking LDA [1]. Another study found the point prevalence of ulcers in LDA users to be 11.9–15.2%, irrespective of the aspirin formulation [2]. Furthermore, several observational studies have suggested that the increasing use of LDA is becoming a major cause of bleeding ulcers [3]. In a Japanese single-institution report, ulcer lesions were endoscopically identified in 38 (12.4%) of 305 patients taking LDA [4].

When patients present with gastrointestinal bleeding, discontinuation of LDA is recommended according to various guidelines [5]. However, discontinuation of LDA can be associated with a recurrence of disease, and this can result in serious outcomes [6]. Thus, it is vitally important to ensure prophylaxis of gastric or duodenal ulcers in patients on LDA therapy.

In this context, a number of controlled studies have reported on the prevention of gastric or duodenal ulcers with regular-dose H2-receptor antagonists or proton pump inhibitors (PPIs) in patients during LDA therapy [7–10]. Based on the evidence obtained to date, a clinical expert consensus statement [5] recommends PPIs as the preferred agents for the prophylaxis of LDA-associated gastrointestinal injury. However, to date, low-dose lansoprazole has not been evaluated in a clinical trial for its prophylactic efficacy in patients with definitive evidence of previous ulcer development.

This study thus aimed to examine the preventive effect of low-dose lansoprazole (15 mg daily) against the recurrence of gastric or duodenal ulcer associated with long-term LDA therapy in patients with definitive evidence of previous ulcer history. Ulcer recurrence was defined as endoscopically confirmed ulcers, and the occurrences of gastric or duodenal bleeding with or without hospitalization were also evaluated. Appendix 1 shows the list of investigators for the Lansoprazole Ulcer Prevention Study Group (low-dose aspirin therapy).

Given that no drug has been proven to be effective for the prevention of gastric or duodenal ulcer associated with LDA therapy in Japan, and given that it is unethical to conduct a placebo-controlled trial in patients at high risk of developing gastric or duodenal ulcers, the present study was designed to compare the efficacy of lansoprazole 15 mg once daily and gefarnate 50 mg twice daily [11, 12]. Gefarnate is a cytoprotective anti-ulcer agent which is approved for the treatment for gastric or duodenal ulcers. These cytoprotective anti-ulcer agents are commonly prescribed as prophylactic drugs to reduce NSAID- or LDA-induced gastrointestinal injury, although they have not been investigated in a controlled trial for the latter indication.

Methods

Design overview

The study protocol was approved by the Ethics Committee of each participating institution, and all patients gave written informed consent to participate in the study. The Independent Data Monitoring Committee planned an interim analysis in advance to investigate whether or not to continue the study on the basis of interim efficacy and safety findings, based on the predefined criteria. An independent statistician performed the interim analysis on behalf of the Independent Data Monitoring Committee. After the committee made the decision to discontinue the double-blind trial, the patients at the 68 participating healthcare institutes were invited to move on to the follow-up trial with open-label lansoprazole treatment lasting up to 6 months. This trial was registered with ClinicalTrials.gov, number NCT00762359.

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Setting and participants

Patients were enrolled in the study if they met the following criteria: those who were being given LDA when they gave informed consent, and who required long-term LDA therapy after the start of the study (day 1) with the investigational drug; and those in whom a history of gastric or duodenal ulcer (or gastroduodenal ulcer) was confirmed by endoscopy, i.e., those who were confirmed to have an ulcer scar on day 1 or were confirmed to have an ulcer or ulcer scar in an endoscopic examination performed prior to day 1 (e.g., photographs, films).

Patients were excluded if they were confirmed to have an open gastric or duodenal ulcer or an active upper gastrointestinal hemorrhage by endoscopy on day 1; aspirin-induced asthma or hypersensitivity to NSAIDs including aspirin, or a history of hypersensitivity; a history of surgery or a planned operation which affects gastric secretion (e.g., upper gastrointestinal tract resection, vagotomy); clinically significant liver or kidney disorder (including liver tests demonstrating aspartate aminotransferase [AST]/alanine aminotransferase [ALT] values 2.5 times or higher than their upper limit of normal, or creatinine levels 2.0 times or higher than its upper limit of normal); or an active cancer.

All patients confirmed to be eligible at each trial site were reassessed for their eligibility, based either on endoscopic images on films or data submitted after randomization, by an independent panel of expert endoscopists.

Randomization and intervention

Patients who met the inclusion criteria were randomly assigned to one of the following two treatment groups: a group receiving the investigational drug (lansoprazole 15 mg orally given once daily) and the cytoprotective anti-ulcer agent, gefarnate placebo (twice daily) or a group receiving gefarnate [11, 12] (50 mg orally given twice daily) and a lansoprazole placebo (once daily), in combination with LDA (81–324 mg given once daily) for a duration of 12 months or longer (up to 30 months). Lansoprazole and gefarnate placebos were used to ensure that all patients followed the same regimen and that blinding was maintained. The treatment-group assignment was done by computer-generated random sequence numbers. Patients were randomly assigned by investigators to receive lansoprazole or gefarnate at a 1:1 ratio according to the unique sequential numbers for the study drugs, which were pre-assigned to each study site before the start of the treatment. When the onset of ulcer was diagnosed endoscopically or LDA was changed to different drugs, the subjects were excluded from the study at that time point.

Outcomes and measurements

The primary endpoint was the recurrence of gastric or duodenal ulcers, defined as patients confirmed to have active-stage or healing-stage ulcers associated with a mucosal defect with whitish exudates measuring 3 mm or greater. All ulcers confirmed on endoscopy and reported from each study site were reconfirmed by the independent expert panel, based on submitted films. The secondary endpoints were the development of gastric and/or duodenal hemorrhagic lesions as observed with endoscopy, treatment discontinuations due to lack of efficacy, gastric and/or duodenal mucosal damage as assessed with a modified Lanza score [13], and gastrointestinal symptoms.

Follow-up procedures

Endoscopy was scheduled every 12 weeks until 12 months of treatment and every 24 weeks after 12 months. Non-scheduled endoscopy was also performed if patients were suspected of having symptoms associated with ulcers or signs and symptoms indicative of gastrointestinal bleeding.

Every 4 weeks, clinical laboratory tests (chemistry, hematology, and urinalysis) were performed, blood pressure was measured, compliance checks (returned tablet counts) were conducted, and patients were asked about any adverse effects they experienced. All patients were scheduled to receive the study treatments in a double-blind fashion until 12 months after the start of the study in the last enrolled patient. After the termination of the double-blind trial, patients at the 68 study sites were invited to participate in the follow-up study, in which all patients were treated once daily with lansoprazole 15 mg. If onset of an ulcer was confirmed on endoscopy in a patient, the patient discontinued their medication, and antiulcer treatment – such as full-dose PPI therapy – was offered for ulcer healing.

Statistical analysis

The 1-year cumulative incidences of ulcer events in patients treated with lansoprazole and gefarnate, in addition to LDA therapy, were assumed to be 6 and 13%, respectively, which suggested that the hazard ratio (HR) of the lansoprazole-treated group relative to the gefarnate-treated group was 0.44 under an exponential assumption of event distributions. We required a total of 64 ulcer events (endpoints) for the two treatment groups to ensure a statistical power of 90% using a log-rank test with a two-sided alpha of 5%. To observe 64 events, we required the enrollment of 406 patients for each treatment group at randomization, for a total of 812 patients for the study, assuming a mean follow-up duration of 1 year and a 1-year dropout rate of 20%.

One interim analysis was planned in advance for the Independent Data Monitoring Committee to perform when half of the required number of ulcer events was observed. The O'Brien-Fleming boundary, based on the information fraction of 0.5, was employed for an overall significance level of $\alpha = 0.05$. To avoid unnecessary trial hazard to subjects assigned to either arm, we planned to discontinue the double-blind trial if the difference in the primary endpoint reached significance at $P = 0.0038$ at the interim analysis.

The cumulative incidences of the primary and secondary endpoints were estimated by using the Kaplan–Meier method and compared between the treatment groups by using the log-rank test. For event-free cases the event times were censored either at the point of the last endoscopy performed or at the point of early withdrawal. We also performed multivariate Cox regression analyses to adjust for possible effects of baseline variables on event times. The final analyses were conducted for the full-analysis set (FAS), defined as all patients who were randomized and received one or more doses of the study medication. In the survival analysis, the patients at risk were defined as all event-free FAS patients who had at least one post-randomization assessment with endoscopy.

Differences in adverse events between the lansoprazole and gefarnate groups were tested for significance by using the χ^2 test.

Analyses were conducted using SAS software (version 9.1.3; SAS Institute, Cary, NC, USA). One and the same statistician (S.M.) had full access to all the trial data and conducted statistical analyses independently of the sponsoring company.

Role of the funding source

Takeda Pharmaceutical Company Limited (the Sponsor) and its contractor provided all financial and material support for the study design, data collection, data analysis, data interpretation, and preparation and review of manuscripts. The Sponsor was also responsible for consultations with the authors and the members of this study group about the study design and about monitoring of the study. The principal investigator (K.S.) was responsible for the study design and for preparation of the manuscript. All co-authors reviewed the manuscript, and necessary revisions were made to accommodate their suggestions and opinions.

Results

Study patients

This prospective, double-blind, randomized, active-controlled trial with an open-label 6-month follow-up study was conducted at a total of 94 healthcare institutions in Japan, in accordance with the principles of good clinical practice and the Declaration of Helsinki. The Independent Data Monitoring Committee performed an interim analysis, based on data that had become available from 414 patients. The cumulative number of ulcer events at the interim analysis was 30 in the gefarnate group and three in the lansoprazole group. The HR was estimated as 0.080 (95% CI 0.023–0.264; $P < 0.001$, 2-sided log-rank test), verifying the efficacy of lansoprazole compared with gefarnate and, accordingly, the Independent Data Monitoring Committee made the decision to terminate the initial part of the study early. Data completion and analysis were performed based on data collected at the termination of the trial. The results discussed here are based on the final data.

Figure 1 shows the flow diagram of this trial. Of the 771 patients enrolled, 461 patients were randomized, while the remaining 310 patients were excluded, primarily because they were not confirmed to have evidence of past gastric or duodenal ulcers on baseline endoscopy after enrollment. Of the 461 patients randomized, 226 were assigned to receive lansoprazole and 235 to receive gefarnate. Of the 235 patients assigned to gefarnate, the study medication was not given to one patient, because malignancy was found in this patient (a violation of the study protocol). Thus, the FAS population comprised a total of 460 patients, with 226 and 234 patients in the lansoprazole group and the gefarnate group, respectively. The numbers of withdrawals were similar in the treatment groups, with 59 withdrawals (26.1%) in the lansoprazole group and 57 (24.3%) in the gefarnate group. The most frequent reasons for withdrawal were adverse events, which occurred in 20 (33.9%) patients in the lansoprazole group and 23 (40.4%) patients in the gefarnate group; followed by protocol deviations (including failure to take the medication) and consent withdrawals in 21 (35.6%) and 13 (22.0%) patients in the lansoprazole group, and 13 (22.8%) and 10 (17.5%) patients, respectively, in the gefarnate group. Additionally, four patients in the gefarnate group withdrew due to lack of efficacy or suspected ulcer-related symptoms/diagnoses. The median duration of follow-up was 7.5 months (range 0.1–17.0) for the lansoprazole group and 5.7 months (range 0.0–16.5) for the gefarnate group. Compliance with the study medication and LDA therapy was similarly high in the two treatment groups. There was no difference between the treatment groups in the frequency distribution of baseline variables (Table 1).

Efficacy

In the FAS population, the cumulative number of gastric or duodenal ulcer recurrences, i.e., the primary endpoint, at the end of the study was 6/226 (2.7%) in the lansoprazole

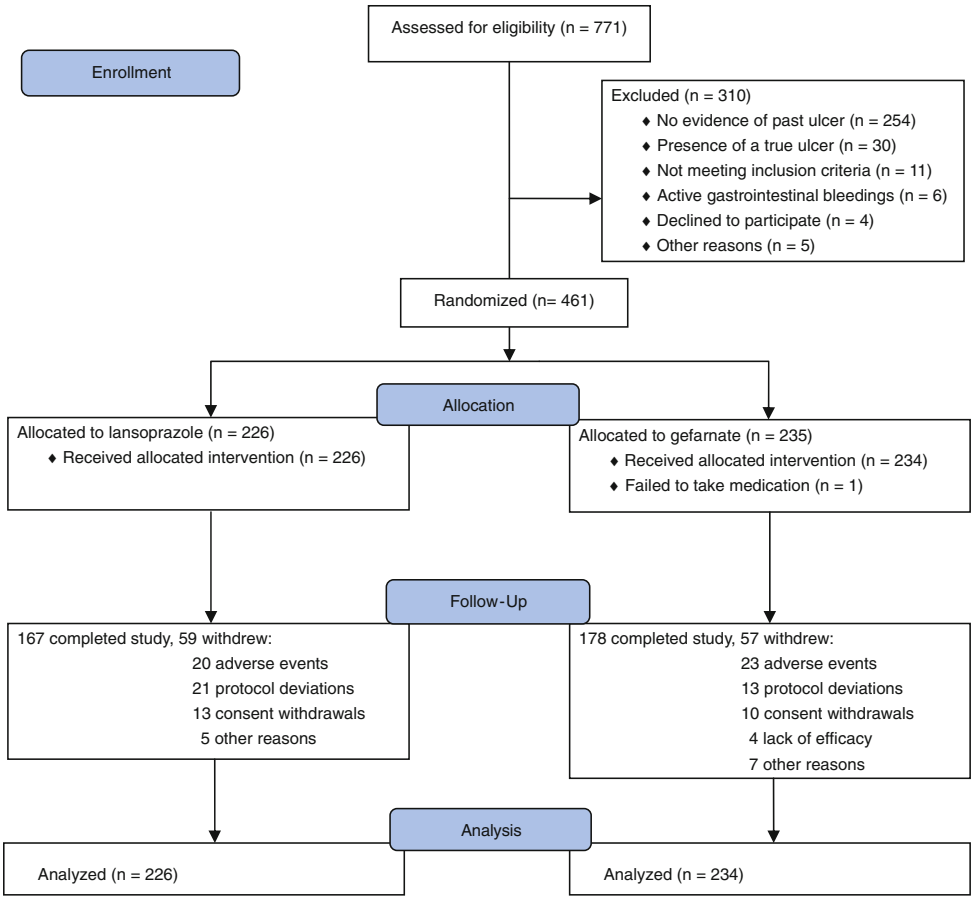

Fig. 1 Patient disposition in this trial (2010 CONSORT flow diagram)

group and 53/234 (22.6%) in the gefarnate group (Table 2). The cumulative recurrences on days 91, 181, and 361 from the start of the study were estimated as 1.5% (95% CI 0.00–3.20), 2.1% (95% CI 0.06–4.08), and 3.7% (95% CI 0.69–6.65), respectively, for the lansoprazole group, compared to 15.2% (95% CI 10.17–20.22), 24.0% (95% CI 17.84–30.21), and 31.7% (95% CI 23.86–39.57), respectively, for the gefarnate group. The HR of the lansoprazole group relative to the gefarnate group was estimated as 0.099 (95% CI 0.042–0.230)—a 90.1% risk reduction, and the difference was highly significant (log-rank test, $P < 0.001$) (Table 2; Fig. 2).

As to the secondary endpoints (Table 2), the risk of developing gastric/duodenal ulcers or hemorrhagic lesions in the lansoprazole group was significantly lower than that in the gefarnate group (log-rank test, $P < 0.001$). Similarly, the risk of having gastric/duodenal ulcers, hemorrhagic lesions, or treatment discontinuations due to lack of efficacy was significantly lower in the lansoprazole group than in the gefarnate group (log-rank test, $P < 0.001$).

The magnitude of risk reduction for gastric or duodenal ulcers (primary endpoint) was generally stable for all subgroups as defined by each baseline variable (Table 3). The analyses in both *Helicobacter pylori*-positive and -negative subgroups showed ulcer risk reductions, with an HR of 0.061 (95% CI 0.019–0.197; $P < 0.001$) and an HR of 0.206 (95% CI 0.060–0.710; $P = 0.02$), respectively, in each of the subgroups in the lansoprazole group as compared to the gefarnate group. Furthermore, the risk reduction, in terms of HR, was estimated as 0.085 (95% CI 0.034–0.216; $P < 0.001$ by a Wald test) after adjustment for the baseline variables, *H. pylori* status, CYP2C19 polymorphism, age, gender, smoking, alcohol consumption, and concomitant use of anticoagulants in a multivariate Cox regression analysis (Table 4).

We also analyzed the sites of the recurrent ulcers to examine whether the ulcer recurred at sites similar to those of the scars observed at the start of the study. Whitish or red scars were reported in 397 patients (86.1% of total). We further obtained data on the location of the scars from all 59 patients in whom ulcers had relapsed. In 36 (61.0%) of these patients, ulcer recurrence was observed at sites similar to those of the scars seen at the start of the study.

Gastrointestinal damage, as assessed by a modified Lanza score [13], from the start of treatment tended to improve in the lansoprazole group, but to worsen in the gefarnate group, throughout the course of treatment (Supplemental Fig. 1).

In the FAS population, the cumulative number of patients who developed gastric or duodenal hemorrhagic

Table 1 Demographic and baseline characteristics of Japanese patients randomized to treatment

	Lansoprazole ($n = 226$)	Gefarnate ($n = 235$)
Mean age (SD), years	69.3 (8.57)	68.7 (8.79)
Sex		
Males	175 (77.4)	192 (81.7)
Females	51 (22.6)	43 (18.3)
Current smoking status	52 (23.0)	53 (22.6)
Alcohol consumption	102 (45.1)	123 (52.3)
Mean duration (SD) of prior LDA (months)[a]	25.4 (13.34)	24.9 (13.54)
Status of concomitant aspirin use		
Aspirin dialminate	27 (11.9)	28 (11.9)
81 mg	26 (11.5)	26 (11.1)
162 mg	1 (0.4)	3 (1.3)
Aspirin	199 (88.1)	207 (88.1)
100 mg	193 (85.4)	194 (82.6)
200 mg	7 (3.1)	13 (5.5)
Underlying disease[b]		
Ischemic heart disease	109 (48.2)	120 (51.1)
Ischemic stroke	96 (42.5)	97 (41.3)
Others	50 (22.1)	49 (20.9)
H. pylori status[c]		
Positive	137 (60.6)	125 (53.2)
Negative	89 (39.4)	109 (46.4)
CYP2C19 polymorphism[d]		
EM	163 (72.1)	181 (77.0)
PM	40 (17.7)	34 (14.5)
Mean compliance rate (SD), %		
Study drug	99.03 (2.268)	98.17 (7.073)
LDA therapy	93.84 (3.319)	93.12 (7.400)

Data are numbers (and % of total) except where otherwise indicated

LDA low-dose aspirin, *EM* Extensive metabolizers, *PM* poor metabolizers

[a] Those who reported taking LDA for >3 years prior to the start of the study medication were construed as having taken it for 3 years

[b] Some patients were included in more than 1 disease category. The category "Others" includes treatments such as carotid arteriosclerosis or carotid artery occlusion

[c] Unknown in 1 patient

[d] Unknown in 46 patients for whom consent was not obtained for the CYP2C19 polymorphism test

Table 2 Effect of lansoprazole on each component of the primary and secondary endpoints

	Lansoprazole[a] ($n = 226$)	Gefarnate[b] ($n = 234$)	Hazard ratio (95% CI)	*P* value[c]
Number at risk at baseline[d]	213	227		
Primary endpoint				
Gastric or duodenal ulcer	6	53	0.099 (0.042–0.230)	<0.001
Secondary endpoints				
Gastric/duodenal ulcer or hemorrhagic lesion	7	56	0.109 (0.050–0.239)	<0.001
Gastric/duodenal ulcer, hemorrhagic lesion or treatment discontinuation due to lack of efficacy	7	59	0.104 (0.047–0.228)	<0.001
Component				
Gastric ulcer	6	40		
Duodenal ulcer	0	15		
Hemorrhagic lesion	2	9		
Treatment discontinuation due to lack of efficacy	0	4		

CI confidence interval

[a] Patients received lansoprazole 15 mg daily

[b] Patients received gefarnate 50 mg twice daily

[c] Log-rank test

[d] The number of patients at risk included all full-analysis set patients who received at least 1 endoscopy assessment post-randomization, and had no acute-stage or healing-stage gastric or duodenal ulcer as confirmed by the Independent Adjudication Committee

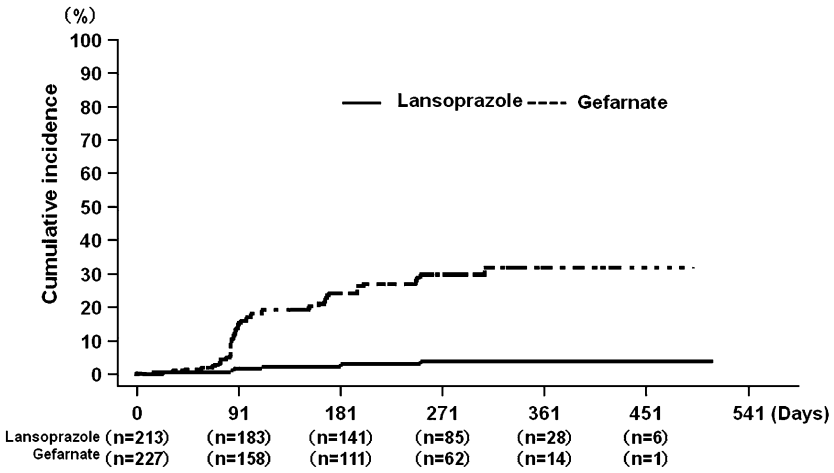

Fig. 2 Kaplan–Meier estimates of the cumulative incidence of gastric or duodenal ulcers and hemorrhagic lesions in the treatment groups

Table 3 Analysis of subgroups as defined by each baseline variable

Baseline characteristics	Recorded number of patients with gastric or duodenal ulcer		Cox regression analysis	
	Lansoprazole	Gefarnate	Hazard ratio (95% CI)	*P* value
H. pylori status				
Positive	3/128[a]	38/122[b]	0.061 (0.019–0.197)	<0.001
Negative	3/85[a]	15/105[b]	0.206 (0.060–0.710)	0.02
CYP2C19				
PM	0/38[c]	9/33[d]	0.000 (0.000 to –[e])	–
EM	5/155[c]	39/175[d]	0.125 (0.049–0.317)	<0.001
Age				
32–64 years	1/57	14/72	0.072 (0.009–0.550)	0.02
65–88 years	5/156	39/155	0.106 (0.042–0.268)	<0.001
Gender				
Male	5/168	43/184	0.104 (0.041–0.264)	<0.001
Female	1/45	10/43	0.082 (0.011–0.643)	0.02
Smoker				
Yes	1/49	16/51	0.048 (0.006–0.365)	0.01
No	5/164	37/176	0.122 (0.048–0.311)	<0.001
Alcohol consumption				
Yes	4/96	24/120	0.170 (0.059–0.491)	0.01
No	2/117	29/107	0.052 (0.012–0.219)	<0.001
Concomitant use of anticoagulants				
Yes	2/47	19/69	0.127 (0.029–0.546)	0.01
No	4/166	34/158	0.091 (0.032–0.256)	<0.001

Data are *n*/at risk; at risk: the number of patients at risk included all full-analysis set patients who had at least 1 post-randomization endoscopy assessment, and had no acute-stage or healing-stage gastric or duodenal ulcer as confirmed by the Independent Adjudication Committee

EM Extensive metabolizers, *PM* Poor metabolizers

[a, b, d] Results of Cox regression analyses; hazard ratio (95% CI), and *P* value: [a] 0.6746 (0.1361–3.3426), $P = 0.63$; [b] 2.2665 (1.2451–4.1258), $P = 0.01$; [d] 0.6970 (0.3373–1.4405), $P = 0.33$

[c] Hazard ratio relative to these subgroups could not be estimated

[e] Could not be estimated

lesions at the end of the study was two of the 226 patients in the lansoprazole group versus nine of the 234 patients in the gefarnate group. The cumulative incidence rate was calculated by the Kaplan–Meier method (Supplemental Fig. 2) and the risk of hemorrhage was shown to be significantly lower in the lansoprazole group than in the gefarnate group. Bleeding ulcers occurred in one patient in the lansoprazole group and five in the gefarnate group. Other gastric or duodenal bleeding was primarily related to erosions. The number of patients who were hospitalized with serious adverse events leading to gastric or duodenal bleeding was one in the lansoprazole group and five in the gefarnate group.

Of the 460 patients randomized to lansoprazole or gefarnate in this trial, 262 who had received lansoprazole or gefarnate were included in an open-label follow-up trial to examine the outcome after another 24 weeks of treatment with lansoprazole, in addition to LDA. During this open-label follow-up trial period, no gastric or duodenal ulcer recurrence was observed in the study participants

Table 4 Results of multivariate Cox regression analysis using baseline variables

Baseline characteristics	Direction estimation	Multivariate analysis	
		Hazard ratio (95% CI)	*P* value
Treatment group	Lansoprazole/gefarnate	0.085 (0.034–0.216)	<0.001
H. pylori status	Positive/negative	2.057 (1.137–3.720)	0.02
CYP2C19	PM/EM	1.434 (0.668–3.076)	0.36
Age	10 years' increase	1.459 (1.045–2.036)	0.03
Gender	Male/female	0.893 (0.437–1.823)	0.76
Smoking status	Yes/no	1.532 (0.820–2.863)	0.19
Alcohol consumption	Yes/no	1.047 (0.588–1.866)	0.88
Concomitant use of anticoagulants	Yes/no	1.200 (0.665–2.166)	0.55

EM Extensive metabolizers, *PM* Poor metabolizers

(Supplemental Table 1). Importantly, compared to the ulcer recurrence in the double-blind phase, no ulcer recurrence was observed from the gefarnate group during the 6 months of the lansoprazole open study, indicating the potent preventive effect of lansoprazole.

Adverse events

With respect to adverse events observed in the double-blind study period (Table 5), diarrhea was noted significantly more frequently in the lansoprazole group than in the gefarnate group, while reflux esophagitis occurred significantly more frequently in the gefarnate group. No serious adverse drug reactions occurred in the lansoprazole group, versus one (liver disorder) in the gefarnate group. No deaths occurred in either group. Of the 21 patients who discontinued lansoprazole, four were suspected of having possible adverse drug reactions, which included stomatitis, abnormal liver function tests, diarrhea, constipation, and palpitation. In the gefarnate group, six patients experienced possible adverse drug reactions, which included dyspepsia, Mallory–Weiss syndrome, eczema, tinnitus, toxic skin eruption, and liver disorder.

From the start of the double-blind study through the continued follow-up trial, four bone fractures were observed in four patients in the lansoprazole group, with three events occurring during the double-blind trial period ($P = 0.08$, χ^2 test, vs. gefarnate group), and the other one event occurring in the open-label follow-up period. Investigators reported the causes of the bone fractures to be factors such as aging, accidental fall occurring as a result of a subject's inattentiveness, and the like; hence, their causal relationship to lansoprazole was denied. No bone fracture occurred in the gefarnate group during the double-blind period.

During the entire study, including the follow-up trial, two deaths occurred, due to ventricular fibrillation and acute myocardial infarction, respectively; their causal relationship to lansoprazole was denied by the investigators. Serious adverse reactions occurred in 51/339 (15.0%) patients, of which 26 occurred in the follow-up trial. Of these, melena occurred in one patient (0.3%) and this was the only event whose causal relationship to lansoprazole could not be denied. Thirty-nine treatment discontinuations occurred in the entire period; of these, 16 occurred in the follow-up period, where the most common event was diarrhea, which occurred in four patients (1.2%).

Discussion

Given that no drug has been proven to be effective for the prevention of gastric or duodenal ulcer associated with LDA therapy in Japan, and given that it is unethical to conduct a placebo-controlled trial in patients at high risk of developing gastric or duodenal ulcers, the present study was designed to compare the efficacy of lansoprazole 15 mg once daily and gefarnate 50 mg twice daily [11, 12]. Gefarnate is a cytoprotective anti-ulcer agent which is approved for the treatment of gastric or duodenal ulcers. These cytoprotective anti-ulcer agents are commonly prescribed as prophylactic drugs to reduce NSAID- or LDA-induced gastrointestinal injury, although they have not been investigated in a controlled trial for the latter indication.

To minimize risks to the patients enrolled in this trial, they were strictly assessed by endoscopic examination for eligibility. In addition, unlike most long-term clinical trials conducted to date in a similar patient population, frequent endoscopic examinations (every 3 or 6 months) were scheduled by the protocol to closely monitor the study subjects for early detection of ulcer recurrence.

While there are arguments for and against *H. pylori* eradication in long-term NSAID users [14], one study showed that *H. pylori* eradication prior to LDA therapy was equivalent to omeprazole therapy in preventing recurrent gastrointestinal bleeding [15], although the study was underpowered to demonstrate such equivalence. However, in other studies, the ulcerogenic effect of LDA was not abolished by *H. pylori* eradication in high-risk patients [7], and 20% of an entire cohort of patients who had developed dyspeptic or bleeding ulcers/erosions during prophylactic

Table 5 Frequency of adverse events

Adverse events that occurred in the double-blind period	Lansoprazole ($n = 226$)	Gefarnate ($n = 234$)	P value
All adverse events	166 (73.5)	168 (71.8)	0.70
Causal relationship to drug not deniable	26 (11.5)	25 (10.7)	0.78
Leading to discontinuations	21 (9.3)	24 (10.3)	0.73
Serious adverse events	27 (11.9)	26 (11.1)	0.78
Causal relationship to drug not deniable	0 (0.0)	1 (0.4)	0.33
Deaths	0 (0.0)	0 (0.0)	–
Adverse events reported in at least 3% of the total in each group			
Nasopharyngitis	54 (23.9)	55 (23.5)	0.93
Constipation	14 (6.2)	8 (3.4)	0.17
Fall	13 (5.8)	9 (3.8)	0.34
Diarrhea	19 (8.4)	2 (0.9)	<0.001
Reflux esophagitis	3 (1.3)	16 (6.8)	0.01
Back pain	10 (4.4)	5 (2.1)	0.17
Elevated blood creatine phosphokinase levels	7 (3.1)	8 (3.4)	0.85
Eczema	5 (2.2)	7 (3.0)	0.61
Hypertension	7 (3.1)	3 (1.3)	0.19

Adverse events reported in patients who received lansoprazole throughout the double-blind and open-label study	Lansoprazole ($n = 339$)
All adverse events	279 (82.3)
Causal relationship to drug not deniable	55 (16.2)
Leading to discontinuations	39 (11.5)
Serious adverse events	51 (15.0)
Causal relationship to drug not deniable	1 (0.3)
Deaths	2 (0.6)
Adverse events reported in at least 3% of the total in each group	
Nasopharyngitis	113 (33.3)
Diarrhea	32 (9.4)
Constipation	23 (6.8)
Fall	19 (5.6)
Hypertension	17 (5.0)
Elevated blood creatine phosphokinase levels	16 (4.7)
Back pain	16 (4.7)

Table data are numbers (%) of patients in whom an event occurred at least 1 time during the trial

treatment with famotidine were all found to be *H. pylori*-negative [10]. Therefore, trial results reported to date are inconsistent, although *H. pylori* eradication is generally recommended in most situations [14, 16]. Besides, because it was difficult to predict the influence of rebound acid hypersecretion occurring after *H. pylori* eradication [17] on the results of the present study, the subjects who required long-term LDA therapy were not obliged to undergo *H. pylori* eradication prior to administration of the study drug, and the protocol was designed to allow patients to be treated with a PPI or *H. pylori* eradication until the day immediately before the start of treatment with lansoprazole or gefarnate, given the varying durations of prior LDA use among the patients. Thus, the study attempted to evaluate the efficacy of lansoprazole vs. gefarnate against ulcer recurrences in an ordinary clinical setting, in which *H. pylori* eradication was implemented at the discretion of the attending physician.

Analyses in both *H. pylori*-positive and -negative subgroups in the present study showed ulcer risk reductions in the lansoprazole group as compared to the gefarnate group, although the risk reduction rate was higher in the *H. pylori*-positive patients. This finding is consistent with a previous study in patients at relatively low risk for ulcer complications [8] and supports the usefulness of low-dose lansoprazole in Japan, where the prevalence of *H. pylori* infection is high [18]. Additionally, although more *H. pylori*-negative patients will need prophylactic treatment for preventing

LDA ulcers in Japan, where the *H. pylori* infection rate is predicted to gradually decrease [19], low-dose lansoprazole should still be effective in these patients as well.

A final analysis of the study data showed that lansoprazole produced a 90.1% reduction in the risk of ulcer recurrence, which was highly significant. The reduction rate is similar to that in a placebo-controlled study conducted in Hong Kong in patients taking LDA [7] and even higher than that in another study in patients with ulcers associated with LDA, where the rate of risk reduction was found to be about 70% [8].

Although the recurrence of ulcers observed by endoscopy was assessed as the primary endpoint in the present study, other clinical endpoints, such as gastrointestinal bleeding and patient hospitalization, were also compared between the treatment groups, because these true clinical outcomes are very important in evaluating the drugs for efficacy. In this study, more patients in the gefarnate group developed gastric or duodenal hemorrhagic lesions and were hospitalized with serious adverse events leading to gastric or duodenal bleeding. Thus, overall, lansoprazole was superior to gefarnate in all endpoints assessed in this study.

Furthermore, there were no new-onset ulcers noted in the additional 6 months' follow-up trial, supporting the idea that lansoprazole provides superior long-term efficacy in preventing LDA-associated gastric/duodenal ulcers, compared to gefarnate.

Of note, the present study represents the longest follow-up (18 months or more) of patients with a definite history of gastric or duodenal ulcer who required long-term LDA therapy, of all reports (3–12 months) published in the literature [7–10].

Thus, lansoprazole appears to have an important role to play in reducing the risk of gastroduodenal ulcers in patients at high risk of developing ulcers who require long-term LDA therapy due to cardiovascular and cerebrovascular disease, while at the same time allowing such antiplatelet therapy to reduce thromboembolic events in these patients.

Acknowledgments Grant support by Takeda Pharmaceutical Company Limited.

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