Background/Aims: The ability of endoscopic submucosal dissection (ESD) to resect large early gastric cancers (EGCs) results in the need to treat large artificial gastric ulcers. This study assessed whether the combination therapy of rebamipide plus a proton pump inhibitor (PPI) offered benefits over PPI monotherapy.

Methods: In this prospective, randomized, multicenter, open-label, and comparative study, patients who had undergone ESD for EGC or gastric adenoma were randomized into groups receiving either rabeprazole monotherapy (10 mg/day, n=64) or a combination of rabeprazole plus rebamipide (300 mg/day, n=66). The Scar stage (S stage) ratio after treatment was compared, and factors independently associated with ulcer healing were identified by using multivariate analyses. Results: The S stage rates at 4 and 8 weeks were similar in the two groups, even in the subgroups of patients with large amounts of tissue resected and regardless of CYP2C19 genotype. Independent factors for ulcer healing were circumferential location of the tumor and resected tissue size; the type of treatment did not affect ulcer healing. Conclusions: Combination therapy with rebamipide and PPI had limited benefits compared with PPI monotherapy in the treatment of post-ESD gastric ulcer (UMIN Clinical Trials Registry, UMIN000007435). (Gut Liver 2016;10:917-924)

Key Words: Stomach ulcer; Therapeutics; Endoscopy; Antiulcer agents; Proton pump inhibitors

INTRODUCTION

Endoscopic submucosal dissection (ESD), an endoscopic resection technique first developed in the late 1990s and early 2000s, has become a standard method for the treatment of early gastric cancers (EGC) and some gastric adenomas in Japan, Korea, and other countries. ESD has advantages over the prototype endoscopic resection procedure, endoscopic mucosal resection (EMR), mainly because ESD enables the resection of large lesions en bloc, enhancing complete resection rates. However, ESD procedures also have drawbacks, including higher rates of complications, such as delayed bleeding, than EMR. In addition, the use of ESD to remove large mucosal EGCs results in larger artificial gastric ulcers, making it necessary to develop therapeutic strategies to heal artificial ulcers after ESD.

Proton pump inhibitors (PPIs) are the major class of drugs currently used to treat peptic ulcers. PPIs have shown efficacy in treating post-ESD artificial gastric ulcers, with significantly lower rates of delayed bleeding than histamine H2-receptor antagonists. However, initial ulcer size has been reported to affect artificial ulcer healing by PPI, as ulcers larger than 4 cm were likely to remain unhealed after 4 weeks of PPI treatment. Thus, strategies are needed to treat large artificial ulcers.

The efficacy of PPI therapy also depends on an individual’s ability to metabolize these drugs. PPIs are metabolized by CYP2C19. However, CYP2C19 genotypes vary, with patients classified into three types: rapid metabolizers (RM), intermediate metabolizers (IM), and poor metabolizers (PM). The PPI rabepra-
zole, while metabolized mainly nonenzymatically, is partially metabolized by CYP2C19 and shows reduced acid inhibition in individuals with the RM genotype. However, these data were obtained in healthy volunteers. Thus, the healing effect of rabeprazole in patients with post-ESD artificial gastric ulcer and different CYP2C19 genotypes has not been assessed.

No optimal therapeutic strategy has yet been established for patients with post-ESD gastric ulcers. Although rebamipide add-on therapy to a PPI has been shown more effective than PPI alone in healing artificial ulcers, that study was performed in a small number of patients, and the effects of the CYP2C19 genotype on ulcer healing were not determined. The aim of this study was to evaluate the effect of combination treatment with rebamipide and a PPI in larger numbers of patients with artificial gastric ulcers after ESD. In addition, CYP2C19 polymorphisms were analyzed in patients with EGC or adenoma who underwent ESD, and the effect of CYP2C19 genotype on the efficacy of rebamipide add-on investigated.

**MATERIALS AND METHODS**

1. **Study setting**

   This prospective, randomized, multicenter, and open-labeled comparative study included patients who underwent ESD for EGC or gastric adenoma in the Department of Medicine and Bioregulatory Science of Kyushu University, Aso lizuka Hospital, Kitakyushu Municipal Hospital, National Hospital Organization Kyushu Medical Center, Saiseikai Fukuoka General Hospital, and Harasanshin Hospital from August 2010 to September 2012. The study protocol was approved by the ethics committee of each institution. In addition, this trial was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Written informed consent was obtained from all participants. This trial was registered with the UMIN Clinical Trials Registry, number UMIN000007435.

2. **Study design**

   Patients aged ≥20 years who underwent ESD for the treatment of EGC or gastric adenoma, in which the tumor was resected en bloc, were included. Patients were indicated for ESD if they had (1) differentiated mucosal cancer without ulcer findings, irrespective of tumor size; (2) differentiated mucosal cancer ≤30 mm with ulcer findings; (3) differentiated cancer ≤30 mm with minute submucosal invasion (<500 µm from the muscularis mucosa); or (4) undifferentiated mucosal cancer ≤20 mm without ulcer findings. Patients were excluded if they (1) were pregnant or possibly pregnant; (2) had a history of allergy to the test drugs; (3) had serious complications; (4) took nonsteroidal anti-inflammatory drugs, including a cyclooxygenase 2 selective inhibitor or low-dose aspirin; or (5) took corticosteroids. Patients who underwent piecemeal tumor resection, with resected specimens having affected horizontal or vertical margins, or who underwent gastrectomy as additional therapy after ESD were also excluded.

   Patients were admitted 1 day before ESD and hospitalized for at least 7 days after ESD. All patients received intravenous omeprazole on the first 2 days after ESD, followed by randomization 1:1 to the PPI rabeprazole (10 mg/day; monotherapy group) or to rabeprazole plus 100 mg rebamipide 3 times/day (combination therapy group) for 54 days. For randomization, the central registration center at Kyushu University assigned a trial drug code to each patient. Patients positive for antibody to Helicobacter pylori underwent eradication therapy after a course of antulcer treatment with a PPI alone or PPI/rebamipide combination. Thus, the success or failure of H. pylori eradication did not influence the healing rate of post-ESD gastric ulcer.

3. **ESD procedure**

   ESD was performed as described. Briefly, marks were made on the normal mucosa surrounding the lesion using a needle knife or argon plasma coagulation to indicate safety margins. The submucosal layer was injected with a solution of 10% glycerin, 0.9% NaCl, and 5% fructose (Glyceol; Chugai Pharmaceutical, Tokyo, Japan) or hyaluronic acid solution (MucoUp; Johnson and Johnson, Tokyo, Japan) to elevate the mucosa. Using an electrosurgical knife, such as an insulation-tipped knife (Olympus, Tokyo, Japan), hook knife (Olympus), flex knife (Olympus), flush knife (Fuji Film, Tokyo, Japan), or clutch cutter (Fuji Film), the normal mucosa surrounding the markings was circumferentially incised and the submucosa beneath the lesion was dissected, with additional injections of Glyceol or MucoUp as required, to remove the entire lesion. Hemostatic forces (Coagrasper; Olympus) or a clutch cutter was used for hemostasis.

4. **Endpoints**

   The primary endpoint was transfer rate to the ulcer scar, as determined by endoscopy after 4 and 8 weeks, in the monotherapy and combination therapy groups. Secondary endpoints included scarring rates according to the size of the resected tissues and differences in CYP2C19 genotypes of the two groups.

5. **Outcome evaluations**

   Artificial ulcer healing was evaluated endoscopically after 4 and 8 weeks by representative blinded gastroenterologists, with ulcer stage evaluated as described. Scar stage (S stage) was defined as healing of the ulcer, whereas healing stage (H stage) indicated that the ulcer had not yet healed. Ulcer size was endoscopically evaluated by inserting a scale thorough a forcps channel. The dissection size was measured by pinning the specimen flat on a rubber plate.

CYP2C19 genotype was assessed in all study subjects by a polymerase chain reaction restriction fragment length polymorphism method with allele-specific primers for identifying...
the CYP2C19 wild-type (*1) gene and the two mutant alleles, CYP2C19*2 (*2) and CYP2C19*3 (*3). The subjects were classified into three genotype groups: RM (*1/*1), IM (*1/*2 and *1/*3), and PM (*2/*2, *3/*3, and *2/*3).

6. Sample size estimation

A previous study reported that 68% of patients who received PPI plus rebamipide improved to S stage, compared with 36% in the PPI monotherapy group (p=0.010).\textsuperscript{10} Based on this finding, and assuming an \( \alpha \)-error <0.05 and a \( \beta \)-error <0.2, at least 52 patients per group would be needed to show a between-group difference. Assuming that 10% of patients screened are ineligible and 10% drop out during the study, 65 patients per arm were set as the target sample size.

7. Statistical analysis

Continuous variables in the two groups were compared using Student t-tests, whereas categorical variables were compared using the chi-square or Fisher exact test. Factors predictive of ulcer scarring were determined by linear logistic regression analyses. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). A p<0.05 was considered statistically significant.

RESULTS

1. Clinical characteristics of the patients in the monotherapy and combination therapy groups

A total of 130 patients were deemed eligible and randomized to the two study groups (Fig. 1). Nine patients in the monotherapy group and 12 in the combination therapy group were excluded from the study owing to the performance of additional gastrectomy, protocol violation, lack of endoscopy, or drop out, leaving 55 patients in the monotherapy group and 54 in the combination therapy group. Table 1 shows the demographic and clinical characteristics of the 130 enrolled patients. There were no significant differences in age, sex, drinking habits, smoking habits, presence or absence of \( H. \text{pylori} \) infection, history of treatment for gastric cancer, tumor locations, macroscopic and histological tumor types, severity of atrophic gastritis, association of ulcer findings with the tumor, size of resected tissue, and size of the post-ESD ulcer or tumor depth between two groups. CYP2C19 genotype was also similar in the two groups.

2. Outcomes of monotherapy and combination therapy for post-ESD gastric ulcers

The transfer rates of post-ESD artificial gastric ulcers to S stage in the monotherapy and combination groups were 19.3% and 9.5%, respectively, at 4 weeks and 84.5% and 81.8%, respectively, at 8 weeks in intention-to-treat analysis (ITT), without significant difference. In per-protocol (PP) analysis, the transfer rates to S stage at 4 weeks (17.3% vs 11.5%, p>0.05) and 8 weeks (85.5% vs 83.3%, p>0.05) were also similar in the monotherapy and combination therapy groups (Table 2). There was no significant add-on effect of rebamipide in the entire population.

As PPI monotherapy may not be sufficient to heal large post-ESD gastric ulcers and rebamipide may have some additive effect, patients were divided by the size of the resected tissue. Receiver operating characteristic curve analysis showed that the cutoff of resected tissue size for distinguishing transfer to S stage at 8 weeks was 42.78 mm in ITT analysis and 42.1 mm in PP analysis. However, the rates of S stage at 4 and 8 weeks in patients with large and small resected tissue size did not differ significantly in the two groups, in either ITT or PP analysis (Table 3). Thus, rebamipide add-on did not have a substantial effect in patients with large post-ESD ulcers.

Another possibility is that the healing of post-ESD ulcer may

![Fig. 1. Flow chart of study participants.](image-url)
Table 1. Clinicopathological Features of Patients and Lesions

| Clinicopathological feature | Monotherapy group (n=64) | Combination therapy group (n=66) | p-value |
|-----------------------------|--------------------------|---------------------------------|---------|
| Age, yr                     | 70.3±8.6                 | 68.7±8.5                        | 0.289   |
| Sex                         |                          |                                 |         |
| Male                        | 41                       | 43                              | 1       |
| Female                      | 23                       | 23                              |         |
| Drinking habit              |                          |                                 |         |
| Absent                      | 30                       | 32                              | 0.863   |
| Present                     | 34                       | 34                              |         |
| Smoking habit               |                          |                                 |         |
| Absent                      | 44                       | 42                              | 0.581   |
| Present                     | 20                       | 24                              |         |
| Helicobacter pylori infection|                          |                                 |         |
| Negative                    | 23                       | 20                              | 0.577   |
| Positive                    | 41                       | 46                              |         |
| History of gastric cancer   |                          |                                 |         |
| Absent                      | 57                       | 61                              | 0.558   |
| Present                     | 7                        | 5                               |         |
| Location                    |                          |                                 |         |
| Upper                       | 5                        | 7                               | 0.396   |
| Middle                      | 27                       | 34                              |         |
| Lower                       | 32                       | 25                              |         |
| Circumference               |                          |                                 |         |
| Lesser curvature            | 32                       | 23                              | 0.273   |
| Greater curvature           | 11                       | 11                              |         |
| Anterior wall               | 11                       | 15                              |         |
| Posterior wall              | 10                       | 17                              |         |
| Atrophic gastritis          |                          |                                 |         |
| Closed                      | 8                        | 12                              | 0.471   |
| Open                        | 54                       | 54                              |         |
| Macroscopic type            |                          |                                 |         |
| 0-I                         | 7                        | 4                               | 0.357   |
| 0-IIa                       | 25                       | 25                              |         |
| 0-IIb                       | 2                        | 0                               |         |
| 0-IIc                       | 30                       | 37                              |         |
| Histological type           |                          |                                 |         |
| Differentiated cancer       | 44                       | 50                              | 0.236   |
| Undifferentiated cancer     | 3                        | 0                               |         |
| Adenoma                     | 17                       | 16                              |         |
| Size of resected tissue, mm | 38.8±14.2                | 40.7±13.8                       | 0.432   |
| Size of post-ESD ulcer, mm  | 42.8±15.7                | 44.5±13.5                       | 0.508   |
| Depth of the tumor          |                          |                                 |         |
| M (mucosal cancer and adenoma) | 58                  | 62                              | 0.092   |
| SM1                         | 2                        | 4                               |         |
| SM2 or deeper               | 4                        | 0                               |         |
| Association of ulcerative findings |          |                                 |         |
| Absent                      | 60                       | 62                              | 1       |
| Present                     | 4                        | 4                               |         |
| Genotype of CYP2C19         |                          |                                 |         |
| RM                          | 20                       | 26                              | 0.346   |
| IM                          | 30                       | 23                              |         |
| PM                          | 8                        | 11                              |         |

Data are presented as mean±SD or number.
Genotype of CYP2C19 was examined for 58 patients in the monotherapy group and 60 patients in the combination therapy group, who agreed to take such genetic tests.
ESD, endoscopic submucosal dissection; M, mucosa; SM, submucosa; RM, rapid metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.
be delayed in patients with the CYP2C19 RM or IM genotype treated with PPI monotherapy and that rebamipide may have some additive effect on PPI. In analyzing the CYP2C19 genotype, the transfer rates to S stage at 8 weeks in patients with RM, IM, and PM were 80.0%, 80.8%, and 100%, respectively, in the monotherapy group, and 81.0%, 81.8%, and 88.9% in the combination therapy group, in ITT analysis. In PP analysis, transfer rates to S stage at 8 weeks were 80.0%, 82.6%, and 100%, respectively, in the monotherapy group, and 81.0%, 85.7%, and 88.9%, respectively, in the combination therapy group. None of the between-group differences was statistically significant in either ITT or PP analysis (Table 4).

Fig. 2 shows the mean sizes of post-ESD ulcers before treatment and 4 and 8 weeks after treatment. The rate of reduction in ulcer size was similar in the monotherapy and combination therapy groups.

Delayed bleeding was observed in one patient in the monotherapy group 22 days after ESD and in one patient in the combination therapy group 14 days after ESD: there was no significant difference.

3. Factors influencing the healing of post-ESD ulcer

As the scarring ratios were similar in the monotherapy and combination therapy groups, factors influencing the healing of post-ESD ulcer at 8 weeks were analyzed. Univariate analysis showed that smoking habit, histological type, size of the resected tissue, and size of the post-ESD artificial ulcer were significant factors affecting scarring (Table 5). Post-ESD ulcer size was excluded from the subsequent multivariate analysis, owing to the strong correlation between resected tissue size and ulcer size (r=0.81). Thus, circumferential location of the tumor and size of the resected tissue were independent factors for scarring (Table 6). Treatment type, whether monotherapy or combination therapy, was not associated with the healing of post-ESD ulcers.

DISCUSSION

Previous studies reported that rebamipide had an additive effect on the treatment of post-ESD gastric ulcer when included with a PPI. However, this study found no difference in the transfer rate to S stage between patients treated with rabepra-
Table 4. Stages of Post-Endoscopic Submucosal Dissection Gastric Ulcer at 4 and 8 Weeks of Treatment in the CYP2C19 Genotype Subgroup

|                             | Monotherapy group | Combination therapy group | p-value |
|-----------------------------|-------------------|---------------------------|---------|
| Intention-to-treat analysis |                   |                           |         |
| 4 Weeks                     |                   |                           |         |
| RM H stage                  | 13                | 24                        | 0.067   |
| S stage                     | 5                 | 1                         |         |
| IM H stage                  | 23                | 18                        | 0.715   |
| S stage                     | 4                 | 5                         |         |
| PM H stage                  | 6                 | 10                        | 0.183   |
| S stage                     | 2                 | 0                         |         |
| 8 Weeks                     |                   |                           |         |
| RM H stage                  | 4                 | 4                         | 1       |
| S stage                     | 16                | 17                        |         |
| IM H stage                  | 5                 | 4                         | 1       |
| S stage                     | 21                | 18                        |         |
| PM H stage                  | 0                 | 1                         | 1       |
| S stage                     | 8                 | 8                         |         |

Per-protocol analysis

|                             | Monotherapy group | Combination therapy group | p-value |
|-----------------------------|-------------------|---------------------------|---------|
| 4 Weeks                     |                   |                           |         |
| RM H stage                  | 13                | 19                        | 0.083   |
| S stage                     | 5                 | 1                         |         |
| IM H stage                  | 21                | 16                        | 0.232   |
| S stage                     | 2                 | 5                         |         |
| PM H stage                  | 6                 | 9                         | 0.206   |
| S stage                     | 2                 | 0                         |         |
| 8 Weeks                     |                   |                           |         |
| RM H stage                  | 4                 | 4                         | 1       |
| S stage                     | 16                | 17                        |         |
| IM H stage                  | 4                 | 3                         | 1       |
| S stage                     | 19                | 18                        |         |
| PM H stage                  | 0                 | 1                         | 1       |
| S stage                     | 8                 | 8                         |         |

RM, rapid metabolizer; H stage, healing stage; S stage, scar stage; IM, intermediate metabolizer; PM, poor metabolizer.

Fig. 2. Rates of reduction of post-endoscopic submucosal dissection (ESD) gastric ulcer size in the monotherapy and combination therapy groups. Repeated measurement analysis interaction: p=0.386.

Table 5. Univariate Analyses of Factors Influencing the Healing of Post-Endoscopic Submucosal Dissection Ulcer at 8 Weeks

|                             | H stage | S stage | p-value |
|-----------------------------|---------|---------|---------|
| Age, yr                     | 72.0±8.3| 68.8±8.7| 0.154   |
| Sex                         |         |         |         |
| Male                        | 11      | 65      | 0.423   |
| Female                      | 8       | 29      |         |
| Drinking habit              |         |         |         |
| Absent                      | 12      | 42      | 0.208   |
| Present                     | 7       | 52      |         |
| Smoking habit               |         |         |         |
| Absent                      | 17      | 57      | 0.017   |
| Present                     | 2       | 37      |         |
| Helicobacter pylori infection|         |         |         |
| Negative                    | 5       | 37      | 0.313   |
| Positive                    | 14      | 57      |         |
| History of gastric cancer   |         |         |         |
| Absent                      | 18      | 84      | 0.687   |
| Present                     | 1       | 10      |         |
| Location                    |         |         |         |
| Upper                       | 1       | 8       | 0.233   |
| Middle                      | 6       | 47      |         |
| Lower                       | 12      | 39      |         |
| Circumference               |         |         |         |
| Lesser curvature            | 4       | 42      | 0.147   |
| Greater curvature           | 3       | 17      |         |
| Anterior wall               | 5       | 18      |         |
| Posterior wall              | 7       | 17      |         |
| Atrophic gastritis          |         |         |         |
| Closed                      | 2       | 15      | 0.732   |
| Open                        | 17      | 77      |         |
| Macroscopic type            |         |         |         |
| 0-I                         | 0       | 11      | 0.495   |
| 0-IIa                       | 8       | 32      |         |
| 0-IIb                       | 0       | 2       |         |
| 0-IIc                       | 11      | 49      |         |
| Histological type           |         |         |         |
| Differentiated cancer       | 18      | 63      | 0.005   |
| Undifferentiated cancer     | 1       | 2       |         |
| Adenoma                     | 0       | 29      |         |
| Size of resected tissue, mm | 50.2±15.4| 36.5±12.9| 0.001  |
| Size of post-ESD ulcer, mm  | 52.4±17.0| 41.3±14.1| 0.003  |
| Depth of the tumor          |         |         |         |
| M (mucosal cancer and adenoma) | 18     | 89     | 0.397   |
| SM1                         | 0       | 4       |         |
| SM2 or deeper               | 1       | 1       |         |
| Association of ulcerative findings |         |         |         |
| Absent                      | 17      | 89      | 0.334   |
| Present                     | 2       | 5       |         |
| Genotype of CYP2C19         |         |         |         |
| RM                          | 8       | 33      | 0.446   |
| IM                          | 9       | 39      |         |
| PM                          | 1       | 16      |         |
| Treatment                   |         |         |         |
| Monotherapy                 | 9       | 49      | 0.803   |
| Combination therapy         | 10      | 45      |         |

Data are presented as mean±SD or number.

H stage, healing stage; S stage, scar stage; ESD, endoscopic submucosal dissection; M, mucosa; SM, submucosa; RM, rapid metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.
In conclusion, rebamipide add-on therapy to PPI did not result in ulcer healing for patients with large post-ESD ulcers, suggesting that rebamipide add-on to PPI may be more effective in patients with large post-ESD ulcers. However, such an additive effect was observed even in patients with large resected tissue. Moreover, CYP2C19 genotype was thought to affect the healing of post-ESD ulcer by PPIs. It was predicted that a PPI alone may be sufficient for the treatment of post-ESD ulcers in patients classified as PM, whereas the addition of rebamipide may be necessary in patients classified as RM and IM. Thus, it is considered that the addition of re- 

Table 6. Multivariate Analyses of Predictive Factors for Nonhealing of Post-Endoscopic Submucosal Dissection Gastric Ulcer at 8 Weeks

|                          | β   | SE  | R   | p-value | OR (95% CI) |
|--------------------------|-----|-----|-----|---------|-------------|
| Size of the resected tissue (larger) | 0.0495 | 0.021 | 0.18 | 0.0213 | 1.05 (1.01–1.10) |
| Smoking habit (no vs yes) | 1.3142 | 0.838 | 0.07 | 0.1171 | 3.73 (0.72–19.29) |
| Location (L vs M vs U) | 0.9833 | 0.561 | 0.11 | 0.0797 | 2.67 (0.89–8.03) |
| Circumference (PW vs AW vs GC vs LC) | 0.5188 | 0.259 | 0.14 | 0.0455 | 1.66 (1.00–2.79) |
| Histological type (DC vs UC vs adenoma) | 1.4649 | 0.796 | 0.12 | 0.0658 | 4.33 (0.91–20.59) |

SE, standard error; OR, odds ratio; CI, confidence interval; L, lower; M, middle; U, upper; PW, posterior wall; AW, anterior wall; GC, greater curvature; LC, lesser curvature; DC, differentiated cancer; UC, undifferentiated cancer.
show substantial benefits, when compared with PPI monotherapy, in the treatment of post-ESD ulcers. Another approach may therefore be necessary to improve the treatment of post-ESD ulcers.

CONFLICTS OF INTEREST

Kazuhiko Nakamura received research grants from Eisai Co., Ltd., AstraZeneca, Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Johnson and Johnson. Eikichi Ihara received research grants from Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., and Otsuka Pharmaceutical Co., Ltd.

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