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Effects of rebamipide, a gastro-protective drug on the Helicobacter pylori *status and inflammation in the gastric mucosa of patients with gastric ulcer: a randomized double-blind placebo-controlled multicentre trial*

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SUMMARY

Aims: To investigate the effects of rebamipide on the *Helicobacter pylori* eradication rate with amoxicillin and omeprazole. The trial also examined its histological effects on gastro-mucosal inflammation after eradication.
Methods: Two hundred and six *H. pylori*-positive patients with active gastric ulcer underwent 8-week based therapy (OA) consisting of 2-week amoxicillin with omeprazole and subsequent 6-week omeprazole. They randomly received either rebamipide (OA-R) or placebo (OA-P) for 16 weeks: combined with the OA based therapy, and subsequently for another 8 weeks. Besides eradication rate, inflammatory findings of gastric mucosa after eradication were evaluated histologically.
Results: Per Protocol Set analysis showed no significant difference in eradication rate between OA-R (64.6%; 95% confidence interval, 54.3–75.0%) and OA-P (67.9%; 95% CI, 57.6–78.3%). Histological findings in the gastric mucosa of the ulcer region, however, indicated a significant improvement ($P = 0.017$) in inflammation scores in OA-R (1.84 ± 0.41) compared with that in OA-P (2.02 ± 0.39) after 16-weeks of treatment. This suppressive effect on inflammation was observed even in the OA-R patients unsuccessfully eradicated.
Conclusion: Rebamipide demonstrated a suppressive effect on the persistent and possibly chronic inflammation in the gastric mucosa of the ulcer region after eradication, but the drug did not improve the eradication rate.

INTRODUCTION

Helicobacter pylori resistant strains to clarithromycin or metronidazole have been increasing rapidly owing to widespread use of antibiotics with proton pump inhibitors for eradication.[1–4] Development of a new therapy without such antibiotics is therefore desirable and an issue for the future. Another issue on follow-up for active peptic ulcers remains controversial whether anti-ulcerative treatment right after eradication is necessary or not. Against this background, we tried an application of rebamipide, a gastro-protective agent to a dual

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therapy of amoxicillin and omeprazole under Japanese clinical practices using various gastro-protective agents.

Rebamipide[5] one of the gastro-protective agents in common use, has been prescribed for digestive disorders in Japan and the Republic of Korea. The drug exhibits preventive or healing effects in gastric mucosa or mucosal lesion by increasing endogenous prostaglandin or by suppressing oxygen-free radicals. Pre-clinical data of the drug demonstrate various action mechanisms including inhibitory effect on the adhesion of *H. pylori* to gastric epithelial cells[6, 7] and suppressive effects on neutrophil activation or inflammatory cytokine production[8, 9] caused by *H. pylori*. Clinical data also shows its unique action decreasing interleukin-8 content in the gastric mucosa of the patients infected with *H. pylori*.[10] Besides, a preliminary clinical report suggests a possibility that the drug improves eradication rate for *H. pylori* infections.[11–13]

The objective of this study was to investigate the additive effect of rebamipide on *H. pylori* eradication rate with amoxicillin and omeprazole. The trial also examined its histological effects on gastro-mucosal inflammation in a post-eradication period.

METHODS

Subjects

Subjects were patients aged 20–74 years with *H. pylori* positive gastric ulcer in active phase diagnosed by endoscopy. *H. pylori* infection was confirmed by any of: ^{13}C-urea breath test (^{13}C-UBT); culture test; or histology along with rapid urease test. Exclusion criteria were set as follows: (i) active duodenal ulcer; (ii) treatment with antibiotics or proton pump inhibitors during one week prior to the study; (iii) gastric ulcers beyond drug therapy such as acute or bleeding cases and history of upper gastrectomy; (iv) malignant tumour; (v) serious complication(s); (vi) drug allergy or hypersensitivity and (vii) pregnancy or possible pregnancy.

Patient profile including medical history as well as informed consent was obtained from each subject.

Design and assessment

The study was carried out as a randomized double-blind placebo-controlled multicentre trial after scientific ethical committees' approval for all the participating institutes. Two hundred and six patients were enrolled to receive a based therapy consisting of 2-week amoxicillin 1500 mg/day (750 mg b.d.) with omeprazole 40 mg/day (20 mg b.d.) for eradication and subsequent 6-week omeprazole 20 mg/day (20 mg q.d.s.) for ulcer healing. They were randomized to two groups, OA-R receiving rebamipide 300 mg/day (100 mg t.d.s.) or OA-P receiving placebo combined with the based therapy for 8 weeks, and subsequently for another 8 weeks (Figure 1). The post-eradication period was designed to study the histological effects of rebamipide on inflammation in the gastric mucosa.

Cure of *H. pylori* infection was determined by culture, histological tests and ^{13}C-UBT, conducted on week 16 of the study. *H. pylori* eradication was judged successful when the results of the three tests were all negative. For the ^{13}C-UBT, ^{13}C-CO_2 levels were measured by mass spectrometry with breath samples collected at baseline and 20 min after 100 mg of ^{13}C-Urea was given. The cut-off (Δ^{13}C) value for a positive result was determined at 2.5‰ over the baseline.[14, 15] The culture and histological tests used each of the three biopsy specimens taken from the antrum and the corpus, and the ulcer region consistent with the active ulcer margin or the centre of the scar.

Histological findings on the presence of *H. pylori*, activity and inflammation were graded 0 (normal), 1 (mild), 2 (moderate) or 3 (marked) according to the updated Sydney System[16] using the mentioned specimens treated with Hematoxylin & Eosin and Giemsa stains. Only one researcher, having no information associated with the subjects, their treatment or clinical data, performed uniform histological grading.

Safety evaluation was conducted according to the recorded adverse events (AEs) including subjective symptoms the patients complained of and objective findings the physician noted.

Statistical methods

The Full Analysis Set (FAS) consists of the enrolled 206 patients, or all the randomized subjects. The Per Protocol Set (PPS) was defined as evaluable subjects characterized by the criteria: (i) the completion of

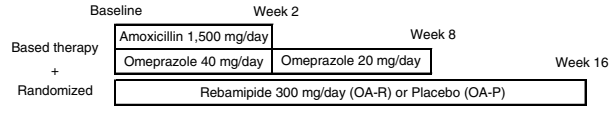

Figure 1. Study regimen.

exposure to treatment; (ii) the availability of measurements of the primary variables; and (iii) the absence of any major protocol violations including violation of entry criteria. Patient characteristics of the two groups before treatment (at baseline) were compared using the Student's *t*-test and the chi-squared test. To calculate the eradication rate of *H. pylori*, 95% confidence intervals[17] were derived using the normal approximation method. Tests of statistical significance were performed with the Mann–Whitney *U*-test for differences in histological findings.

Significance level was set to *P*-value of 0.05 (in a two-sided test).

RESULTS

Characteristics of the evaluable subjects

Two hundred and six patients were enrolled in this study and randomized into the two groups of OA-R: 104 patients and OA-P: 102 (Figure 2). The PPS of the subjects consists of 160 patients (OA-R: 82; OA-P: 78). Forty-six patients (OA-R: 22, OA-P: 24) were excluded from the PPS for the following reasons: unfinished treatment (OA-R: 16; OA-P: 20) including the patients having no consultation since their first visit (OA-R: 2; OA-P: 3); age discrepancy (OA-P: 2); gastric cancer (OA-R: 1); duodenal ulcer (OA-R: 1); indefinite diagnosis of *H. pylori* infection (OA-P: 2); failure of eradication assessment (OA-R: 2); concomitant use of antimicrobial agent (OA-R: 2). One hundred and ninety-eight patients (OA-R: 101; OA-P: 97) were evaluated for safety (AEs). Three of the 104 OA-R patients excluded from safety assessment were consistent with the two cases lost to follow-up and a gastric cancer case. Excluded five of the 102 OA-P patients were the three lost to follow-up and two deviated from the age criteria.

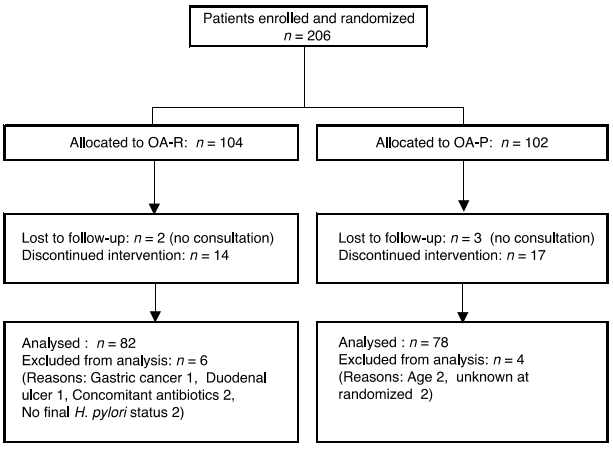

Figure 2. CONSORT flow diagram showing entries, withdrawals from the study, and patients from Per Protocol Set. OA-R: omeprazole-amoxicillin-rebamipide; OA-P: omeprazole-amoxicillin-placebo.

Patient characteristics of the two groups, including: age, sex, smoking habit, complications, histories of eradication and gastric ulcer (first/recurrence/unknown) were similar (Table 1).

Eradication rates

The eradication results of this study are given in Table 2. The PPS analysis result showed no significant

Table 1. Comparison of patient characteristics between the two treatment groups (OA-R, OA-P) in the full analysis set population

Treatment group	OA-R ($n = 104$)	OA-P ($n = 102$)	*P*-value
Mean age (years)	51.5 ± 12.2	50.1 ± 12.0	0.400*
Sex (men)	81	77	0.809**
Out/in patient (out)	93	87	0.495**
Complicated disease (+)	21	17	0.223**
Smoking habit (+)	73	68	0.688**
History of *H. pylori* eradication (+)	0	4	0.125**
History of gastric ulcer (first/recurrence/unknown)	29/68/7	33/63/6	0.776**

*t-test, **chi-squared test.

Table 2. *H. pylori* eradication rates and 95% confidence intervals for both per protocol and full analysis sets

Analysis set	Treatment group	Eradication rate	95% CI*	*P*-value**
PPS	OA-R	64.6% (53/82)	54.3–75.0	0.783
	OA-P	67.9% (53/78)	57.6–78.3	
FAS	OA-R	51.0% (53/104)	41.4–60.6	0.997
	OA-P	52.0% (53/102)	42.3–61.7	

*95% CI calculated by normal approximation.
**chi-squared test.

difference in eradication rate ($P = 0.783$) between OA-R (64.6%; 95% confidence interval: 54.3–75.0%) and OA-P (67.9%; 95% CI: 57.6–78.3%). The eradication rates of the two groups for the FAS were also comparable ($P = 0.997$): OA-R (51.0%; 95% CI: 41.4–60.6%) and OA-P (52.0%; 95% CI: 42.3–61.7%).

Inflammation scores

Table 3 shows the mean activity and inflammation scores by the updated Sydney System in histological examination of the gastric mucosa at baseline (before eradication), week 8 and 16. Both activity and inflammation scores of the two groups at baseline were comparable. In both groups, the scores of inflammation as well as activity significantly decreased after treatment, while improvement in inflammation shows a tendency to be more moderate and continuous after eradication than that in activity.

The inflammation score in the ulcer region on week 16 proved to be lower with a statistical significance ($P = 0.017$) in OA-R (1.84 ± 0.41) than that in OA-P (2.02 ± 0.39). A sub-group analysis by eradication result (success or failure) possibly associated with inflammation or activity scores revealed that even the unsuccessful eradication group of OA-R yielded improvement in inflammation on week 16 with a significantly low score (1.91 ± 0.43; $P = 0.016$) compared with OA-P (2.26 ± 0.45) where the inflammation score turned to revert on week 8 (Figure 3).

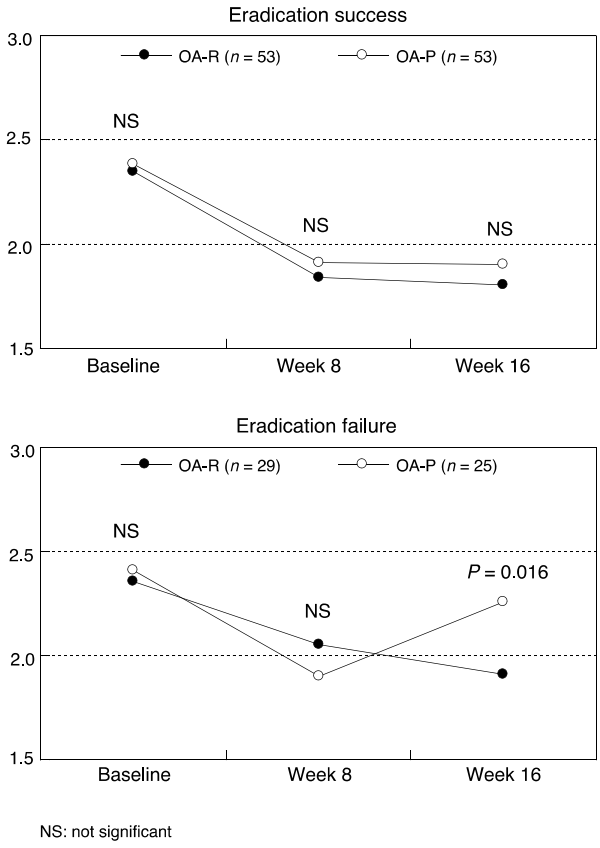

Figure 3. Sub-group analyses of inflammation scores in the ulcer region by eradication success or failure. Time courses of mean inflammation scores are shown in the graphs. The differences between the two treatment groups (OA-R, OA-P) are compared using the Mann–Whitney *U*-test.

Table 3. Time courses of histological findings in the antrum, corpus and ulcer region on each point of baseline (before *H. pylori* eradication), week 8 and 16: activity and inflammation scores (mean ± s.d.) shown in the table. The differences between the two treatment groups (OA-R, OA-P) were compared using Mann–Whitney *U*-test. The inflammation scores of OA-R were lower than those of OA-P on week 16

		Treatment group	Baseline		Week 8		Week 16	
Activity	Antrum	OA-R ($n = 82$)	1.05 ± 0.70	N.S.	0.13 ± 0.38	N.S.	0.21 ± 0.52	N.S.
		OA-P ($n = 78$)	1.21 ± 0.71		0.08 ± 0.32		0.28 ± 0.63	
	Corpus	OA-R	1.05 ± 0.68	N.S.	0.17 ± 0.42	N.S.	0.15 ± 0.52	N.S.
		OA-P	0.89 ± 0.81		0.18 ± 0.48		0.14 ± 0.44	
	Ulcer region	OA-R	1.82 ± 0.83	N.S.	0.34 ± 0.63	N.S.	0.29 ± 0.58	N.S.
		OA-P	1.74 ± 1.00		0.25 ± 0.62		0.38 ± 0.74	
Inflammation	Antrum	OA-R	2.18 ± 0.50	N.S.	1.95 ± 0.23	N.S.	1.84 ± 0.49	N.S.
		OA-P	2.25 ± 0.47		1.88 ± 0.40		1.91 ± 0.39	
	Corpus	OA-R	1.97 ± 0.48	N.S.	1.57 ± 0.55	N.S.	1.48 ± 0.54	N.S.
		OA-P	1.84 ± 0.53		1.61 ± 0.52		1.52 ± 0.62	
	Ulcer region	OA-R	2.35 ± 0.48	N.S.	1.90 ± 0.39	N.S.	1.84 ± 0.41	0.017
	OA-P		2.39 ± 0.56		1.90 ± 0.35		2.02 ± 0.39	

N.S.: not significant.

Safety assessment

AEs were observed in 5.9% of OA-R (6/101) and 12.4% of OA-P (12/97) with no significant difference. All of the AEs developed in the period from the start to week 2. Gastrointestinal symptoms including diarrhoea, vomiting, soft stools and stomatitis accounted for 61.1% (11/18) of the whole patients having AEs (OA-R: 3; OA-P: 8). The remaining cases were skin hypersensitivity such as rash or urticaria reported in five patients (OA-R: 1; OA-P: 4), dizziness and taste disorder each in one patient (both in OA-R, respectively).

All the events were judged nonserious, while seven patients (OA-R: 2; OA-P: 5) discontinued the study drug. These results demonstrated that treatment with rebamipide did not affect the patients' safety.

DISCUSSION

Several clinical trials have produced the results of applying gastro-protective agents to *H. pylori* eradication. Documents on sucralfate[18] and ecabet sodium[19] for instance, have reported comparable high eradication rates in combined use of antibiotics with these gastro-protective drugs instead of proton pump inhibitor. Addition of cetraxate hydrochloride to the triple therapy (with proton pump inhibitor and two antibiotics) has been also reported to improve eradication rate.[20] These studies, however, were not conducted by double-blind method.

We therefore decided to study the potentiating effect of a notable gastro-protective drug, rebamipide on *H. pylori* eradication in the dual therapy with amoxicillin and omeprazole. Our expectation was that an improved eradication rate with combination of rebamipide and the background dual therapy would yield a more useful regimen hardly inducing *H. pylori* resistant strains, since the reported eradication rate (on the order of 50∼60%),[21] in the dual therapy was not enough to treat *H. pylori* infection in clinical practice for its advantage of impossible drug-resistance production.[22]

Contrary to our prospect, the result we obtained was negative for *H. pylori* eradication by rebamipide addition. It may be inappropriate to generalize a conclusion common to gastro-protective agents from the data. However, we should understand the importance of precise data accumulation from such a well-controlled study to establish a new *H. pylori* eradication therapy using a gastro-protective agent.

Besides the disappointing data, we achieved a positive result of rebamipide effect on the histological inflammation in the gastric mucosa. Rebamipide significantly decreased chronic inflammation scores in the ulcer region. We presumed that the data demonstrated the known rebamipide action suppressing *H. pylori*-induced activation of inflammatory cells[23–25] and production of inflammatory cytokines.[26, 27]

From this study for 16-week treatment, we proved improvement effect of rebamipide on the mucosal chronic inflammation. The drug's effect on the inflammation, however, may probably reach the whole background gastric mucosa instead of the specific region as inferred from a study data by Haruma *et al.*[28] They obtained the result that a long-term administration of rebamipide for a year improved chronic inflammation as well as neutrophil infiltration in the gastric mucosa and decreased serum gastrin levels in spite of stable *H. pylori* colonization. We may consider that our study result supports the effectiveness of rebamipide on the mucosal chronic inflammation from the above Haruma's data and a well-known fact of diffused *H. pylori* colonization on the gastric mucosa.

Recent achievements have revealed that *H. pylori* eradication will bring a drastic change to the physiological function of the gastric mucosa. Neutrophil infiltration in the gastric mucosa will disappear following *H. pylori* eradication in a few months. The gastric mucosa will be rapidly normalized from the excessive or suppressed dynamic state of gastric secretion under *H. pylori* infection. Monocyte infiltration will also decrease, however, very slowly and exist for several months to a few years[29–32] after eradication. This fact means that the damage to the gastric mucosa under *H. pylori* infection will be present for a certain period even after eradication. The persistent chronic inflammation has not been elucidated yet. Other questions have arisen from some reports about a high incidence of new erosion in the stomach or duodenum in early post-eradication[33] and relapse cases into peptic ulcers in spite of eradication.[34]

These post-eradication problems may involve various factors, but persistent chronic inflammation in the gastric mucosa after eradication should be studied as one of the causes of such phenomena.

Moreover, an appropriate anti-ulcer therapy for active peptic ulcers in post-eradication has presented a controversial issue. On one hand, some reports argue that active peptic ulcers will cure successfully only by antibiotic eradication without a follow-up anti-ulcer

drug.[35–37] On the other hand, some documents support a view that gastric ulcers different from a duodenal ulcer should be treated with an anti-ulcer drug for a certain period after eradication.[38]

The above background suggests a possibility of rebamipide as a medication fit for post-eradication follow-up in terms of chronic inflammation alleviation and accelerative cure of peptic ulcers. This issue has been awaiting a further study.

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