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ORIGINAL ARTICLE

Comparison of the efficacy of irsogladine maleate and famotidine for the healing of gastric ulcers after *Helicobacter pylori* eradication therapy: a randomized, controlled, prospective study

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Abstract

Objective. *Helicobacter pylori* eradication therapy alone cannot heal gastric ulcers in Japanese patients. Irsogladine has previously been shown to accelerate the healing of gastric ulcers after *H. pylori* eradication therapy. And we previously reported that histamine H_2 receptor antagonists inhibit gastric ulcer relapse after *H. pylori* eradication therapy. We therefore compared the efficacy of irsogladine with famotidine as appropriate treatments for ulcers after eradication therapy. ***Methods.*** Gastric ulcer patients with *H. pylori* infection ($n = 119$) were randomized to treatment with irsogladine 4 mg/day ($n = 60$) or famotidine 40 mg/day ($n = 59$) following 1-week *H. pylori* eradication therapy. After treatment, assessments of gastric ulcer healing were performed. ***Results.*** The ulcer healing rates in patients receiving irsogladine and famotidine were 85.2% (46/54) and 79.6% (43/54), respectively, and were not significantly different ($p = 0.4484$). In the famotidine group, the healing rate was significantly lower in patients who drink alcohol than in those who do not (60.0% vs. 91.2%; $p = 0.0119$). However, in the irsogladine group the healing rate did not differ between patients who drink alcohol and those who do not. Furthermore, the healing rate in smokers was significantly higher in the irsogladine group (88.0%) than in the famotidine group (59.1%) ($p = 0.0233$). ***Conclusions.*** Irsogladine and famotidine are both acceptable in treatment after *H. pylori* eradication therapy in gastric ulcer patients. Findings also suggest that irsogladine is more beneficial than famotidine in patients who drink alcohol and smoke.

Key Words: *Famotidine, gastric ulcer, Helicobacter pylori* eradication, irsogladine, randomized clinical trial

Introduction

For gastric ulcers associated with *Helicobacter pylori* infection, a triple therapy consisting of proton pump indicator (PPI), amoxicillin, and clarithromycin is recommended [1,2]. Higuchi et al. demonstrated that triple therapy eradicated *H. pylori* in 84% of patients and that gastric ulcers were healed in 49% of Japanese patients [3].

One of the reasons for this effect is that gastric acid secretion in gastric ulcer patients is significantly increased at 1 month after eradication in Japanese patients [4]. We have also found that after eradication mononuclear cells only gradually disappeared over a period of 3 years (unpublished data). After eradication, the gastric mucosa thus appears to be exposed to excessive gastric acid and inflammation, and treatment with gastric acid-suppressive agents, as well as anti-inflammatory agents, is therefore considered reasonable. Hiraishi et al. confirmed that irsogladine, a mucosal protective drug widely used in Japan, China and Korea, promoted the healing of gastric ulcers after eradication therapy compared with placebo [5]. Irsogladine exhibits efficacy in various models

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of gastric mucosal injury [6–9] by activation of intercellular communication [10], prevention of reduction of gastric mucosal blood flow [6,11], an anti-inflammatory effect [12], and prevention of the loss of mucosal hydrophobicity [7] via an increase in cAMP production resulting from inhibition of phosphodiesterase [13]. We previously reported that histamine H_2 receptor antagonists (H_2RAs) inhibit gastric ulcer relapse after *H. pylori* eradication [14].

We therefore compared the efficacy of irsogladine with famotidine as appropriate treatments for ulcers after eradication therapy.

Methods

Subjects

The subjects were outpatients and hospitalized patients aged 20 years or older at the time when written informed consent was obtained. Patients who tested positive for *H. pylori* and who were diagnosed with a single ulcer ≥5 mm in diameter on endoscopy. The diagnosis of *H. pylori* infection was confirmed with either rapid urease test or microscopy. The following patients were excluded from the study: patients with concomitant hemorrhagic ulcer, multiple ulcers, linear ulcer, erosive lesion, non-steroidal anti-inflammatory drug (NSAID)-induced ulcer, or duodenal ulcer (scar not excluded), as well as patients with concomitant serious hepatic, renal, or cardiac disease, patients with concomitant malignant tumor, pregnant women or women suspected of being pregnant, lactating women, and patients otherwise judged inappropriate for inclusion in the study by a physician-in-charge.

Study design and assessment

This was a randomized, parallel-group, comparative study that was approved by the Institutional Review Board of Oita University.

Eradication therapy consisted of triple therapy with twice-daily oral administration of omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 10 mg, amoxicillin 750 mg, and clarithromycin 200 mg or 400 mg after breakfast and dinner for 1 week. After confirmation of the safety of eradication therapy, the patients were randomly assigned to receive either irsogladine at 4 mg/day (group I) or famotidine at 40 mg/day (group F) in an 8-week treatment phase. The random assignment procedure was performed using random numbers generated by the SAS program (SAS Institute, Cary, NC, USA).

Patients in whom gastric ulcer was diagnosed by endoscopy at the beginning of the study and moved to the scarring stage at the end of the study were considered healed patients, and the rates of healed patients in each group eligible for efficacy analysis were calculated. The rate of healing of ulcer in each group was estimated to be 85%, and the confidence interval and exclusion rate were assumed to be ±10% and 10%, respectively. Fifty-five patients were required per group to enhance the reliability of findings.

The primary endpoint was the diagnosis of gastric ulcer by the investigator. To ensure the reliability of the gastric ulcer assessment for all patients, the ulcer stage was evaluated on endoscopic images by two members of the study sites under blinded condition. Background factors including age, gender, past history of gastric ulcer, drinking status (with drinkers defined as those consuming alcohol at least 20 g/day), smoking status (with smokers defined as those smoking at least 10 cigarettes/day), complications, ulcer site and ulcer diameter were compared between groups (Table I).

Statistical analysis

The patients entering the treatment phase were examined as the full analysis set (FAS), after excluding those with disease not eligible for the study or without data for efficacy analysis, with statistical testing performed with a two-sided significance level of 5%.

Based on gastric ulcer findings, the gastric ulcer healing rate was calculated by the treatment group, and the comparison between groups was performed using a χ^2 test. Furthermore, analysis was also performed for the per protocol set (PPS), and the robustness of results was examined. The assessment by the investigator at each site was regarded as final regarding findings for gastric ulcer. A χ^2 test or

Table I. Comparison of characteristics of patients receiving irsogladine (Group I) and famotidine (group F) in the full analysis set.

Treatment group	Group I (n = 54)	Group F (n = 54)
Mean age (years)	58.3 ± 12.0	58.0 ± 12.9
Gender (male/female)	38/16	37/17
History of gastric ulcer (±)	6/48	9/45
Alcohol habit (±)	25/29	20/34
Smoking habit (±)	25/29	22/32
Complicated disease (±)	10/44	7/47
Site of lesion		
Corpus	26	26
Angle	20	22
Antrum	8	6
Mean size of lesion (mm)	13.4 ± 5.3	13.3 ± 5.2
(Min–Max)	(5–25)	(5–25)
Eradication rates (%)	88.9	85.2

Fisher's exact probability test was performed for comparison of healing rates by subgroup. The unpaired *t*-test or χ^2 test was performed to check for imbalance of background factors according to the type of data, with a two-sided significance level of 15%.

Results

Patient characteristics

Between December 2005 and April 2009, 120 Japanese patients were enrolled in the study and received 1-week of *H. pylori* eradication. Although 119 patients were enrolled in the treatment phase, 11 patients were not eligible for FAS analysis because they did not visit or withdrew from the study while it was being performed, or because no data were available for them at the end of the study for other reasons (Figure 1). Patient background factors are shown in Table I. Eradication rates did not differ between groups. The number of patients who failed eradication was six in group I and eight in group F.

Ulcer healing rates

The frequency of unsuccessful eradication was similar between groups, and it is not expected to affect differences in subsequent healing rates. Among the healed patients, there was no significant difference ($p = 0.4484$) in healing rates between groups I (85.2% [46/54]) and F (79.6% [43/54]) in the FAS. On analysis of the PPS, the healing rates in groups I and F were 86.5% (45/52) and 81.1% (43/53), respectively, with no significant difference between the groups ($p = 0.4521$). When healing rates were confirmed by ulcer diameter, no significant differences were found between groups I and F in healing rate for ulcers of any diameter (Table II). Examination of gastric ulcer healing rates in the FAS revealed healing rates of 50.0% (3/6) and 50.0% (4/8), respectively, in patients with unsuccessful eradication in groups I and F, with no significant difference between groups.

A significantly lower rate of ulcer healing was seen in patients who drink alcohol (60.0% [12/20]) than in those who do not (91.2% [31/34]) in group F ($p = 0.0119$). However, ulcer healing rates in group I were similar in patients who drink alcohol (84.0%

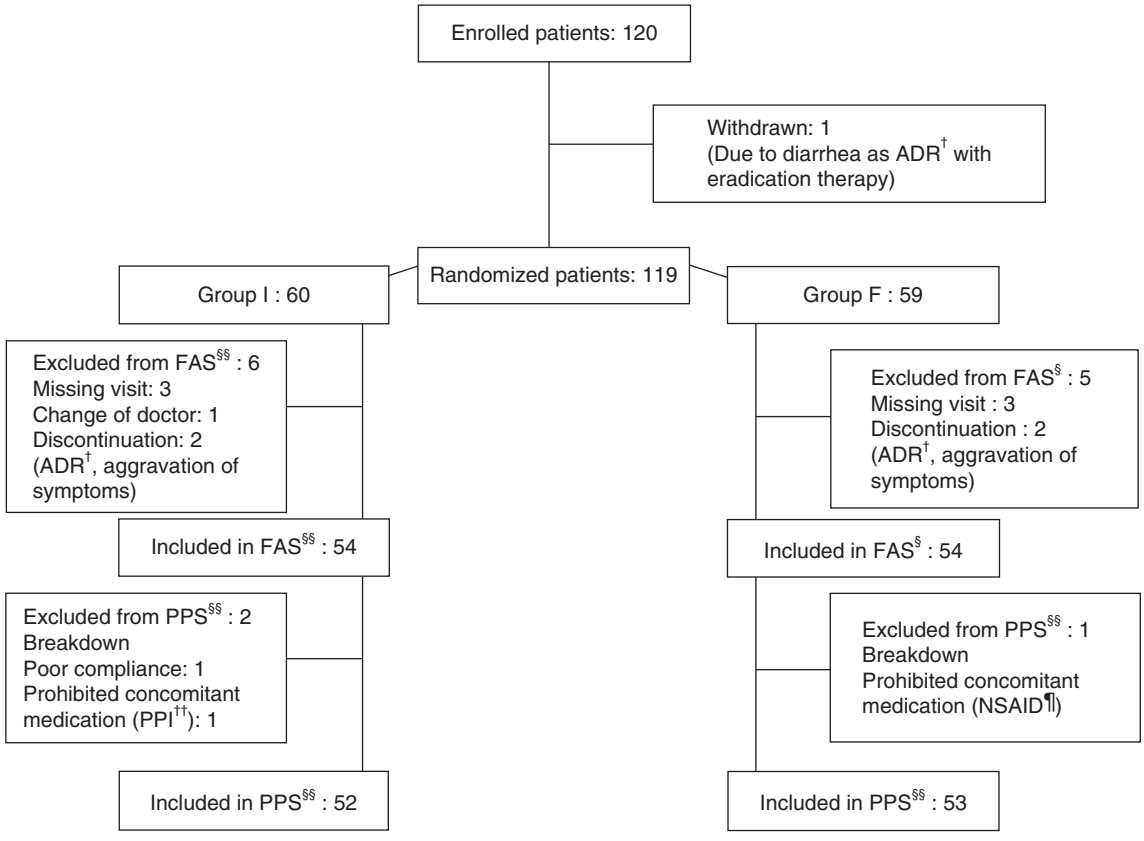

Figure 1. Flow diagram showing the enrolled patients and dropouts from the study. †Adverse drug reaction; §Full analysis set; ¶Non-steroidal anti-inflammatory drug; ††Proton pump inhibitor; §§Per protocol set. Group I = irsogladine, 4 mg/day group; Group F = famotidine, 40 mg/day group.

Table II. Healing rates for ulcers of different sizes.

Diameter	Group I	Group F	*p*-Value
5–10 mm	90.0% (9/10)	100.0% (9/9)	$p = 1.0000$ (F)
10–15 mm	87.5% (14/16)	84.2% (16/19)	$p = 1.0000$ (F)
≥15 mm	82.1% (23/28)	68.0% (17/25)	$p = 0.2322$ (C)
Total	85.2% (46/54)	79.6% (43/54)	$p = 0.4484$ (C)

[21/25]) and those who do not (86.2% [25/29]) ($p = 1.0000$) (Figure 2).

Furthermore, ulcer healing rates were significantly lower in smokers (59.1% [13/22]) than in non-smokers (93.8% [30/32]) in group F ($p = 0.0041$). However, smoking status had no effect on healing rate in group I, with a similar rate of healing seen in smokers (88.0% [22/25]) and non-smokers (82.8% [24/29] ($p = 0.7112$). Ulcer healing rates in smokers were significantly higher in group I (88.0% [22/25]) than in group F (59.1% [13/22]) ($p = 0.0233$) (Figure 3).

Safety assessment

Of the 120 subjects enrolled in the study, safety was assessed in 119 subjects, excluding one for whom treatment was discontinued before entry into the treatment phase. The proportions of patients in whom adverse drug reactions were observed during treatment with the study drug during the treatment phase were 1.7% (1/60) in group I and 1.7% (1/59) in group F, with no significant difference between the groups. There was one patient each (drug eruption) in groups I and F who discontinued treatment with the study drug due to adverse drug reactions, and no differences in safety of treatment were observed between the two groups.

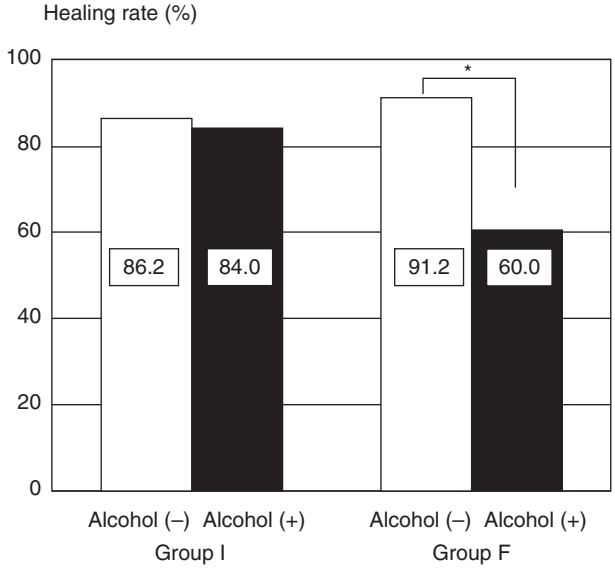

Figure 2. Healing rates by drinking status in the two treatment groups in the full analysis set. Group I Alcohol (–) ($n = 29$), Group I Alcohol (+) ($n = 25$); Group F Alcohol (–) ($n = 34$), Group F Alcohol (+) ($n = 20$). *$p = 0.0119$.

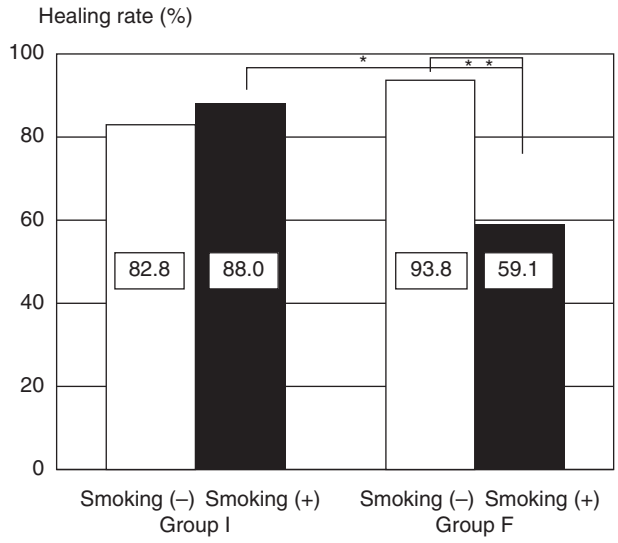

Figure 3. Healing rates by smoking status in the two treatment groups in the full analysis set. Group I Smoking (–) ($n = 29$), Group I Smoking (+) ($n = 25$); Group F Smoking (–) ($n = 32$), Group I Smoking (+) ($n = 22$). *$p = 0.0233$; **$p = 0.0041$.

Discussion

Hiraishi et al. confirmed that, compared with placebo, irsogladine significantly enhanced gastric ulcer healing after *H. pylori* eradication therapy [5]. However, no previous study has compared the effects of irsogladine with a H_2RA.

In the present study, gastric ulcer healing rates after eradication therapy were 85.2% with irsogladine and 79.6% with famotidine, and they were not significantly different. It thus appeared that there was no difference between irsogladine and famotidine in promotion of ulcer healing following triple therapy, and that either drug can be used for the treatment of gastric ulcer after eradication.

However, gastric ulcer healing rates were significantly lower in patients who drink alcohol than those who do not in the famotidine group. A relationship between alcohol consumption and gastric mucosal injury has been suggested [15], and Miwa et al. reported that, in Japan, alcohol consumption may be one cause of gastric ulcer recurrence following successful eradication [16].

Notably, ethanol is known to increase intracellular Ca^{2+} concentration and reduce intracellular

communication [17,18]. Irsogladine reportedly inhibits an increase in intracellular Ca^{2+} concentration [19] as well as a decrease in activation of intracellular communication [10,19], and its effects might not be influenced by alcohol consumption. Moreover, it is also reported that one of the mechanisms of gastric mucosal injury by alcohol is associated with a decrease in the angle of contact of the gastric mucosa with ethanol [7]. In addition, irsogladine inhibits the decrease in gastric mucosal contact angle with ethanol and ethanol gastric mucosal injury [7], and these gastric mucosal protective effects may also be unaffected by alcohol.

In the present study, the gastric ulcer healing rate was significantly lower in smokers than in non-smokers in the famotidine group. Previously, smoking was found to be closely associated with peptic ulcer, and it has been reported that gastric ulcer is more likely to occur in smokers, that it tends to heal poorly in them, and tends to recur [20–22]. There are many reasons for the development of gastric ulcers, and decreased gastric mucosal blood flow is considered a particularly important one in smokers [23–25]. Since irsogladine improves gastric mucosal blood flow, most likely via enhanced cAMP and/or NO production [6,11], a decrease in gastric mucosal blood flow may be inhibited in smokers.

Thus, irsogladine and famotidine are both acceptable treatments for ulcer healing after *H. pylori* eradication therapy in gastric ulcer patients. However, irsogladine appears to be more beneficial than famotidine in patients who drink alcohol or smoke.

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