Alimentary Pharmacology & Therapeutics

Clinical trial: irsogladine maleate, a mucosal protective drug, accelerates gastric ulcer healing after treatment for eradication of *Helicobacter pylori* infection – the results of a multicentre, double-blind, randomized clinical trial (IMPACT study)

H. HIRAISHI*, K. HARUMA†, H. MIWA‡ & H. GOTO§

*Department of Gastroenterology, Dokkyo Medical University, Tochigi, Japan; †Internal Medicine Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Okayama, Japan; ‡Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; §Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence to:
Dr H. Hiraishi, Department of Gastroenterology, Dokkyo Medical University, Mibu, Tochigi 321-0293, Japan.
E-mail: hiraishi@dokkyomed.ac.jp

Publication data
Submitted 4 September 2009
First decision 10 September 2009
Resubmitted 26 January 2010
Accepted 28 January 2010
Epub Accepted Article 2 February 2010

SUMMARY

Background
Helicobacter pylori eradication therapy alone is not sufficient to heal all gastric ulcers.

Aim
To verify the efficacy of treatment with irsogladine maleate between the termination and assessment of treatment for eradicating *H. pylori* in a double-blind study.

Methods
Three hundred and twenty-two patients with a single *H. pylori*-positive gastric ulcer were given eradication treatment, then assigned randomly to a treatment group [given 4 mg/day irsogladine maleate (n = 150)] or a control group [given a placebo (n = 161)]. The gastric ulcer healing rates were compared after 7 weeks of treatment.

Results
The healing rate was significantly higher in the irsogladine maleate group (83.0%) than in the placebo group (72.2%; χ^2 test, P = 0.0276). In the subgroup analysis of cases of eradication failure, the gastric ulcer healing rate was significantly higher in the irsogladine maleate group (57.9%) than in the placebo group (26.1%; χ^2 test, P = 0.0366).

Conclusions
Irsogladine maleate was effective for treating gastric ulcer after *H. pylori* eradication. The high healing rates observed in patients with or without successful eradication demonstrate the usefulness of irsogladine maleate treatment regardless of the outcome of eradication.

Aliment Pharmacol Ther **31**, 824–833

doi:10.1111/j.1365-2036.2010.04250.x

INTRODUCTION

For gastric ulcers associated with *Helicobacter pylori* (*H. pylori*) infection, a triple therapy to eradicate the bacterium is recommended that consists of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin.[1, 2] Remarkable reductions in the relapse rate of gastric ulcers have been reported with the use of this combination therapy.[3–5] Some authors believe that eradication of *H. pylori* should be performed after the gastric ulcer has been treated, whereas others believe that eradication treatment should be initiated when the gastric ulcer is first identified and *H. pylori* has been diagnosed. However, the eradication treatment is often started at the time of diagnosis of a gastric ulcer because the treatment for *H. pylori* eradication seems to have no adverse effect on ulcer healing.[6, 7] Although it has been reported in studies from Europe and the United States that eradication treatment alone is sufficient to cure peptic ulcers,[8–10] these results have been obtained predominantly for duodenal ulcers and therefore cannot be extrapolated to the treatment of gastric ulcers, which occur frequently in the Japanese population.[11] Lai *et al.* have reported that the rate of healing of gastric ulcers is significantly lower than the rate of healing of duodenal ulcers after the eradication of *H. pylori*. They demonstrated the need for the continued treatment of gastric ulcers after eradication therapy.[12] Higuchi *et al.* reported that the therapeutic effects of *H. pylori* eradication alone were insufficient to cure gastric ulcers in Japanese patients and that further treatment after eradication therapy is necessary for gastric ulcers in Japanese patients, unlike Caucasian patients.[13] Moreover, the rate of eradication of *H. pylori* has decreased recently due to the development of increasing resistance to clarithromycin,[14, 15] which suggests that another drug therapy should be administered immediately after the eradication regimen has been performed until eradication is assessed.

During the period after the eradication treatment until the time of assessment, which is performed at least 4 weeks after the completion of eradication therapy, the results of the treatment remain unknown. Murakami *et al.* reported that 72.0% of gastric ulcer relapses are observed during this period.[16] This suggests the need for further anti-ulcer treatment before the assessment of eradication because the risk of relapse is high, particularly in patients in whom eradication of *H. pylori* has failed. However, because the administration of PPIs and some histamine H_2 receptor antagonists (H_2RAs) is known to affect the assessment of eradication,[17–20] it is desirable that these drugs are not given for at least 4 weeks before the eradication is assessed. Therefore, an anti-ulcer drug that does not interfere with the assessment of *H. pylori* eradication is required for use after eradication treatment.

Irsogladine maleate is an enhancer of gastric mucosal protective factors that is often prescribed in Japan, Korea and China. It increases the production of intracellular cyclic adenosine monophosphate (cAMP) by inhibiting phosphodiesterase activity[21] and thus activates intracellular communication,[22] prevents a reduction in gastric mucosal blood flow,[23, 24] increases anti-inflammatory activity[21] and prevents the reduction of mucosal hydrophobicity.[25] Its efficacy has been demonstrated in various models of gastric mucosal injury.[23, 26]

In a pilot study of irsogladine maleate given after *H. pylori* eradication treatment, the rate of healing of gastric ulcers was 79.2%.[27] The present study was designed to verify the usefulness of irsogladine maleate when given during the period from immediately after the completion of *H. pylori* eradication treatment until the patient is assessed for eradication of the bacterium.

MATERIALS AND METHODS

Patients

Patients of Japanese ethnic origin were recruited at the outpatient departments of 44 hospitals and clinics in Japan and provided written consent prior to their participation in this study. The patients were aged 20 years or older at the time of inclusion. All patients had been proven positive for *H. pylori* and had a single gastric ulcer that had been confirmed by endoscopy (5 mm or more across the longest diameter). The ulcers had no evidence of regeneration of the peripheral epithelium (active stage). The diagnosis of *H. pylori* infection was confirmed either by the rapid urease test[28] or the ^{13}C-urea breath test.[29] The patients were enrolled in the study within 3 days of the diagnosis of *H. pylori*-positive gastric ulcer disease.

Patients were excluded if they (i) had previously undergone *H. pylori* eradication treatment; (ii) had an acute gastric mucosal lesion (AGML); (iii) had an ulcer with exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) in the preceding 4 weeks, which was confirmed by interview; (iv) had a linear ulcer; (v) had a

concomitant duodenal ulcer; (vi) had an ulcer that was resistant to anti-ulcer drugs, as judged by the physician on that basis of an interview about the history of treatment of the gastric ulcer and the previous failure of anti-ulcer drugs; (vii) had a history of gastrectomy or vagotomy; (viii) had an ulcer that required surgical treatment; (ix) had a gastric ulcer with a high risk of bleeding (classified as IIb or III on Forrest's classification (patients classified as IIa were enrolled only when the investigator deemed that there was no risk of haemorrhage during the 8-week study period); (x) were hypersensitive to any drugs; (xi) were being treated with drugs that were contraindicated for coadministration with the medications used in this study; (xii) were pregnant or suspected to be pregnant; (xiii) had participated in another clinical study within a 12 weeks period before their informed consent was given; or (xiv) had a serious comorbidity.

Study design and assessment

This was a randomized, double-blind, placebo-controlled, parallel-group comparison study and was approved by the institutional review boards of all of the participating study sites. The eradication treatment comprised a triple therapy that consisted of 30 mg of lansoprazole, 750 mg of amoxicillin and 200 mg of clarithromycin, each given orally twice a day after breakfast and supper for 1 week. The method of eradication used in this study is the standard therapy that is recommended by guidelines that are accepted in Japan.[1] The dose of clarithromycin can be either 400 mg/day or 800 mg/day; both have the same efficacy for bacterial eradication. However, a dose of 400 mg/day has been reported to be safer.[30] Therefore, in this study, 400 mg/day clarithromycin was used.

After the eradication treatment, the investigators confirmed that the patients had not suffered any complications with respect to severe hepatic, cardiac, renal or blood disease due to the treatment and that they had complied with the therapy throughout the 1 week period. The patients were then randomized to either the irsogladine maleate group (4 mg/day group; IM group) or the placebo group (P group). Both irsogladine maleate and the placebo were given orally twice a day after breakfast and supper for a 7-week period. During the treatment period, the patients visited the study site once during the third week of the study for the measurement of the safety parameters.

The primary endpoint of the study was gastric ulcer healing, as judged by the investigators. Patients who exhibited scarring of the ulcer, which had been diagnosed endoscopically as active at the baseline, were considered to have a healed ulcer. The ratio of the number of healed patients in each group to the number of patients in the efficacy analysis population was calculated. 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 Endoscopic Image Evaluation Committee, who were independent of the study sites. These individuals evaluated the endoscopic images of all patients in a manner independent of each other. They were both blinded to the treatment group and study site of the patient.

At the end of the study, bacterial eradication was evaluated by the ^{13}C-urea breath test. The co-administration of antimicrobial agents, antiprotozoal drugs, PPIs, H_2RAs, and bismuth preparations, which might affect the evaluation of the eradication of the bacterium, was contraindicated during the 7-week treatment period. Laboratory blood tests and urinalyses were all performed on the day of the final visit of the study. Subjective symptoms and objective findings were examined by an interview at each visit, and any new events were recorded. Adverse events were followed-up until the baseline state had been returned to or until they were no longer clinically significant.

Statistical analysis

In a preliminary study that was conducted before this study, the rate of gastric ulcer healing due to the combination of eradication treatment and IM was 80% (28/35 patients).[27] Higuchi *et al.* reported the rate of gastric ulcer healing with eradication treatment alone to be 56%.[13] Therefore, the number of subjects required to detect a significant difference with a 5% two-sided significance level and an 80% power of detection was 160 per group, assuming a healing rate of 75% in the IM group and of 60% in the P group and considering the likelihood that some subjects would be excluded from the analysis.

Of the patients who progressed to the treatment period, those that remained after the exclusion of patients who had a non-indicated disease or for whom there were no data for the efficacy analysis were included in the full analysis set (FAS). The rate of gastric ulcer healing and the 95% confidence intervals (CI) were calculated for both groups based on the endoscopic

findings. The two-sided significance level was 5% ($P \leq 0.05$) using the chi-square test. The results of the gastric ulcer assessment performed by the investigators at each site were considered to be the final judgment, although the results of the overall evaluation by the Endoscopic Image Evaluation Committee were also examined. The rates of gastric ulcer healing were also analysed in the per protocol set (PPS), and the robustness of these results was examined.

RESULTS

Characteristics of the evaluable subjects

A total of 322 Japanese patients who were enrolled in the study between May 2007 and August 2008 underwent eradication treatment for 1 week. Eleven of these patients were withdrawn from the study before treatment with irsogladine maleate or placebo. Therefore, 311 patients were randomized into the two groups (IM group, $n = 150$; P group, $n = 161$). Of these patients, 19 were judged to be ineligible to be included in the FAS. These comprised one patient with type III early gastric cancer, two patients who had incomplete endoscopic findings at the completion of the study, and 16 patients who dropped out from the study (Figure 1).

The background demographic factors of the patients are shown in Table 1. In the FAS, the rates of eradication of *H. pylori* were 86.5% (122/141) in the IM group and 84.8% (128/151) in the P group.

Endpoint (ulcer healing)

The proportion of patients who showed endoscopic evidence of the clinical progression of their ulcers to the scarred stage (i.e. the healing rate) at the completion of the study was significantly higher in the IM

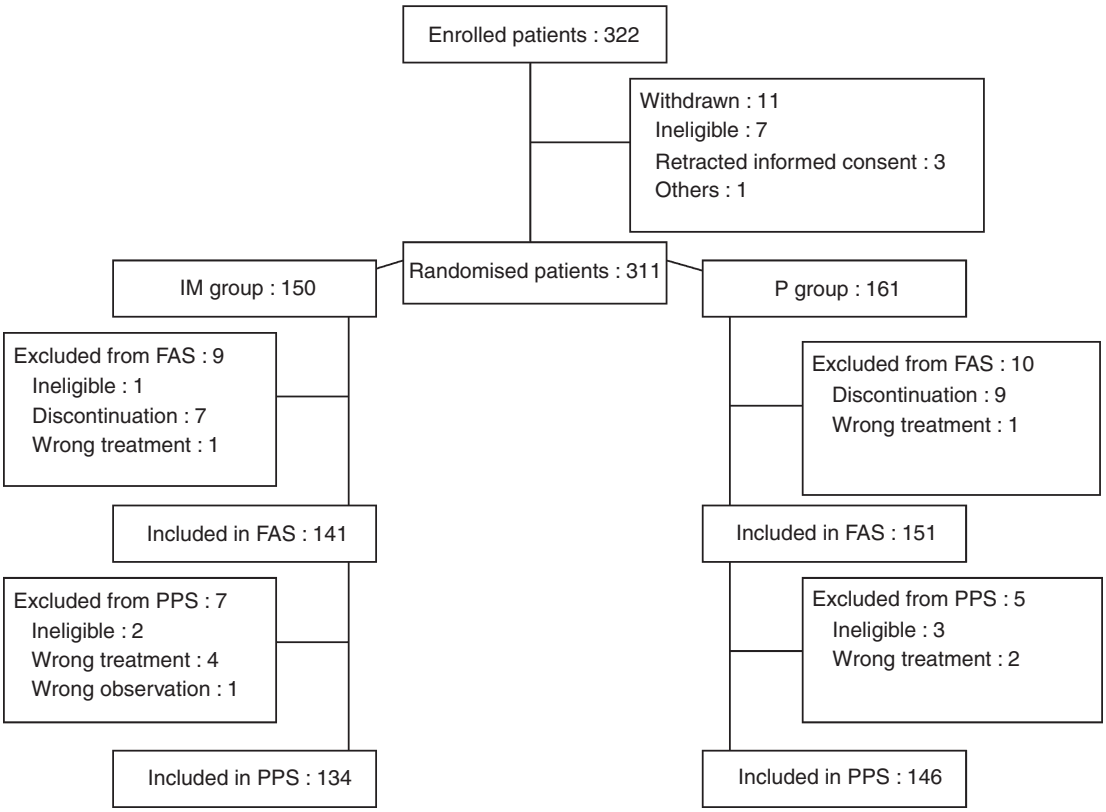

Figure 1. Flow diagram showing the enrolled patients and dropouts from the study. IM group, irsogladine maleate (4 mg/day); P group, placebo group; FAS, full analysis set; PPS, per protocol set. Withdrawn (ineligible = gastric cancer; others = history of eradication therapy). IM group excluded from FAS (ineligible = gastric cancer; wrong treatment = no image taken). IM group excluded from PPS (ineligible = gastric cancer; wrong treatment = prohibited treatment/wrong dose; wrong observation = prescription error). P group excluded from FAS (wrong treatment = no image taken). P group excluded from PPS (ineligible = gastric cancer/multiple ulcers/rectal cancer; wrong treatment = prohibited treatment).

Table 1. Comparison of patient characteristics in the two treatment groups: irsogladine maleate (IM) and placebo (P) in the FAS analysis

Treatment group	IM group (n = 141)	P group (n = 151)
Mean age (years)	52.3 ± 11.4	52.4 ± 11.6
Gender (male)	86	106
History of gastric ulcer	77	86
Smoking habit (+)	95	102
Complicated disease (+)	117	120
Site of lesion (1)		
Body	71	73
Angle	65	74
Antrum	5	4
Site of lesion (2)		
Anterior wall	10	7
Lesser curvature	92	105
Posterior wall	35	36
Greater curvature	4	3
Mean size of lesion (mm)	13.1 ± 6.3	13.1 ± 6.4
Range	5–32	5–40

(A) Student's t-test; (C): χ^2 test; (F) Fisher's exact test.

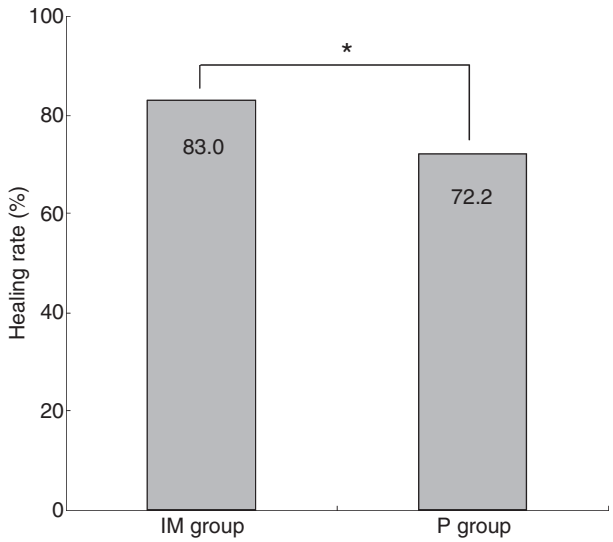

Figure 2. Healing rates in the two treatment groups in the FAS. Irsogladine maleate (IM) group (n = 141), placebo (P) group (n = 151), *P = 0.0276 (χ^2 test), delta value = 10.8% [95% confidence interval (CI): 1.3–20.3%].

group [83.0% (117/141)] than in the P group [72.2% (109/151)] in the FAS (P = 0.0276) (Figure 2).

Subsequent analysis of the PPS revealed healing rates of 83.6% (112/134) in the IM group and 72.6% (106/146) in the P group (P = 0.0271). These rates were similar to those obtained in the FAS, which indicated the robustness of the results related to this primary endpoint.

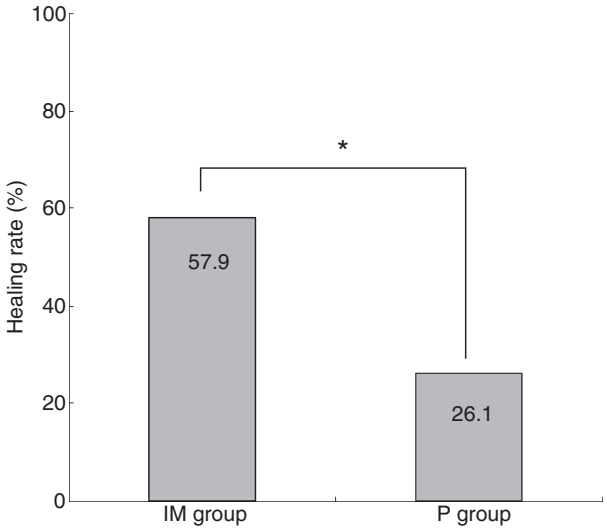

Figure 3. Healing rates in cases of eradication failure in the two treatment groups. IM group (n = 19), P group (n = 23), * P = 0.0366 (χ^2 test), delta value = 31.8% (95% CI: 3.3–60.4%).

The central evaluation of gastric ulcer healing performed by the Endoscopic Image Evaluation Committee for reference purposes gave rates of healing of 82.1% (115/140) in the IM group and 71.1% (106/149) in the P group in the FAS (P = 0.0276), and of 82.7% (110/133) in the IM group and 71.5% (103/144) in the P group in the PPS (P = 0.0274). These results were consistent with those obtained by the investigators. As a result of the evaluation by the Endoscopic Image Evaluation Committee, one patient in the IM group with a gastric erosion, and two patients in the P group, one with a duodenal ulcer and one with an ulcer in the healing stage, were excluded from the analysis because their disease process was 'non-indicated', based on their baseline endoscopic images. Therefore, the results obtained from the evaluation by the Endoscopic Image Evaluation Committee included one fewer patient in the IM group and two fewer patients in the P group as compared with the populations included in the FAS analysis.

According to the intention-to-treat (ITT) analysis, which counted the discontinuations and patients who did not have endoscopic findings at the end of the study as 'uncured cases', a significantly higher efficacy

was apparent in the IM group [78.0% (117/150)] than in the P group [67.7% (109/161)] ($P = 0.0417$), which was similar to the results of the FAS analysis.

In a subgroup analysis of the FAS, the rates of gastric ulcer healing in cases where eradication had failed were 57.9% (11/19) in the IM group and 26.1% (6/23) in the P group ($P = 0.0366$). Therefore, the rate of healing was significantly higher in the IM group than in the P group (Figure 3).

The values that were obtained in the FAS analysis after adjustment for gender, which was the demographic background factor that showed bias, were similar to those obtained before adjustment by the Mantel–Haenszel test ($P = 0.0351$).

Safety assessment

Safety was assessed in 311 patients. Of the 322 patients who were enrolled initially in the study, 11 patients (five in the IM group and six in the P group) were excluded because they had dropped out before they progressed to the treatment period.

The proportions of patients who exhibited adverse drug reactions during the treatment period were 7.3% (11/150) in the IM group and 7.5% (12/161) in the P group; this difference was not significant between the groups (Table 2). None of the adverse drug reactions showed a particularly high incidence in the IM group when compared with the P group.

Table 2. Adverse events during treatment with irsogladine maleate (IM) or placebo (P)

Adverse event/treatment group	IM group ($n = 150$)	P group ($n = 161$)
Gastric cancer	1	
Abdominal distension	1	
Constipation	3	2
Diarrhoea	2*	1
Ischaemic enterocolitis	1	
Reflux oesophagitis		1
Stomatitis	1*	
Rash/urticaria/drug eruption	3*	2
'Lumpy' feeling in the throat		1
Reduced white blood cell count	1	1
Elevated hepatic function parameters (ALT†, GGT‡, bilirubin)		3
Increased triglycerides		1
Total (number of patients)	11 (7.3%)	12 (7.5%)

* Same patient.
†Alanine aminotransferase.
‡ Gamma-glutamyl transpeptidase.

In the IM group, early gastric cancer was diagnosed in one patient during the follow-up period. Although the target lesion that was present at the baseline had healed and eradication was successful in this patient, findings that were indicative of an ulcer at another site were observed on the endoscopy performed at the completion of the study. Therefore, a follow-up examination was performed. Although biopsies were performed in this patient at several time points, which included at the completion of the study and during the follow-up period, these yielded no malignant findings. A follow-up endoscopy that was performed 6 months after the study had been completed detected group IV findings. Subsequently, a laparoscopic partial gastrectomy was performed successfully and the diagnosis of gastric cancer (group V) was confirmed. The investigator reported that a causal relationship between gastric cancer and IM treatment following *H. pylori* eradication was unlikely, although this could not be ruled out completely.

The administration of the study drug during the treatment period was discontinued due to adverse drug reactions in three patients (drug eruption in two patients and ischaemic enteritis in one patient) in the IM group and two patients (drug eruption and choking symptoms) in the P group, which indicated that the treatment with IM had no serious adverse effects with regard to patient safety.

DISCUSSION

We examined the effect of treatment with irsogladine maleate immediately after *H. pylori* eradication in Japanese patients with *H. pylori*-positive gastric ulcers. It has been reported that the incidence of gastric ulcer is higher than that of duodenal ulcer in the Japanese population.[11] It is also known that gastric acid contributes less to the formation of gastric ulcers than to the formation of duodenal ulcers and that secretion of gastric acid is lower in the Japanese population than in Caucasian populations.[31, 32] Therefore, it is highly likely that treatment with a mucosal protective agent would be selected for the treatment of gastric ulcers in Japanese patients in preference to a gastric acid secretion inhibitor. Although irsogladine maleate is available commercially for the treatment of gastric ulcers, no results of randomized controlled trials of the

ulcer-healing effects of irsogladine maleate after eradication treatment have been reported.

In this study, *H. pylori* eradication was performed first in patients with an *H. pylori*-positive gastric ulcer and the patients were then randomized to the irsogladine maleate group or the placebo group. The rates of ulcer healing were compared between these groups at the completion of the study.

We found that treatment with irsogladine maleate before the assessment of *H. pylori* eradication improved the healing rate compared with placebo treatment in patients who had undergone *H. pylori* eradication therapy. In the FAS analysis, the healing rate was significantly higher in the irsogladine maleate group (83.0%) than in the placebo group (72.2%). Similarly, the healing rate was significantly higher in the irsogladine maleate group (83.6%) than in the placebo group (72.6%) in the PPS. In the PPS, seven patients in the irsogladine maleate group and five patients in the placebo group were excluded from the FAS. This comparatively small number of exclusions suggested that this clinical study was well controlled and highly reliable. The close correlation between the results obtained by the investigators and those obtained in a central evaluation by the Endoscopic Image Evaluation Committee also confirmed the reproducibility of this study.

A subgroup analysis of the efficacy of irsogladine maleate revealed a significantly higher rate of healing of gastric ulcers in the irsogladine maleate group in cases in which *H. pylori* eradication has not been successful, with rates of 57.9% in the irsogladine maleate group and 26.1% in the placebo group. This demonstrated that treatment with irsogladine maleate accelerated the rate of gastric ulcer healing in such patients. The low healing rate of 26.1% among patients in the placebo group in whom eradication treatment had failed suggested that eradication alone followed by observation and no further treatment is potentially risky. Whereas the eradication rate in this study was relatively high (85.6%), this rate has been decreasing in recent years in clinical practice[33] and is now reported to be below 80% in most places[34] or even below 70% in some places.[33] Therefore, it is likely that additional treatment of the ulcer during the period from immediately after eradication until the assessment of eradication will be warranted in the future.

Treatment with PPIs has been observed to affect the results of the ^{13}C-urea breath test to assess eradication.[17–19] This effect might be due to the proliferation of bacteria other than *H. pylori* and an increase in gastric pH that is accompanied by a reduced level of urease activity in *H. pylori* and a reduced urease activity accompanying the increase in gastric pH,[35, 36] in addition to the antimicrobial effects of the PPIs themselves.[37] Although H_2RAs do not have antimicrobial activity themselves,[38] it has been reported that they affect the assessment of eradication because of concomitant changes in the gastric pH, which are similar to those induced by PPIs.[18, 20] Given that a significant reduction in the ^{13}C-urea breath test has also been reported after treatment with H_2RAs, with no increase in the rate of false negative results,[39] H_2RAs should be administered with care. This is particularly the case in patients with positive, but low titres from the ^{13}C-urea breath test. Irsogladine maleate is considered suitable for the treatment of ulcers after eradication therapy because it inhibits neither urease activity (unpublished observation from Nippon Shinyaku Pharmaceutical Co., Ltd., Kyoto, Japan) nor secretion of gastric acid.[40, 41] Consequently, irsogladine maleate is likely to have no effect on the assessment of *H. pylori* eradication. This is particularly important because *H. pylori* is reported to cause not only gastric ulcers but also gastric cancer.[42] Therefore, the results of eradication treatment must be assessed accurately to prevent a relapse of the gastric ulcer and the development of gastric cancer.[43, 44]

Higuchi *et al.* reported that the rate of eradication was 83.6% (ITT) in the triple therapy group that received a PPI, 1500 mg of amoxicillin and 800 mg of clarithromycin daily for 1 week, and that the rate of ulcer healing was 49.2% (ITT) at 8 weeks after triple therapy in Japan.[13] In our study, the rate of eradication was 84.8% (FAS), and the rates of ulcer healing were 72.2%/67.7% (FAS/ITT) at 7 weeks after triple therapy in the placebo group. The eradication rate was almost the same in the two studies, but our study gave a higher rate for ulcer healing. The cause of the different results in these two studies remains unclear because the average ulcer diameters in both were almost equal (12 mm and 13 mm). It has been shown that the rate of healing of gastric ulcers after the successful eradication of *H. pylori* depends on the size of the ulcer. Sung *et al.* reported rates of ulcer healing of 84% and 96% at 5 weeks and 9 weeks after the eradication of *H. pylori*, respectively.[45] The average diameter of gastric ulcers in their study was 8.2 mm. In contrast, Higuchi *et al.* demonstrated that although the overall healing rate of gastric ulcers with an average

diameter of 12 mm was 49.2% at 8 weeks after eradication of *H. pylori*, individual healing rates depended on the diameter of the ulcer, and corresponded to 89%, 54% and 5% for ulcers of <10 mm, 10 to <15 mm, and ≥15 mm respectively.[13] Therefore, it seems that *H. pylori* eradication alone is effective for smaller ulcers of <10 mm, but adjuvant treatments after eradication are necessary for larger ulcers.

It should be noted that this randomized control trial has a number of limitations. First, we enrolled low-risk patients with uncomplicated ulcers. It is uncertain whether our findings can be extrapolated to patients with bleeding ulcers, ulcers that are a result of the use of NSAIDs, or extremely large ulcers (>20 mm). Secondly, as described previously, Japanese people have a greater tendency to develop gastric ulcers than duodenal ulcers.[11] Further studies are needed to be performed to assess whether the results can be generalized to other populations, such as Western and other Asian populations.

With regard to the evaluation of safety, the incidence of adverse drug reactions did not differ between the irsogladine maleate and placebo groups. The single case of gastric cancer that was observed in the irsogladine maleate group was considered incidental and not the result of oncogenesis that was attributable to treatment with irsogladine maleate after *H. pylori* eradication. This finding suggests a limitation in the endoscopic diagnosis of gastric ulcers. Some gastric ulcers are difficult to differentiate from type III early gastric cancers, which necessitates either a biopsy of the ulcer or the documentation of complete healing of the ulcer to exclude gastric malignancy. No other notable adverse events were observed in either group in this study and irsogladine maleate was shown to be a safe medication.

In conclusion, we performed a multicentre cooperative study at 44 study sites in Japan. This study has demonstrated the efficacy of irsogladine maleate in the treatment of *H. pylori*-induced, uncomplicated gastric ulcers after attempted eradication of *H. pylori* in Japanese patients. The high rates of ulcer healing in patients in whom eradication treatment was either successful or unsuccessful demonstrated the usefulness of irsogladine maleate treatment, and showed that it improved healing independently of the outcome of eradication. Moreover, because PPIs and some H_2RAs affect the assessment of eradication, whereas irsogladine maleate does not, and it is less expensive than gastric acid inhibitors, irsogladine maleate is an appropriate therapeutic agent to use after eradication therapy for *H. pylori*.

ACKNOWLEDGEMENTS

Declaration of personal interests: The authors thank Professor Seitaro Ohkuma, Department of Pharmacology, Kawasaki Medical School, Okayama, for the treatment randomization. The authors also thank the following investigators: Toshiharu Chikama, Koetsu Morita, Masao Yamauchi, Kazuhiko Koike, Hironobu Kohda, Toshimichi Ito, Akio Shirane, Sigeki Ri, Taihei Murakami, Harufumi Oizumi, Shumei Sagawa, Tadayuki Igarashi, Yasushi Amada, Hironori Masuyama, Seiji Eto, Masae Banno, Tetsuya Sanji, Mitsukuni Azuma, Tokuyuki Yokohata, Ikkyou Kawa, Yoshio Kobori, Terue Sakakibara, Kazumichi Harada, Gakuyou Karasawa, Hironori Kowazaki, Kenichi Murase, Nobuo Fujino, Yoshiki Yamamoto, Syunichi Fukao, Mitsuo Ishiguro, Sumio Toyoda, Tsutomu Sakai, Keiichi Oki, Hitoshi Hongo, Kazuyo Fujimura, Ryuuji Yoshimura, Masumi Kawasaki, Sadamune Hatakeyama, Koji Mori, Hiroaki Tanaka, Tetsuya Nakashima, Kouji Nishida, Akira Shirachi and Naozo Kamiya. Contributions: H. Hiraishi designed the study, contributed to data acquisition, was responsible for writing the manuscript and participated in the statistical analysis; H. Goto participated in the writing of the manuscript and was responsible for the statistical analysis; K. Haruma and H. Miwa participated in patient management and data collection. All authors have seen and approved the final version of the manuscript. *Declaration of funding interests:* This study was supported by a grant from Nippon Shinyaku Co., Ltd., Kyoto, Japan. All authors declare that they have no conflicts of interest and that the work is original.

REFERENCES

1 The Guideline Committee of the Japanese Society for Helicobacter Research. Guidelines for diagnosis and treatment. *Helicobacter Res* 2000; **4**: 444–54.

2 Malfertheiner P, Megraud F, O'Morain C, *et al.* Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2–2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167–80.

3 Asaka M, Sugiyama T, Kato M, *et al.* A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in Japanese peptic ulcer patients. *Helicobacter* 2001; **6**: 254–61.

4 Miwa H, Sasaki N, Sugano K, *et al.* Recurrent peptic ulcers in patients following successful *Helicobacter pylori* eradication: a multicenter study of 4940 patients. *Helicobacter* 2004; **9**: 9–16.

5 Leodolter A, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, Malfertheiner P. A meta-analysis comparing eradication, healing and relapse rates in patients with *Helicobacter pylori*-associated gastric or duodenal ulcer. *Aliment Pharmacol Ther* 2001; **15**: 1949–58.

6 Annibale B, D'Ambra G, Luzzi I, *et al.* Does pretreatment with omeprazole decrease the chance of eradication of *Helicobacter pylori* in peptic ulcer patients? *Am J Gastroenterol* 1997; **92**: 790–4.

7 Okada M, Oki K, Shirotani T, *et al.* A new quadruple therapy for the eradication of *Helicobacter pylori.* Effect of pretreatment with omeprazole on the cure rate. *J Gastroenterol* 1998; **33**: 640–5.

8 Hosking SW, Ling TK, Chung SC, *et al.* Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment; randomized controlled trial. *Lancet* 1994; **343**: 508–10.

9 Gisbert JP, Pajares JM. Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer? *Aliment Pharmacol Ther* 2005; **21**: 795–804.

10 Atherton JC. Can peptic ulcers be healed with 7 days of proton-pump-inhibitor-based triple therapy? *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 346–7.

11 Watanabe Y, Kawai K. Descriptive and analytical epidemiology of peptic ulcer disease in Japan. *Gastroenterol Jpn* 1991; **26**(Suppl 3): 258–61.

12 Lai KC, Hui WM, Wong BC, Hu WH, Lam SK. Ulcer-healing drugs are required after eradication of *Helicobacter pylori* in patients with gastric ulcer but not duodenal ulcer haemorrhage. *Aliment Pharmacol Ther* 2000; **14**: 1071–6.

13 Higuchi K, Fujiwara Y, Tominaga K, *et al.* Is eradication sufficient to heal gastric ulcers in patients infected with *Helicobacter pylori*? A randomized, controlled, prospective study. *Aliment Pharmacol Ther* 2003; **17**: 111–7.

14 Perez Aldana L, Kato M, Nakagawa S, *et al.* The relationship between consumption of antimicrobial agents and the prevalence of primary *Helicobacter pylori* resistance. *Helicobacter* 2002; **7**: 306–9.

15 Osato MS, Reddy R, Reddy SG, *et al.* Pattern of primary resistance of *Helicobacter pylori* to metronidazole or clarithromycin in the United States. *Arch Intern Med* 2001; **161**: 1217–20.

16 Murakami K, Sato R, Okimoto T, *et al.* Maintenance therapy with H_2-receptor antagonist until assessment of *Helicobacter pylori* eradication can reduce recurrence of peptic ulcer after successful eradication of the organism; prospective randomized controlled trial. *J Gastroenterol Hepatol* 2006; **21**: 1048–53.

17 Chey WD, Spybrook M, Carpenter S, *et al.* Prolonged effect of omeprazole on the ^{14}C-urea breath test. *Am J Gastroenterol* 1996; **91**: 89–92.

18 Chey WD, Woods M, Scheiman JM, Nostrant TT, DelValle J. Lansoprazole and ranitidine affect the accuracy of the ^{14}C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997; **92**: 446–50.

19 Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB. Effect of proton pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. *Ann Intern Med* 1998; **129**: 547–50.

20 Cutler AF, Elnaggar M, Brooks E, O'Mara K. Effects of standard and high dose ranitidine on ^{13}C-urea breath test results. *Am J Gastroenterol* 1998; **93**: 1297–9.

21 Kyoi T, Noda K, Oka M, Ukai Y. Irsogladine, an anti-ulcer drug, suppresses superoxide production by inhibiting phosphodiesterase type 4 in human neutrophils. *Life Sci* 2004; **76**: 71–83.

22 Ueda F, Kameda U, Yamamoto O, Shibata Y. Beta-adrenergic regulation of gap-junctional intercellular communication in cultured rabbit gastric epithelial cells. *J Pharmacol Exp Ther* 1994; **271**: 397–402.

23 Kyoi T, Oka M, Noda K, Ukai Y. Irsogladine prevents monochloramine-induced gastric mucosal lesions by improving the decrease in mucosal blood flow due to the disturbance of nitric oxide synthesis in rats. *J Pharmacol Sci* 2003; **93**: 314–20.

24 Sato M, Manabe N, Hata J, *et al.* Effect of irsogladine maleate on NSAID-induced reduction of gastric mucosal blood flow in anesthetized dogs. *Digestion* 2009; **79**: 73–8.

25 Tatsumi Y, Tanino M, Kodama T, *et al.* Irsogladine maleate may preserve gastric mucosal hydrophobicity against ethanol in phospholipids independent way in rats. *Jpn J Pharmacol* 1998; **77**: 293–9.

26 Zhang X, Tajima K, Kageyama K, Kyoi T. Irsogladine maleate suppresses indomethacin-induced elevation of proinflammatory cytokines and gastric injury in rats. *World J Gastroenterol* 2008; **14**: 4784–90.

27 Masuyama H, Ishida M, Morita K, *et al.* An open-label, multi-center study of irsogladine maleate for gastric ulcer healing after eradication of *Helicobacter pylori*. *Ther Res* 2008; **29**: 415–22.

28 Marshall BJ, Warren JR, Francis GJ, *et al.* Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. *Am J Gastroenterol* 1987; **82**: 200–10.

29 Ohara S, Kato M, Asaka M, Toyota T. Studies of ^{13}C-urea breath test for diagnosis of *Helicobacter pylori* infection in Japan. *J Gastroenterol* 1998; **33**: 6–13.

30 Nemoto S, Chino F, Ohkubo H, *et al.* Results of the drug use result survey of triple therapy with lansoprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in patients with peptic ulcer. *J Clin Ther Med* 2006; **22**: 21–30.

31 Tahir H, Sumii K, Haruma K, *et al.* A statistical evaluation on the age and sex distribution of basal serum gastrin and gastric acid secretion in subjects with or without peptic ulcer disease. *Hiroshima J Med Sci* 1984; **33**: 125–30.

32 Feldman M, Richardson CT, Lam SK, Samloff IM. Comparison of gastric acid secretion rates and serum pepsinogen I and II concentrations in Occidental and Oriental duodenal ulcer patients. *Gastroenterology* 1988; **95**: 630–5.

33 Robles-Jara C, Robles-Medranda C, Moncayo M, Landivar B, Parrales J. Is a 7-day *Helicobacter pylori* treatment enough for eradication and inactivation of gastric inflammatory activity? *World J Gastroenterol* 2008; **14**: 2838–43.

34 Graham DY. Efficient identification and evaluation of effective *Helicobacter pylori* therapies. *Clin Gastroenterol Hepatol* 2009; **7**: 145–8.

35 McGowan CC, Cover TL, Blaser MJ. The proton pump inhibitor omeprazole inhibits acid survival of *Helicobacter pylori* by a urease-independent mechanism. *Gastroenterology* 1994; **107**: 1573–8.

36 Sharma BK, Santana IA, Wood EC, *et al.* Intragastric bacterial activity and nitrosation before, during, and after treatment with omeprazole. *Br Med J* 1984; **289**: 717–9.

37 Iwahi T, Satoh H, Nakao M, *et al.* Lansoprazole, a novel benzimidazole proton pump inhibitor, and its related compounds have selective activity against *Helicobacter pylori*. *Antimicrob Agents Chemother* 1991; **35**: 490–6.
38 Rektorschek M, Weeks D, Sachs G, Melchers K. Influence of pH on metabolism and urease activity of *Helicobacter pylori*. *Gastroenterology* 1998; **115**: 628–41.
39 Murakami K, Sato R, Okimoto T, *et al.* Influence of antiulcer drugs used in Japan on the result of ^{13}C-urea breath test for the diagnosis of *Helicobacter pylori* infection. *J Gastroenterol* 2003; **38**: 937–41.
40 Okabe S, Takeuchi K, Ishihara Y, Kunimi H. Effect of 2,4-diamino-6-(2,5- dichlorophenyl)-s-triazine maleate (MN-1695) on gastric secretion and on experimental gastric ulcers in rats. *Pharmacokinetics* 1982; **24**: 683–9.
41 Okabe S, Takeuchi K, Okamoto N, Hirosawa R. Effect of 2,4-diamino-6-(2,5- dichlorophenyl)-s-triazine maleate (MN-1695) on gastric secretion and on experimental gastric ulcers in rats (2). Comparison with other antiulcer drugs. *Pharmacokinetics* 1984; **27**: 79–86.
42 Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology* 1999; **114**: 1169–79.
43 Uemura N, Okamoto S, Yamamoto S, *et al. Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784–9.
44 Fukase K, Kato M, Kikuchi S, *et al.* Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392–7.
45 Sung JJY, Chung SCS, Ling TKW, *et al.* Antibacterial treatment of gastric ulcers associated with *Helicobacter pylori*. *N Engl J Med* 1995; **332**: 139–42.