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Original Article

Efficacy and Safety of Rebamipide versus Its New Formulation, AD-203, in Patients with Erosive Gastritis: A Randomized, Double-Blind, Active Control, Noninferiority, Multicenter, Phase 3 Study

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Background/Aims: The mucoprotective drug rebamipide is used to treat gastritis and peptic ulcers. We compared the efficacy of Mucosta® (rebamipide 100 mg) and its new formulation, AD-203 (rebamipide 150 mg), in treating erosive gastritis.

Methods: This double-blind, active control, noninferiority, multicenter, phase 3 clinical trial randomly assigned 475 patients with endoscopically proven erosive gastritis to two groups: AD-203 twice daily or Mucosta® thrice daily for 2 weeks. The intention-to-treat (ITT) analysis included 454 patients (AD-203, n=229; Mucosta®, n=225), and the per-protocol (PP) analysis included 439 patients (AD-203, n=224; Mucosta®, n=215). The posttreatment assessments included the primary (erosion improvement rate) and secondary endpoints (erosion and edema cure rates; improvement rates of redness, hemorrhage, and gastrointestinal symptoms). Drug-related adverse events were evaluated.

Results: According to the ITT analysis, the erosion improvement rates (posttreatment) in AD-203-treated and Mucosta®-treated patients were 39.7% and 43.8%, respectively. According to the PP analysis, the erosion improvement rates (posttreatment) in AD-203-treated and Mucosta®-treated patients were 39.3% and 43.7%, respectively. The one-sided 97.5% lower limit for the improvement rate difference between the study groups was −4.01% (95% confidence interval [CI], –13.09% to 5.06%) in the ITT analysis and −4.44% (95% CI, –13.65% to 4.78%) in the PP analysis. The groups did not significantly differ in the secondary endpoints in either analysis. Twenty-four AD-203-treated and 20 Mucosta®-treated patients reported adverse events but no serious adverse drug reactions; both groups presented similar adverse event rates.

Conclusions: The new formulation of rebamipide 150 mg (AD-203) twice daily was not inferior to rebamipide 100 mg (Mucosta®) thrice daily. Both formulations showed a similar efficacy in treating erosive gastritis. **(Gut Liver 2021;15:841-850)**

Key Words: Adverse drug reaction; Gastritis; Intention-to-treat analysis; Phase III clinical trial; Rebamipide

INTRODUCTION

Gastritis is one of the most common diseases in Korean adults. Generally, its diagnosis is based on endoscopic findings, such as erosion, edema, redness, and hemorrhage. Especially, erosion as a distinct mucosal defect is observed during acute exacerbation of acute gastritis and chronic gastritis.[1] The incidence of gastritis in Korea is higher than that of other digestive diseases, and the prevalence of gastritis has been gradually increasing;[2] thus, there is an increasing demand for effective gastritis therapies.

Gastritis treatment mainly involves the control of symptoms and improvement in gastric lesions, which can be achieved with drugs that suppress gastric acid secretion, modulate gastrointestinal (GI) motility, and protect the gastric mucosa. Acid suppressing agents, such as proton pump inhibitors (PPIs) and H_2-receptor antagonists, are commonly used with an excellent therapeutic effect in clinical practice. Especially, PPIs are effective and relatively safe drugs. However, they have following limitations; a slow onset of action due to the mechanical limitation of prodrugs, a diminished inhibitory effect on gastric acid secretion when administered after a meal, and the difficulty in controlling nocturnal acid breakthrough.[3] In addition, PPIs have several adverse effects in the stomach, such as oxyntic cell and enterochromaffin-like cell hyperplasia and the occurrence of hyperplastic and fundic gland polyps due to hypergastrinemia.[4-6] Furthermore, some studies have suggested that long-term PPI use might affect the progression of atrophic gastritis and the development of gastric cancer.[7,8]

To overcome these limitations, gastric mucoprotective agents are frequently used alone or in combination with acid-suppressing agents. Owing to the well-documented protective effect of rebamipide on the GI tract, the drug is one of the most commonly used mucoprotective agents for acute and chronic gastritis, as well as peptic ulcers, in the real world.[9-11] Rebamipide promotes the healing of gastric mucosa injury by inducing the synthesis of prostaglandin and mucous glycoprotein, inhibiting the production of reactive oxygen radicals and inflammatory cytokines, and suppressing the activity of leukocytes.[12] It effectively improves endoscopic and histological parameters, along with symptom control, in patients with chronic gastritis.[10] Pharmacokinetically, rebamipide is primarily absorbed from the proximal portion of the small intestine,[13] and its elimination half-life in blood plasma is approximately 2 hours.[14] Therefore, achieving therapeutic effects in patients requires thrice-daily administration of rebamipide. However, most acid-suppressing agents are administered once or twice per day, and low compliance to the thrice-daily administration of rebamipide, which diminishes its optimal therapeutic efficacy, has become a general concern.

Recent efforts to improve patient adherence for drug intake have resulted in the release of incrementally modified drug formulations. If a drug requiring thrice-daily administration is modified to a drug that is taken once or twice a day, it can improve the therapeutic effect by increasing patients' compliance via a reduced dosing frequency. Recently, AD-203 (rebamipide 150 mg; Addpharma Co., Ltd., Yongin, Korea), a new matrix-type sustained-release formulation of rebamipide using a low-viscosity water-soluble polymer, was developed to decrease dosing frequency from rebamipide 100 mg thrice a day to rebamipide 150 mg twice a day. However, whether a twice-daily dose of AD-203 improves lesions in patients with gastritis remains unclear. Therefore, we conducted a randomized, double-blind, active control, non-inferiority, multicenter, phase 3 clinical study to compare AD-203 (twice per day) with rebamipide (thrice per day) based on safety, as well as improvements in endoscopic findings and GI symptoms, in patients with gastritis.

MATERIALS AND METHODS

1. Study population

This study was a randomized, double-blind, active control, non-inferiority, multicenter, phase 3 clinical trial conducted in Korea from September 2019 to February 2020. Patients with gastritis were recruited from the following 25 medical centers: Korea University Guro Hospital (Seoul), Gachon University Gil Medical Center (Incheon), Konkuk University Medical Center (Seoul), Gyeongsang National University Hospital (Jinju), Korea University Ansan Hospital (Ansan), Korea University Anam Hospital (Seoul), Kosin University Gospel Hospital (Busan), National Health Insurance Service Ilsan Hospital (Goyang), Pusan National University Hospital (Busan), Seoul National University Bundang Hospital (Seongnam), Cha University Bundang Medical Center (Seongnam), Seoul National University Hospital (Seoul), Seoul National University Boramae Medical Center (Seoul), Soonchunhyang University Cheonan Hospital (Cheonan), Yeungnam University Medical Center (Daegu), Wonju Severance Christian Hospital (Wonju), Inha University Hospital (Incheon), Chonnam National University Hospital (Gwangju), Jeonbuk National University Hospital (Jeonju), Chung-Ang University Hospital (Seoul), Chungnam National University Hospital (Daejeon), Kyungpook National University Chilgok Hospital (Daegu), Hanyang University Medical Center (Seoul), The Catholic University of Korea Incheon St. Mary's Hospital

(Incheon), and Dongguk University Ilsan Hospital (Goyang).

We enrolled patients aged 20 to 75 years with acute or chronic gastritis and one or more gastric erosions on baseline esophagogastroduodenoscopy (EGD). The exclusion criteria were as follows: (1) patients with a history of peptic ulcer or reflux esophagitis; (2) patients who had undergone a GI surgery, such as an operation to inhibit gastric acid secretion and an esophagogastric surgery; (3) patients with a history of GI malignancy; (4) patients who had used any H_2-receptor antagonists, PPIs, gastrin receptor antagonists, anticholinergic drugs (muscarinic receptor antagonists), prokinetics, prostaglandin analogs, or gastric mucosal protective agents within 2 weeks of the investigational product administration; (5) patients who should take corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirins, or anti-thrombotic agents during the study period; (6) women who were pregnant or lactating; (7) women of childbearing age not using contraception; (8) patients with significant impairments in the hematologic, renal, cardiac, pulmonary, hematopoietic, and endocrine systems; and (9) patients with known hypersensitivity to rebamipide. The body mass index, smoking status, alcohol consumption, concurrent diseases, and concomitant medication of each patient at baseline were recorded.

This trial was conducted following the principles of good clinical practice and the Declaration of Helsinki guidelines. The study protocol was approved by the Institutional Review Board of each of the 25 participating institutions, including the Korea University Guro Hospital (IRB number: 2019GR0347). Informed consent was obtained from all subjects at the time of enrollment. This trial was registered as a standard, randomized clinical trial (ClinicalTrials.gov: NCT04066530).

2. Randomization

Random allocation lists (1:1 ratio) were generated using a computer program and distributed to each institution. Subjects who participated in the clinical study underwent electrocardiography, blood tests, urinalysis, and EGD screening tests. Based on the screening test results, the eligible patients were randomly allocated to the test group (AD-203) or the control group (Mucosta®; Korea Otsuka Pharmaceutical Co., Ltd., Seoul, Korea). This study was conducted in a double-blind manner.

According to the allocation, patient numbers were assigned and used by the investigators to describe the investigational products provided to the subjects by clinical trial pharmacists. Participants received either AD-203 twice per day with a placebo thrice per day or Mucosta® thrice per day with a placebo twice per day for 2 weeks. Each patient visited the treating hospital for the follow-up EGD 2 weeks after initiating the medication. Compliance was determined by the number of remaining tablets per drug type at the follow-up visit. If the drug compliance was ≥80%, the data of the patient were included in the final outcome measurements.

3. Study assessments

1) Efficacy

Each patient underwent an EGD at baseline and 2 weeks after treatment initiation. Based on the EGD, gastric erosion was scored from 1 to 4 (1, no visible erosion; 2, one or two erosions; 3, three to five erosions; 4, more than five erosions) (Supplementary Table 1).[15] The EGD results after treatment were assessed as follows: very much improved (4 to 1 or 3 to 1), much improved (4 to 2 or 2 to 1), minimally improved (4 to 3 or 3 to 2), no change (same score), or worse (any increase in score). The primary efficacy endpoint was the improvement rate of erosions, defined as the percentage of patients classified as much improved or very much improved at the follow-up EGD 2 weeks after treatment initiation. Before the start of the clinical trial, the principal investigators from the participating institution discussed how to assess endoscopic erosion. To ensure a unified assessment, all EGD examinations were recorded and evaluated by the principal investigators, who reconfirmed the data if the sub-investigators conducted the EGD.

The secondary efficacy endpoints were the cure rates of erosion and edema, the improvement rates of redness and hemorrhage, and the improvement rate of GI symptoms 2 weeks after treatment initiation. Cure of erosions was defined as the disappearance of all erosions. Edema was scored from 1 to 2, redness from 1 to 4, and hemorrhage from 1 to 5 (Supplementary Table 1);[16] the improvement of these endoscopic findings were defined as ≥50% reduction of the initial scores at the follow-up EGD 2 weeks after treatment initiation. The GI symptoms were self-reported and consisted of epigastric pain, dyspepsia, nausea/vomiting, reflux, abdominal distention, anorexia, heartburn, and belching.[17] The severity of GI symptoms was scored from 0 to 3: 0, absent; 1, no interference; 2, minimum interference; and 3, marked interference with normal daily activities or with sleep. The frequency of GI symptoms was scored from 0 to 3: 0, absent; 1, once a week; 2, two or three times a week; and 3, more than three times a week. Symptom scores were obtained by the sum of the severity score and frequency score, with the maximum score of 48. The improvement of GI symptoms was defined as ≥50% reduction of the initial GI symptom scores.[17]

2) Safety

Safety assessments included adverse events (AEs) and adverse drug reactions (ADRs), including any GI symptoms and abnormalities in the electrocardiography, laboratory findings, or vital signs. Blood samples were obtained at the end of the therapy.

4. Sample size and statistical analysis

We estimated the sample size to achieve a non-inferiority margin (i.e., 14%), assuming that the efficacy rate of gastric mucosal protective agents such as rebamipide and eupatilin for gastric erosions determined by EGD was 47.7%, based on previous studies.[15,18,19] The erosion improvement rate of AD-203 was considered non-inferior to that of Mucosta® (control group) if the one-sided 97.5% (equivalent to two-sided 95%) lower limit was greater than −14%, which was the pre-specified non-inferiority margin.[15] Based on this threshold parameter, the study was designed to enroll 236 patients per group using the following conditions: a type 1 error of 2.5%, statistical power of 80%, the one-sided test, and a dropout rate of 15%.

The patient data were subjected to three types of analysis: safety set, intention-to-treat (ITT) set, and per-protocol (PP) set. The safety analysis included all data from randomly assigned subjects who took the study drugs. The ITT set analysis included all subjects who had data of primary efficacy evaluation parameters after the treatment with the clinical trial drugs. The PP set analysis was focused on subjects from the ITT analysis with data indicating that these subjects had completed the clinical trial according to the protocol. Safety data were principally based on the safety analysis. Efficacy parameters were presented as frequency and proportion (with 95% confidence interval) in each group. Statistical analyses of these parameters were performed using the t-test or Wilcoxon rank-sum test for continuous data and the chi-square or Fisher exact test for categorical data. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

1. Allocation of patients

To evaluate the efficacy and safety of AD-203 and to determine whether AD-203 was non-inferior to Mucosta® in patients with gastritis, 593 patients were recruited from 25 tertiary hospitals in Korea from September 2019 to February 2020. Among those, 475 were randomly assigned to either the AD-203 (n=238) or Mucosta® (n=237) group. Nine patients in the AD-203 group and 12 in the Mucosta® group were excluded from the ITT analysis because of protocol violation and missing data. Therefore, 454 patients (AD-203, n=229; Mucosta®, n=225) were included in the ITT analysis set. Before performing the PP analysis, five patients in the AD-203 group and 10 in the Mucosta® group were excluded because of poor compliance, protocol violation, prohibited drug intake, and consent withdrawal. Consequently, the data for 439 patients (AD-203, n=224; Mucosta®, n=215) were used in the PP analysis. Fig. 1 presents the flowchart of patient progression through the study with reasons for premature discontinuation.

2. Demographics and clinical characteristics

Table 1 shows the demographic and clinical characteristics of patients in the two groups. There were no differences between the two groups in terms of age, sex, height, weight, body mass index, smoking status, alcohol consumption, and GI symptom scores (Table 1). The baseline endoscopic findings (erosion, edema, redness, and hemorrhage) of the patients were also comparable between the two groups (Table 2).

3. Compliance

Drug compliance rates throughout the treatment period were 96.9% and 94.5% in the AD-203 and the Mucosta® groups, respectively; the drug compliance rate was significantly higher in the AD-203 group than in the Mucosta® group (p<0.0001). Furthermore, the proportion of patients with ≥80% drug compliance in the AD-203 group was higher than that in the Mucosta® group (98.7% [226/229] vs 96.0% [216/225]); however, this did not reach statistical significance (p=0.074).

4. Primary efficacy assessment

Based on the ITT analysis, the erosion improvement rates 2 weeks after treatment initiation were 39.7% (91/229) and 43.8% (98/224) in the AD-203 and Mucosta® groups, respectively. The one-sided 97.5% lower limit for the improvement rate difference between the two groups was −4.01% (95% confidence interval, −13.09% to 5.06%), which was higher than the non-inferiority margin of −14.0%. In the PP analysis, the erosion improvement rates 2 weeks after treatment initiation were 39.3% (88/224) and 43.7% (94/215) in the AD-203 and Mucosta® groups, respectively, and the one-sided 97.5% lower limit for the improvement rate difference between the two groups was −4.44% (95% confidence interval, −13.65% to 4.78%), which was also higher than the non-inferiority margin of −14.0%. Based on the ITT and PP analysis results, AD-203 was not inferior to Mucosta® in improving gastric erosions (Table 3).

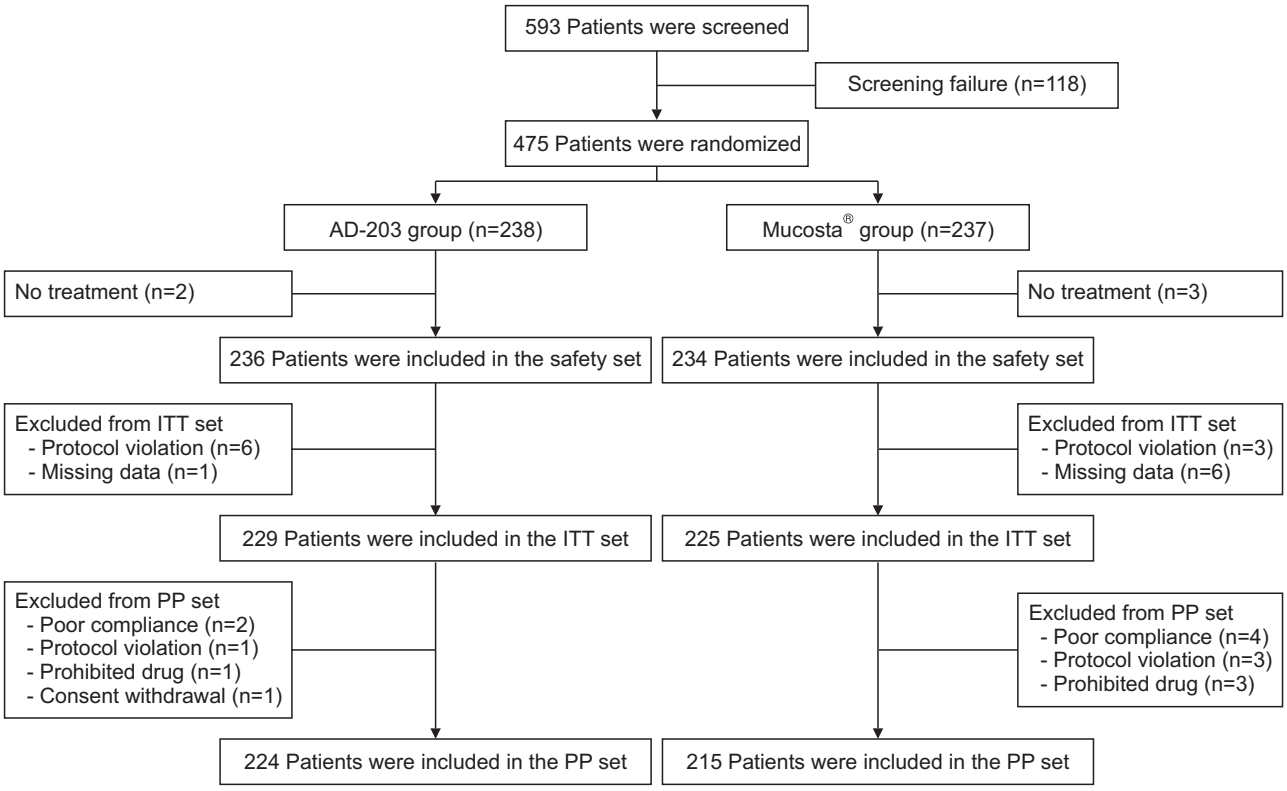

Fig. 1. Flowchart of the patients included in the study.
ITT, intention-to-treat; PP, per-protocol.

Table 1. Baseline Demographic Characteristics of the Study Patients

Characteristics	AD-203 (n=229)	Mucosta® (n=225)	p-value
Age, yr	47.1±12.2	46.8±12.2	0.698
Sex			0.801
Men	93 (40.6)	94 (41.8)	
Women	136 (59.4)	131 (58.2)	
Height, cm	165.2±8.7	165.2±8.6	0.910
Weight, kg	64.4±12.0	65.9±13.3	0.392
Body mass index, kg/m^2	23.5±3.1	24.0±3.3	0.166
Smoking status			0.354
Non-smoker	171 (74.7)	174 (77.3)	
Smoker	43 (18.8)	32 (14.2)	
Ex-smoker	15 (6.6)	19 (8.4)	
Alcohol consumption			0.677
Non-drinker	92 (40.2)	88 (39.1)	
Drinker	132 (57.6)	129 (57.3)	
Ex-drinker	5 (2.2)	8 (3.6)	
Concurrent disease			0.185
Present	115 (50.2)	99 (44.0)	
Absent	114 (49.8)	126 (56.0)	
Concomitant medication			0.620
Present	202 (88.2)	195 (86.7)	
Absent	27 (11.8)	30 (13.3)	
Gastrointestinal symptom scores			
Total	10.0±9.5	9.1±9.1	0.187
Severity	5.1±4.9	4.4±4.7	0.154
Frequency	5.2±4.8	4.6±4.6	0.181

Data are presented as mean±SD or number (%).

Table 2. Baseline Endoscopic Findings in the Study Patients

Endoscopic findings	AD-203 (n=229)	Mucosta® (n=225)	p-value
Erosion			0.748
1 (no erosion)	0	0	
2 (1–2 erosions)	82 (35.8)	78 (34.7)	
3 (3–5 erosions)	81 (35.4)	75 (33.3)	
4 (>5 erosions)	66 (28.8)	72 (32.0)	
Edema			0.214
1 (none)	118 (51.5)	129 (57.3)	
2 (pale/whiter and slightly accentuated hexagonal area gastric pattern)	111 (48.5)	96 (42.7)	
Redness			0.576
1 (none)	39 (17.0)	38 (16.9)	
2 (minimal but obvious change)	114 (49.8)	117 (52.0)	
3 (conspicuous patchy discoloration)	60 (26.2)	61 (27.1)	
4 (color change is beefy-red in intensity)	16 (7.0)	9 (4.0)	
Hemorrhage			0.420
1 (none)	138 (60.3)	136 (60.4)	
2 (1 hemorrhagic lesion)	30 (13.1)	37 (16.4)	
3 (2–5 hemorrhagic lesions)	36 (15.7)	38 (16.9)	
4 (6–10 hemorrhagic lesions)	19 (8.3)	11 (4.9)	
5 (>10 hemorrhagic lesions or large area of a confluent hemorrhage)	6 (2.6)	3 (1.3)	

Data are presented as number (%).

Table 3. Primary Efficacy Assessment: The Erosion Improvement Rate in the AD-203 and Mucosta® Groups

Analysis	AD-203	Mucosta®	Difference (95% CI)*	p-value
Intention-to-treat set				
No. of patients	229	224†		
Erosion improvement rate	91 (39.7)	98 (43.8)	–4.01 (–13.09 to 5.06)	0.387
Per protocol set				
No. of patients	224	215		
Erosion improvement rate	88 (39.3)	94 (43.7)	–4.44 (–13.65 to 4.78)	0.346

Data are presented as number (%).
CI, confidence interval.
*Difference is expressed as a one-sided 97.5% lower limit of the difference rate between the AD-203 and Mucosta® groups; †One patient who did not undergo follow-up endoscopy was excluded from the assessment.

5. Secondary efficacy assessment

The erosion cure rates determined using the ITT analysis were 34.5% (79/229) and 35.7% (80/224) in the AD-203 and the Mucosta® groups, respectively (Table 4). The variation in the erosion cure rate between the two groups was not statistically significant (p=0.786). Furthermore, the edema cure rate and the improvement rates of redness and hemorrhage did not substantially vary between the AD-203 and Mucosta® groups (31.0% vs 29.5%, p=0.721; 38.9% vs 39.7%, p=0.850; and 27.1% vs 28.6%, p=0.722, respectively). The AD-203 and Mucosta® groups presented GI symptom improvement rates of 54.6% (125/229) and 55.1% (124/225), respectively, which were not statistically different (p=0.910) (Table 5).

The erosion cure rates determined using the PP analysis were 33.9% (76/224) and 35.8% (77/215) in the AD-203 and the Mucosta® groups, respectively, which did not statistically differ (p=0.679). Furthermore, there were no differences in the cure rate of edema and the improvement rates of redness and hemorrhage between the AD-203 and Mucosta® groups (31.3% vs 29.3%, p=0.657; 38.4% vs 39.5%, p=0.806; and 26.8% vs 28.4%, p=0.710, respectively). The improvement rates of GI symptoms did not differ between the AD-203 and Mucosta® groups (54.9% [123/224] and 55.3% [119/215], p=0.927).

6. Safety

During the study period, 24 patients in the AD-203 group (10.2%, 27 cases) and 20 patients in the Mucosta® group (8.5%, 26 cases) reported AEs. Among those who reported AEs, 17 patients in the AD-203 group (7.2%, 17 cases) and 12 patients in the Mucosta® group (5.1%, 17 cases) were confirmed to have an ADR (Table 6). GI disorders were the most common events, and the occurrence of AEs and ADRs did not significantly vary between the two groups (p=0.546 and p=0.350, respectively). One patient

Table 4. Secondary Efficacy Assessment: Analysis of Other Endoscopic Findings in the AD-203 and Mucosta® Groups

Analysis	AD-203	Mucosta®	p-value
Intention-to-treat set			
No. of patients	229	224*	
Erosion cure	79 (34.5)	80 (35.7)	0.786
Edema cure	71 (31.0)	66 (29.5)	0.721
Redness improvement	89 (38.9)	89 (39.7)	0.850
Hemorrhage improvement	62 (27.1)	64 (28.6)	0.722
Per protocol set			
No. of patients	224	215	
Erosion cure	76 (33.9)	77 (35.8)	0.679
Edema cure	70 (31.3)	63 (29.3)	0.657
Redness improvement	86 (38.4)	85 (39.5)	0.806
Hemorrhage improvement	60 (26.8)	61 (28.4)	0.710

Data are presented as number (%).
*One patient who did not undergo follow-up endoscopy was excluded from the assessment.

Table 5. Secondary Efficacy Assessment: Analysis of Gastrointestinal Symptoms in the AD-203 and Mucosta® Groups

Analysis	AD-203	Mucosta®	p-value
Intention-to-treat set			
No. of patients	229	225	
Total symptom improvement	125 (54.6)	124 (55.1)	0.910
Severity	128 (55.9)	127 (56.4)	0.906
Frequency	126 (55.0)	124 (55.1)	0.985
Per protocol set			
No. of patients	224	215	
Total symptom improvement	123 (54.9)	119 (55.3)	0.927
Severity	126 (56.3)	122 (56.7)	0.917
Frequency	123 (54.9)	119 (55.3)	0.927

Data are presented as number (%).

in the Mucosta® group discontinued the drug due to AEs. The AE was dizziness, and its severity was mild. There were no reports of serious AEs or ADRs.

DISCUSSION

In the present study, we evaluated the efficacy and safety of AD-203, a new sustained-release rebamipide formulation (twice a day) for treating gastritis. Interestingly, AD-203, as the newly developed formulation, and Mucosta®, as the currently used therapeutic (thrice a day), presented similar efficacy in improving the endoscopic findings and GI symptoms in patients with gastritis. In addition, there was no difference in the reported ADRs between the AD-203 and Mucosta® groups.

Rebamipide is an amino acid derivative of 2-quinolinone that enhances the defense system in the gastric mucosa via several mechanisms. In addition to inhibiting reactive oxygen species in the gastric mucosa, rebamipide stimulates prostaglandin and the prostaglandin EP4 receptor, leading to reduced gastric acid and enhanced mucus glycoprotein synthesis.[12] Rebamipide also exerts anti-inflammatory effects by inhibiting superoxide anion production from neutrophils and interleukin-8 production,[12] and it may influence angiogenesis, a major part of ulcer healing and tissue regeneration, that is affected by cyclooxygenase-2, vascular endothelial growth factor, nitric oxide synthase 2, and matrix metalloproteinase-2.[20,21] Furthermore, rebamipide reportedly activates endothelial growth factor and its receptor expression in the gastric mucosa of rats, thereby facilitating cell proliferation and re-epithelialization.[22] Based on these mechanisms, rebamipide is currently used to treat gastritis, peptic ulcers, and artificial ulcers occurring after endoscopic resection for gastric epithelial neoplasms.

In a prospective study of 30 patients with chronic gastritis nonresponsive to PPIs, 8-week rebamipide treatment improved the refractory symptoms of dyspepsia, along with the endoscopic and histological features of chronic gastritis, irrespective of *Helicobacter pylori* infection.[10] Other studies have showed that long-term rebamipide treatment improved the histological profile of gastritis and decreased the serum gastrin levels in *H. pylori*-associated

Table 6. Incidence of Adverse Drug Reactions of the Two Medications

Variable	AD-203 (n=236)		Mucosta® (n=234)		p-value
	No. (%)	Case	No. (%)	Case	
Gastrointestinal disorders	4 (1.7)	4	3 (1.3)	4	
Nausea	3 (1.3)	3	0		
Abdominal distension	0		1 (0.4)	1	
Abdominal pain	0		1 (0.4)	1	
Constipation	0		1 (0.4)	1	
Diarrhea	0		1 (0.4)	1	
Dyspepsia	1 (0.4)	1	0		
Infections	2 (0.8)	2	2 (0.9)	2	
Nasopharyngitis	1 (0.4)	1	1 (0.4)	1	
Epididymitis	0		1 (0.4)	1	
Pharyngotonsillitis	1 (0.4)	1	0		
Skin disorders	1 (0.4)	1	2 (0.9)	2	
Dry skin	0		1 (0.4)	1	
Eczema	1 (0.4)	1	0		
Pruritus	0		1 (0.4)	1	
Musculoskeletal disorders	2 (0.8)	2	2 (0.9)	2	
Myalgia	2 (0.8)	2	1 (0.4)	1	
Arthralgia	0		1 (0.4)	1	
Nervous system disorders	2 (0.8)	2	2 (0.9)	2	
Dizziness	1 (0.4)	1	1 (0.4)	1	
Headache	1 (0.4)	1	1 (0.4)	1	
Respiratory and thoracic disorders	2 (0.8)	2	2 (0.9)	2	
Cough	0		1 (0.4)	1	
Oropharyngeal pain	1 (0.4)	1	0		
Palpitations	0		1 (0.4)	1	
Chest discomfort	1 (0.4)	1	0		
Psychiatric disorders	1 (0.4)	1	1 (0.4)	1	
Depression	0		1 (0.4)	1	
Insomnia	1 (0.4)	1	0		
Laboratory abnormalities	2 (0.8)	2	1 (0.4)	1	
Leukopenia	0		1 (0.4)	1	
Blood creatine phosphokinase increase	2 (0.8)	2	0		
Others	1 (0.4)	1	1 (0.4)	1	
Hemangioma	1 (0.4)	1	0		
Benign prostatic hyperplasia	0		1 (0.4)	1	
Total	17 (7.2)	17	12 (5.1)	17	0.350

gastritis[23] and chronic inflammation in the lesser curvature of the gastric corpus after *H. pylori* eradication.[24] In a randomized, multicenter, controlled trial, the effect of rebamipide on the prevention of peptic ulcers was similar to that of misoprostol in patients on long-term NSAID therapy.[25] This suggests that rebamipide is a potential therapeutic option to prevent NSAID-induced peptic ulcers.

In the present study, the overall improvement and the cure rates of gastric erosions were approximately 40% and 35%, respectively. These results were similar to the efficacies of previous rebamipide and other mucoprotective agents, such as eupatilin and sulglycotide, in patients with gastritis.[17,18] The improvement rate of GI symptoms in the present study was approximately 50%, which is also similar to the results of previous studies on rebamipide, eupatilin, or sulglycotide use in patients with gastritis.[9,17,18,26]

Noncompliance is among the most commonly reported iatrogenic causes of treatment failure. Especially, the prescribed number of daily doses is inversely related to compliance.[27] Failure to comply with dosage regimens can lead to suboptimal disease control, rebound symptoms, or increased readmission due to abrupt cessation.[28,29] To achieve the mucoprotective efficacy of rebamipide, the drug should be taken thrice per day, but this currently prescribed medication regimen can reduce the patients' adherence to rebamipide intake. Furthermore, considering that rebamipide is usually combined with acid-suppressing agents (PPIs or H_2-receptor antagonists) and NSAIDs in the treatment or prevention of gastritis and peptic ulcers, reducing the thrice-daily administration of rebamipide to that of the co-administered drugs (once or twice per day) is a critical factor for improving the adherence of patients

to treatment.[29] Thus, the sustained-release formulation of rebamipide, AD-203, was developed to mitigate the tendency to noncompliance.

The present study focused on the non-inferiority of AD-203 to Mucosta® in the treatment of gastric erosions. Both formulations significantly improved not only the endoscopic features (erosion, edema, redness, and hemorrhage) but also the GI symptoms of gastritis, and there was no difference in efficacy between AD-203 and Mucosta®. Based on the safety profiles, there were no significant differences in the occurrence of AEs and ADRs between the study groups. Furthermore, although the proportion of patients with ≥80% drug compliance did not significantly vary between the groups, the drug compliance rate was significantly higher in the AD-203 group than in the Mucosta® group. This result suggests that AD-203 could increase drug adherence, which will result in optimal disease control.

In conclusion, this study demonstrated that AD-203 administered twice daily is not inferior to Mucosta® administered thrice daily in treating gastric erosions and improving GI symptoms. With its excellent efficacy and safety profile, AD-203 represents a promising option for treating gastritis and facilitating convenience and adherence by reducing the administration frequency.

CONFLICTS OF INTEREST

G.H.K. and B.W.K. are editorial board members of the Journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. This study was supported by Addpharma Co., Ltd. (Youngin, Korea). No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Analysis and interpretation of data: G.H.K., J.J.P. Drafting of the manuscript: G.H.K. Study design: J.J.P. Acquisition of data in each institute: G.H.K., H.L.L., M.K.J., H.J.P., S.W.J., O.J.L., H.K., H.J.C., S.T.L., J.W.K., H.H.J., I.K.C., H.S.K., D.H.L., K.O.K., Y.J.L., S.J.P., S.J.C., B.W.K., K.H.K., S.W.J., J.G.K., I.K.S., T.N.K., J.K.S. All authors read and approved the final manuscript.

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