

Endoscopic Evaluation of Non-steroidal Anti-inflammatory Drug (NSAID)-induced Gastric and Duodenal Ulcers during Prophylaxis with Lansoprazole

Nobuhiro Sakaki, Kiyoshi Ashida, Yuji Mizokami, Masahiro Asaka, Shigeyuki Matsui, Tatsuya Kanto, Hideyuki Hiraishi, Naoki Hiramatsu, Kentaro Sugano

Nobuhiro Sakaki, Foundation for Detection of Early Gastric Carcinoma, Tokyo, Japan

Kiyoshi Ashida, Department of Gastroenterology and Hepatology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

Yuji Mizokami, Department of Endoscopy, Tsukuba University Hospital, Ibaraki, Japan

Masahiro Asaka, Department of Cancer Preventive Medicine, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Shigeyuki Matsui, Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan

Tatsuya Kanto, Naoki Hiramatsu, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan

Hideyuki Hiraishi, Department of Gastroenterology, Dokkyo University School of Medicine, Tochigi, Japan

Kentaro Sugano, Division of Gastroenterology, Department of Medicine, Jichi Medical University, Tochigi, Japan

Correspondence to: Nobuhiro Sakaki, MD, PhD, Foundation for Detection of Early Gastric Carcinoma, 2-6-12 Nihonbashi-Kayabacho, Chuo-ku, Tokyo 103-8790, Japan. sakaki@soiken.or.jp

Telephone: +81-3-3668-6801 Fax: +81-3-3668-7594

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ABSTRACT

AIM: There are very few detailed reports on the features of gastric and/or duodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) during ulcer prophylaxis. In this study, lansoprazole (LPZ) and gefarnate (GFN) were compared for efficacy in the prophylaxis of gastric and duodenal ulcers in high-risk patients receiving NSAID therapy.

MTTHODS: All ulcers that had developed during prophylaxis with LPZ (15 mg once daily) and GFN (50 mg twice daily) in a prospective, randomized, double-blind trial were compared for their endoscopic features by a panel of expert endoscopists based on their endoscopic images, in accordance with a predetermined set of criteria.

RESULTS: A total of 15 and 46 patients had developed gastric or duodenal ulcers during prophylaxis with LPZ and GFN, respectively,

during the double-blind trial. Of the 14 gastric ulcers that had developed in those given LPZ, 13 (93%) were “small” and “shallow”, while, in contrast, 31% of 35 gastric ulcers were “medium” or “large” and 29% were deep” in those given GFN. On the other hand, 8 out of 11 patients had “deep” duodenal ulcers in the GFN group while 1 patient a “medium” and “shallow” duodenal ulcer in the LPZ group.

CONCLUSIONS: The study results demonstrated that ulcers developing during secondary prophylaxis with LPZ and GFN differ in their size and depth. These findings may be useful when devising a strategy for the prevention of gastric and duodenal ulcers in high-risk patients receiving NSAID therapy in a routine clinical setting.

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Key words: Endoscopy; Lansoprazole; Non-steroidal anti-inflammatory drugs; Peptic ulcer; Prophylaxis

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INTRODUCTION

With the increasing aging of the population, non-steroidal anti-inflammatory drugs (NSAIDs) are increasingly used due to an increase in the prevalence of a wide range of diseases that respond to NSAIDs in Japan. However, they are reported to disrupt the mucosal resistance to gastric acid, through diverse mechanisms, including the suppression of prostaglandin production in the gastric mucosa, and a recent pooled analysis of 12 randomized trials^[1] demonstrated that increasing age is associated with both frequent and more serious NSAID-induced ulcers.

Few reports are available on the prevention of gastric and duodenal ulcers associated with NSAID therapy including low-dose aspirin. In Japan in particular, no double-blind, controlled study has been conducted to obtain evidence on the prevention of gastroduodenal ulceration during low-dose aspirin (LDA) or NSAID therapy, with no drugs approved for coverage by the Japanese

national health insurance system for the prevention of gastric and duodenal ulcers.

A double-blind parallel-group study was conducted to compare the proton pump inhibitor lansoprazole (LPZ) with the cytoprotective agent gefarnate (GFN) for prophylaxis of gastric and duodenal ulcers during chronic NSAID therapy, with the primary endpoint defined as the incidence of endoscopically confirmed gastric or duodenal ulcers, which demonstrated that LPZ provided significantly better protection against gastric and duodenal ulcer recurrence in patients with a history of gastric or duodenal ulcers^[2].

In clinical trials of a pharmacological agent, endoscopically confirmed ulcer is currently being used as a surrogate endpoint^[3,4]. However, to date, no detailed reports are available on the endoscopic features of ulcers occurring in patients receiving long-term NSAID therapy during secondary ulcer prophylaxis.

Additionally, not only the risk of ulcers but also their size and depth in high-risk patients need to be taken into account in formulating a secondary ulcer prevention strategy for these patients, as they are likely to affect the therapeutic outcome.

Therefore, we conducted a subgroup analysis of the patients who developed ulcers during secondary prophylaxis in the above-mentioned study to characterize the ulcers recurring during chronic NSAID therapy in patients with endoscopically confirmed gastric or duodenal scars at baseline.

METHODS

Outline of the double-blind study

A prospective double-blind, randomized parallel-group comparison study was conducted in patients on long-term NSAID therapy at a total of 99 institutions in Japan^[2]. Patients were randomized to receive LPZ at 15 mg once daily ($n=185$), or GFN at 50 mg twice daily ($n=81$) as the active control.

Subjects

Patients with endoscopically confirmed gastric or duodenal ulcer scars were enrolled in the double-blind study^[2]. Precise inclusion/exclusion criteria for the double-blind study were described previously^[2]. Patients were enrolled in the study if they met the following criteria: those who were being given NSAID when they gave informed consent, and who required long-term NSAID therapy after the start of the study (day 1) with the investigational drug; and those in whom a history of gastric or duodenal ulcer was confirmed by endoscopy, i.e., if they were confirmed to have an ulcer scar on day 1 or in an endoscopic examination performed prior to day 1 (e.g., photographs, films) to have an ulcer or ulcer scar. Of the 386 patients randomized, 61 patients who had developed endoscopically confirmed gastric or duodenal ulcers during the double-blind study were enrolled in the present subgroup analysis to have their major ulcers reevaluated by an expert panel of endoscopists in the present subgroup analysis. These patients consisted of 15 patients in the LPZ group [14 with gastric ulcers (body, 2; angle, 1; antrum, 11) and 1 with duodenal ulcer (bulb)] and 46 patients in the GFN group [35 with gastric ulcers (body, 11; angle, 8; antrum, 16) and 11 with duodenal ulcer (bulb, 7; post-bulbar, 4)].

Assessment of ulcers

Endoscopy was performed every 12 weeks for the initial 12 months of treatment and every 24 weeks after that. Additional endoscopy was also performed if patients had symptoms associated with ulcers or signs and symptoms indicative of gastrointestinal bleeding. When ulcers were diagnosed endoscopically by the investigators during

the study, an independent panel of expert endoscopists (consisting of 3 experienced gastroenterological endoscopists) evaluated the endoscopic photographs to confirm the status of the gastric/duodenal ulcer lesions.

Gastric and duodenal ulcers were defined as mucosal defects with a white coat measuring 3 mm or larger in diameter. All ulcers confirmed by the panel of expert endoscopists to meet the criteria were evaluated for endoscopic features using the photographic images of the ulcers, where each ulcer was classified in terms of their size as “small” (3–9 mm), “medium” (10–19 mm), or “large” (≥ 20 mm); in terms of their depth as “shallow” or “deep”; according to whether they had “coagulated blood in the ulcer base”; or whether they were located in similar sites to the ulcers or ulcer scars at baseline. Patients were further stratified by their treatment group (LPZ or GFN) and *H. pylori* infection status (positive or negative).

Each endoscopist of the panel evaluated the features of the ulcers, blinded to the study medications. The results were assessed for agreement among the endoscopists by using the kappa statistics.

Detection of *H. pylori* infection

H. pylori infection status was determined for each patient based on measurement of anti-*H. pylori* antibodies using an E-plate Eiken *H. pylori* antibody assay kit (Eiken Chemical Co., Ltd.) at a central laboratory. Patients were judged to be ‘negative’ if the antibody level was < 10 U/mL.

Statistical analysis

Categorical variables were compared by using χ^2 test, Cochran-Mantel-Haenszel test and Fisher’s exact test. Continuous variables were compared by using Student *t*-test. *P* values of less than 0.05 were considered to indicate statistical significance. Cohen’s kappa was calculated to determine inter-observer agreement among the panel of expert endoscopists.

RESULTS

NSAID use in the subjects

The major NSAIDs used in the double-blind study were loxoprofen sodium, meloxicam, diclofenac and etodolac. The NSAIDs and their dosages used in the double-blind study were not significantly different between the treatment arms or between those who developed ulcers and those who did not.

Clinical characteristics

The mean age of those who developed gastric or duodenal ulcer was 62.3 and 65.8 years in the LPZ group (5 men, 33.3%) and the GFN group (19 men, 41.3%), respectively. Table 1 shows the baseline characteristics of the patients. The endoscopic evaluations of the 61 ulcers by the endoscopists were examined by using kappa statistics as a measure of agreement, which suggested that the ulcer features as described by the endoscopists were generally concordant and reliable: ulcer size (kappa coefficient: NS and KA, 0.7455; KA and YM, 0.6110; NS and YM, 0.7754), depth (NS and KA, 0.6174; KA and YM, 0.7626; NS and YM, 0.5004), and presence of coagula (NS and KA, 0.7123; KA and YM, 0.6726; NS and YM, 0.6726). Although the ulcer size data were not evaluated for ordinality, the kappa coefficients calculated for all raters also showed significant agreement for each of the evaluations performed by the endoscopists.

Gastric ulcers

Gastric ulcers were found in 14 patients in the LPZ group (Table 2). The lesions were “small” and “shallow” (Figures 1, 2) except in 1

Table 1 Baseline characteristics of the ulcer patients in the two groups.

	LPZ group (n=15)	GFN group (n=46)	P Value
Mean age (SD) years	62.3 (12.03)	65.8 (9.76)	0.3186
Sex			0.5832
Male	5	19	
Female	10	27	
Current smoker	5	19	0.5832
Alcohol consumption	5	16	0.9183
Mean duration (SD) of prior NSAID (months) ¹	22.6 (16.52)	17.0(14.44)	0.2530
Status of concomitant NSAID use			0.4246
Loxoprofen sodium hydrate	4	19	
Meloxicam	4	11	
Diclofenac sodium	2	6	
Etodolac	4	4	
Others	1	6	
Underlying disease ²			
Rheumatoid arthritis	7	21	0.9454
Osteoarthritis	4	17	0.4664
Low back pain	0	3	0.3104
Other	8	20	0.5060
<i>H. pylori</i> status			0.2070
Positive	6	27	
Negative	9	19	
CYP2C19 polymorphism ³			0.4545
EM	10	30	
PM	4	7	

Values are numbers (%), except where otherwise indicated. All categorical variables were compared by using χ^2 test and continuous variables by using Student t-test. ¹ Patients who reported taking NSAIDs for >3 years prior to the study were classified as having used it for 3 years; ² Some patients were included in more than 1 disease categories. "Other" includes conditions such as lumbar spinal stenosis or intervertebral disc hernia; ³ EM, extensive metabolizers; PM, poor metabolizers; unknown in 37 patients from whom consent was not obtained for the CYP2C19 polymorphism test.

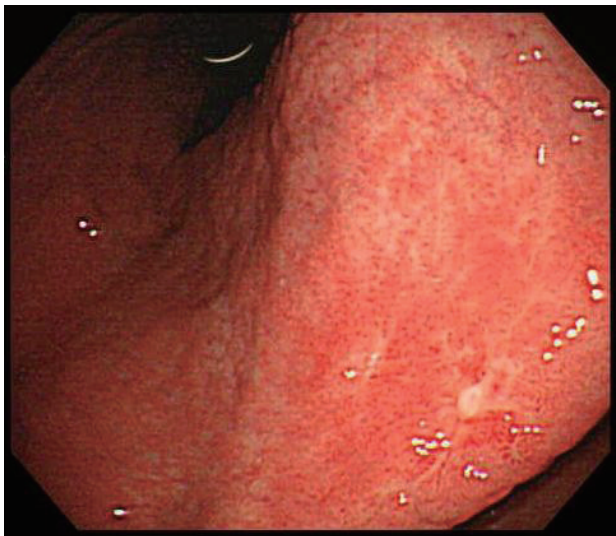


Figure 1 A small, shallow gastric ulcer occurred in a 37-year-old woman 78 days after the start of LPZ (15 mg once daily) therapy. The ulcer was located in a different site than the previously documented scar.

patient ("medium" and "shallow"), with blood coagula found in the ulcer base in 2 patients. Ten of these ulcers were found at different sites than the baseline ulcer scars, with 4 found in similar sites.

In contrast, gastric ulcers developed in 35 patients in the GFN group, who consisted of 24 patients with "small" ulcers, 8 with "medium" ulcers, and 3 with "large" ulcers. These lesions were "shallow" in 25 patients and "deep" in 10 patients, with blood coagula found in 6 patients. 60% of these ulcers were found at different sites than the baseline ulcer scars, with 40% found in similar sites. Figures 3 and 4 illustrate the ulcers that were

Table 2 Endoscopic features of the gastric or duodenal ulcers.

Gastric ulcers	LPZ group n=14 (%)	GFN group n=35 (%)
Ulcer size ²		
Small [3-9 mm]	13 (92.9)	24 (68.6)
Medium [10-19 mm]	1 (7.1)	8 (22.9)
Large [\geq 20 mm]	0	3 (8.5)
Ulcer depth ²		
Shallow	14	25 (71.4)
Deep	0	10 (28.6)
Blood coagula ²		
No	12 (85.7)	29 (82.9)
Yes	2 (14.3)	6 (17.1)
Ulcer location ^{1,2}		
Different	10 (71.4)	21 (60.0)
Similar	4 (28.6)	14 (40.0)
Duodenal ulcers	LPZ group n=1 (%)	GFN group n=11 (%)
Ulcer size ²		
Small [3-9 mm]	0	6 (54.5)
Medium [10-19 mm]	1 (100)	5 (45.5)
Large [\geq 20 mm]	0	0
Ulcer depth ²		
Shallow	1 (100)	3 (27.3)
Deep	0	8 (72.7)
Blood coagula ²		
No	1 (100)	9 (81.8)
Yes	0	2 (18.2)
Ulcer location ^{1,2}		
Different	1 (100)	3 (27.3)
Similar	0	8 (72.7)

¹ Similar, occurring at similar sites to baseline scars; different, occurring at different sites than baseline scars; ² Results of Cochran-Mantel-Haenszel test comparisons between LPZ and GFN group are shown in tables 3 and 4.

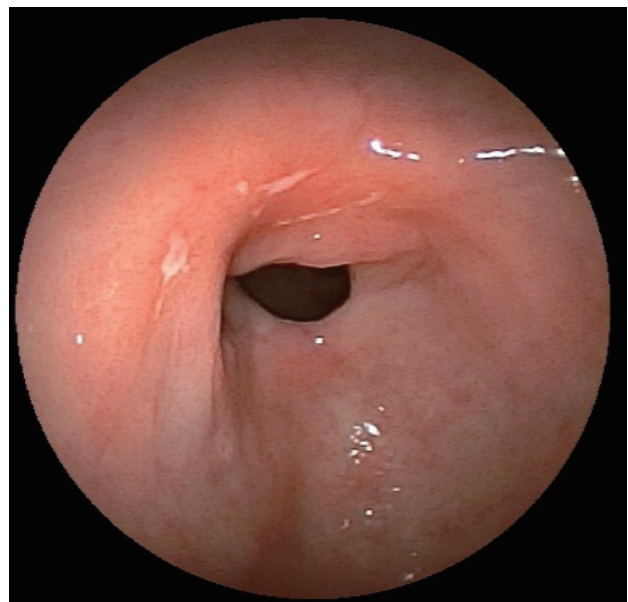


Figure 2 A small, shallow gastric ulcer developed at a similar site to the previously documented scar in an 80-year-old woman 79 days after the start of LPZ (15 mg once daily).

characteristic of the GFN group.

Duodenal ulcers

One duodenal ulcer developed in the LPZ group versus 11 patients in the GFN group (Table 2), who consisted of 6 patients with "small" ulcers and 5 with "medium" ulcers. These lesions were "shallow" in 3 patients and "deep" in 8 patients, with blood coagula seen in 2 patient, where approximately 30% of ulcers developed in different sites than the baseline scars. Figures 5 and 6 illustrate "deep" duodenal ulcers, which were typically found in the GFN group.

Table 3 Gastric ulcers and *H. pylori* infection.

Gastric ulcers	LPZ group n=14		GFN group n=35	
	<i>H. pylori</i> -positive n=5 (%)	<i>H. pylori</i> -negative n=9 (%)	<i>H. pylori</i> -positive n=19 (%)	<i>H. pylori</i> -negative n=16 (%)
Ulcer size ¹				
Small (3–9 mm)	5 (100)	8 (88.9)	14 (73.7) ¹¹	10 (62.5) ¹¹
Medium (10–19 mm)	0	1 (11.1)	4 (21.0) ¹¹	4 (25.0) ¹¹
Large (≥ 20 mm)	0	0	1 (5.3) ¹¹	2 (12.5) ¹¹
Ulcer depth ²				
Shallow	5 (100)	9 (100)	15 (78.9) ²²	10 (62.5) ²²
Deep	0	0	4 (21.1) ²²	6 (37.5) ²²
Blood coagula ³				
No	3 (60.0)	9 (100)	16 (84.2) ³³	13 (81.3) ³³
Yes	2 (40.0)	0	3 (15.8) ³³	3 (18.7) ³³
Ulcer location ^{4,5}				
Different	2 (40.0)	8 (88.9)	11 (57.9) ⁴⁴	10 (62.5) ⁴⁴
Similar	3 (60.0)	1 (11.1)	8 (42.1) ⁴⁴	6 (37.5) ⁴⁴

^{1,2,3,4} Cochran-Mantel-Haenszel test comparisons between the LPZ and GFN groups adjusting for *H. pylori*: ¹ $P=0.0607$, ² $P=0.0205$, ³ $P=0.9155$, ⁴ $P=0.5872$; ⁵ Similar, occurring at similar sites to ulcer scars at baseline; different, occurring at different sites than ulcer scars at baseline; ^{11,22,33,44} Fisher's exact test comparisons between *H. pylori*-positive and -negative subjects in the GFN group: ¹¹ $P=0.4042$, ²² $P=0.2903$, ³³ $P=0.8195$, ⁴⁴ $P=0.7848$.

Table 4 Duodenal ulcers and *H. pylori* infection.

Duodenal ulcers	LPZ group n=1		GFN group n=11	
	<i>H. pylori</i> -positive n=1 (%)	<i>H. pylori</i> -negative n=0 (%)	<i>H. pylori</i> -positive n=8 (%)	<i>H. pylori</i> -negative n=3 (%)
Ulcer size ¹				
Small (3–9 mm)	0	0	4 (50.0) ¹¹	2 (66.7) ¹¹
Medium (10–19 mm)	1 (100)	0	4 (50.0) ¹¹	1 (33.3) ¹¹
Large (≥ 20 mm)	0	0	0 ¹¹	0 ¹¹
Ulcer depth ²				
Shallow	1 (100)	0	1 (12.5) ²²	2 (66.7) ²²
Deep	0	0	7 (87.5) ²²	1 (33.3) ²²
Blood coagula ³				
No	1 (100)	0	6 (75.0) ³³	3 (100) ³³
Yes	0	0	2 (25.0) ³³	0 ³³
Ulcer location ^{4,5}				
Different	1 (100)	0	1 (12.5) ⁴⁴	2 (66.7) ⁴⁴
Similar	0	0	7 (87.5) ⁴⁴	1 (33.3) ⁴⁴

^{1,2,3,4} Cochran-Mantel-Haenszel test comparisons between the LPZ and GFN groups adjusting for *H. pylori*: ¹ $P=0.3711$, ² $P=0.0614$, ³ $P=0.5930$, ⁴ $P=0.0614$; ⁵ Similar, occurring at similar sites to ulcer scars at baseline; different, occurring at different sites than ulcer scars at baseline; ^{11,22,33,44} Fisher's exact test comparisons between *H. pylori*-positive and -negative subjects in the GFN group: ¹¹ $P=0.6374$, ²² $P=0.0867$, ³³ $P=0.3613$, ⁴⁴ $P=0.0867$.

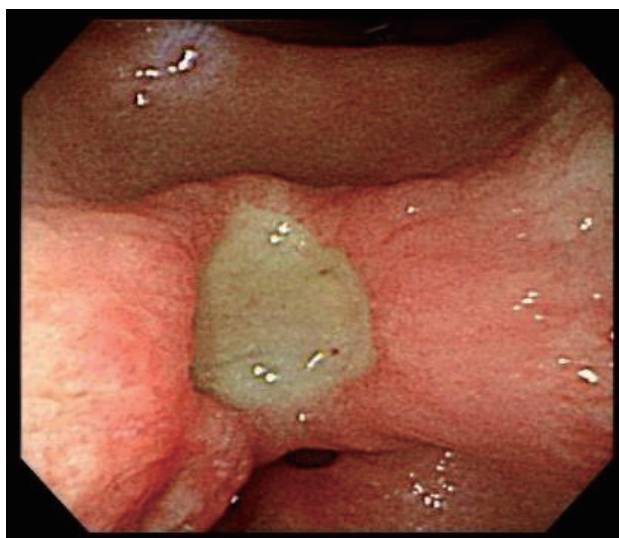


Figure 3 A large, deep gastric ulcer occurred at a similar site to the previously documented scar in a 54-year-old woman 10 days after the start of GFN (50 mg twice daily).

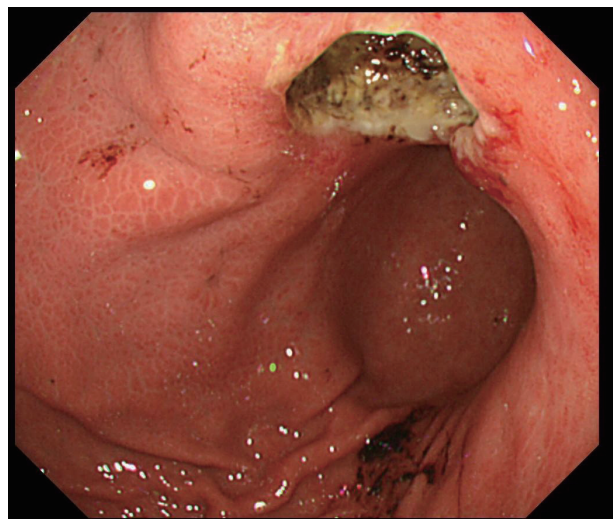


Figure 4 A large, deep gastric ulcer developed at a similar site to the previously documented scar in a 73-year-old woman 286 days after the start of GFN (50 mg twice daily), where the presence of blood coagula was also suspected.

Influence of *H. pylori* infection: (1) Gastric ulcers. Of the 14 patients with gastric ulcers in the LPZ group, 5 and 9 patients were positive and negative, respectively, for *H. pylori* infection. Most gastric ulcers were “small” and “shallow” without blood coagula, although ulcer recurrence tended to be seen in similar sites to the baseline scars in *H.*

pylori-positive patients in the LPZ group (Table 3). Of the 35 patients with gastric ulcers in the GFN group, 19 and 16 patients were positive and negative, respectively, for *H. pylori* infection. There was no significant correlation between ulcer size, depth or presence of blood coagula and *H. pylori* status in the GFN group (Table 3).

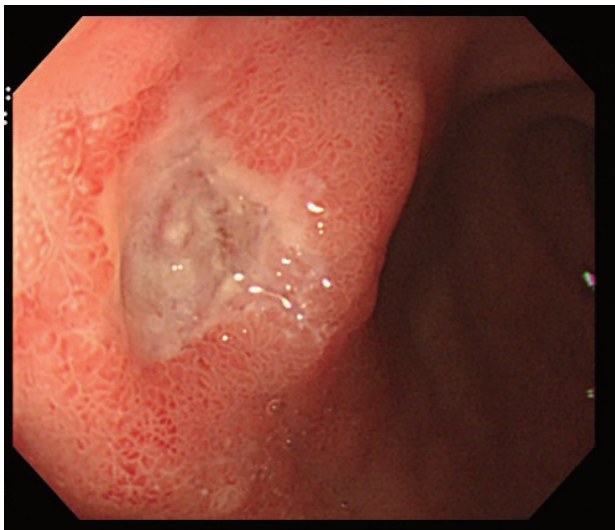


Figure 5 A medium-sized, deep duodenal ulcer developed at a similar site to the previously documented scar in a 67-year-old woman 28 days after the start of GFN (50 mg twice daily).

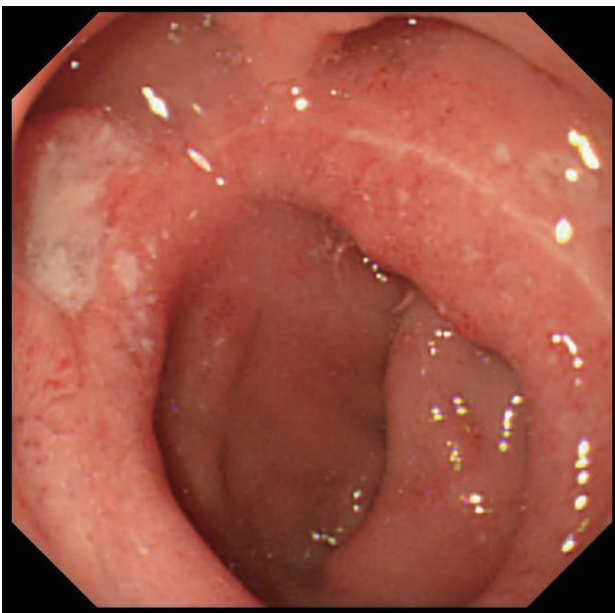


Figure 6 A small, deep duodenal ulcer occurred at a similar site to the previously documented scar in a 58-year-old male 85 days after the start of GFN (50 mg twice daily).

(2) Duodenal ulcers. Only one patient developed duodenal ulcer in the LPZ group and was positive for *H. pylori* infection; and, of those with duodenal ulcers in the GFN group ($n=11$), 8 and 3 patients were positive and negative, respectively, for *H. pylori* infection (Table 4). Those who developed duodenal ulcers in the GFN group exhibited clearly distinct features depending on their *H. pylori* status with 88% of *H. pylori*-positive patients had “deep” ulcers in similar sites to the baseline scars, although there was no correlation between *H. pylori* status and ulcer size or presence of blood coagula (Table 4).

DISCUSSION

A multicenter, double-blind study demonstrated that low-dose LPZ was superior to GFN in reducing the risk of gastric or duodenal ulcer in patients who required long-term NSAID therapy with the cumulative incidence of gastric or duodenal ulcer at the end of the

study being 15/183 (8.2%) in the LPZ group and 46/181 (25.4%) in the GFN group. The risk for ulcer development was significantly (long-rank test, $P < 0.0001$) lower in the LPZ group than in the GFN group, with the hazard ratio being 0.2510 (95% CI, 0.1400 to 0.4499), which signifies a 74.9% risk reduction. Given that all subjects had a history of gastric or duodenal ulcer, it is clear from these results that LPZ was effective against recurrence of NSAID-induced ulcers.

However, given that not only the rate of ulcer occurrence but also the size and depth of these ulcers need to be taken into account when selecting an appropriate treatment strategy for individual patients, NSAID-induced ulcers during ulcer prophylaxis need to be characterized, with the differences in morphological features, such as size and depth, between gastric and duodenal ulcers in mind.

Thus, the gastric and duodenal ulcers occurring or recurring during ulcer prophylaxis with LPZ or GFN were compared in this retrospectively reviewed sub-analysis for their size, associated blood coagula, site of recurrence, although the overall rate of ulcer recurrence during prophylaxis with LPZ or GFN was prospectively analyzed in the double-blind study^[2] without differentiating between gastric and duodenal ulcers. The incidence of gastrointestinal bleeding associated with NSAID use has previously been reported in the double-blind study^[2]. We have thus confined ourselves in this study to comparing the endoscopic features of gastric and duodenal ulcers developing during prophylaxis with LPZ and GFN to provide additional insights into differences between the prophylactic agents used.

To the best of our knowledge, no placebo- or active-controlled study in a similar sample size has been conducted in Japan or provided an in-depth analysis of the endoscopic features of gastric or duodenal ulcers developing during ulcer prophylaxis. At the time that the double-blind study was designed, it was thought unethical to include a placebo arm, as the study involved high-risk patients, i.e., those with a history of gastric or duodenal ulcers.

While gastric or duodenal ulcers developed in 15 patients given the PPI LPZ, most of these ulcers (13/15) were “small” (< 10 mm in size), and all of these ulcers were “shallow”, regardless of their size. In contrast, gastric or duodenal ulcers developed in 46 patients given the cytoprotective agent GFN, with about one-half of these being larger in size and deep. Additionally, 73.3% of all ulcers in patients given LPZ were found at different sites than the baseline scars, while 40% of gastric ulcers and 72.7% of duodenal ulcers in those given GFN were found at similar sites to the baseline scars.

In this study, ulcers were defined as well-demarcated mucosal defects measuring 3 mm or larger, consistent with the criteria commonly used in previous studies^[3,4]. An ulcer is usually defined as a tissue defect involving the submucosal or deeper layer. However, it is commonly observed that ulcers vary in their clinical course depending on their depth, where mucosal breaks confined within the submucosal layer tend to be transient and tend not to recur in similar sites to old scars, while those involving the proper muscle or deeper layer often recur in similar sites to old scars, in agreement with our earlier study^[5] which showed that no relapse occurred in patients with “shallow” ulcers, whereas relapse was common in patients with “deep” ulcers, during 2-year follow-up of maintenance therapy with a half-dose of an H^2 receptor antagonist.

Thus, taken together, the study results demonstrated that all ulcers found in patients given LPZ were transient, acute ulcers, while about 40% of all gastric and duodenal ulcers were deep in GFN group, with the majority of these lesions, particularly duodenal ulcers, found at similar sites to the baseline scars.

As reported in the double-blind study^[2], the rates of recurrence of gastric and duodenal ulcers were markedly low in both *H. pylori*-

positive and -negative patients in the LPZ group, while a higher recurrence rate was observed in the *H. pylori*-positive patients than in the *H. pylori*-negative patients in the GFN group. When the features of ulcers that had developed during the double-blind study were examined for correlation with *H. pylori* status, ulcers were found to have recurred in more *H. pylori*-negative patients in the LPZ group, while they were all “small” and “shallow”, which may have contributed to no significant difference in ulcer features between *H. pylori*-negative and -positive patients. In contrast, there was no significant difference in ulcer features between *H. pylori*-negative and -positive patients in the GFN group. Again, while “deep” duodenal ulcers tended to develop in similar sites to the baseline scars in *H. pylori*-positive patients, this finding appears to have limited clinical implications, given the small sample size.

While Sakamoto *et al*^[6] reported that *H. pylori* infection and NSAID use work additively, our study results suggest that *H. pylori* status may not need to be taken into account when patients requiring long-term NSAID therapy are receiving concurrent, continuous prophylaxis with low-dose LPZ.

The study results also suggest that high-risk patients with a history of gastric or duodenal ulcers who receive long-term NSAID therapy need to be closely monitored (e.g., using endoscopic follow-up) even when they are concomitantly given a cytoprotective agent, given their risk of developing “large”, “deep” ulcers. Additionally, the study findings indicate that symptomatic therapy may be adequate even in patients with a history of prior ulcer development when they are being treated with LPZ as secondary ulcer prophylaxis.

In parallel with the double-blind study of LPZ for prevention of NSAID-induced gastric and duodenal ulcers^[2], of which this study is a part, a companion double-blind study for prevention of low-dose aspirin (LDA)-induced gastric and duodenal ulcers has been conducted and its results reported by Sugano *et al*^[7], followed by a report, similar to the present one, on the features of ulcers that had developed during the double-blind study^[8]. A comparison of these two sub-analyses reveals that while LPZ offered slightly less protection against NSAID-induced gastric and duodenal ulcer recurrence in this study, the features of ulcers that had developed during both double-blind studies were consistent, suggesting that LPZ offered as good protection against NSAID-induced ulcers as against LDA-induced ulcers.

In conclusion, this clinical study showed that LPZ was highly effective for prevention of gastroduodenal ulcers. Additionally, no recurrence of “large” and “deep” ulcers was observed in patients receiving ulcer prophylaxis with LPZ. This appears to provide the rationale for evaluating ulcer size and depth when endoscopic ulcer occurrence is being used as a surrogate endpoint for ulcer prevention studies. Our study findings may assist in devising a prophylactic strategy against gastroduodenal ulcers during NSAID therapy in a routine clinical setting.

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Peer reviewer: Tetsuya Mine, Professor and Chief, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Tokai School of Medicine; Magdy Amin El-Serafy, 5-Street 278-Maadi, Cairo, Egypt.