Original Article

Efficacy and Safety of AlbisD Compared With Omeprazole 20 mg in Patients With Non-erosive Reflux Disease: A Randomized, Open-label, Active-controlled, Pilot Study

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Background/Aims

Proton pump inhibitors (PPIs) are frequently used to treat non-erosive reflux disease (NERD), but their effect is limited. It is not known whether a potential alternative, AlbisD, containing ranitidine hydrochloride, sucralfate hydrate, and tripotassium dicitrato bismuthate, is effective and safe in treating NERD. The aim of the study is to evaluate the efficacy and safety of AlbisD compared with omperazole in patients with NERD.

Methods

This was a multicenter, randomized, open-label, parallel-group, non-inferiority comparative study. A total of 126 patients with NERD were randomly allocated to either AlbisD twice daily or omeprazole 20 mg once daily for 4 weeks from February 2016 to August 2016. The study patients had histories of heartburn or regurgitation of moderate severity (> score 2) and a frequency of at least 2 episodes per week, and had no mucosal breaks of the esophagus on endoscopy. The primary efficacy variable was complete cure of heartburn at week 4. Secondary efficacy variables evaluating symptoms of heartburn and acid reflux as well as safety profiles were compared in the 2 groups at week 2 and 4 after treatment.

Results

A total of 113 patients completed the study (57 and 56 in AlbisD and omeprazole groups, respectively). The proportion of patients with complete cure of heartburn at week 4 was not significantly different between the AlbisD and omeprazole groups (35.1% vs 32.1% respectively, *P* = 0.740). There were no significant differences between the 2 groups in the any secondary variables including proportions of days without heartburn or acid reflux over 4 weeks (including daytime and nighttime). Adverse events were similarly reported in the 2 groups (7 [12.3%] vs 6 [10.7%]), and there were no serious adverse events.

Conclusions

The efficacy and safety of AlibsD in treating NERD patients are not inferior to those of omeprazole. Therefore, AlbisD can be an alternative to PPIs for NERD.

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Key Words

Bismuth; Gastroesophageal reflux; Omeprazole; Ranitidine; Sucralfate

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Introduction

Gastroesophageal reflux disease (GERD) is defined as troublesome symptoms or complications provoked by reflux of gastric contents into the esophagus.[1] The prevalence of GERD is up to 20-30% in Western countries while it is approximately 5% in Asia.[2] However, it becomes a prevalent disease in Korea with a recent report of the prevalence being 10% of the population probably because of adopting western diet styles.[3] Patients with GERD frequently suffer from typical symptoms such as heartburn and acid reflux, although from throat irritation, hoarseness, chronic cough, and asthma attacks.[1] Patients with typical symptoms of GERD can be classified based upon the presence or absence of erosive esophagitis on endoscopy. Those with typical symptoms but no demonstrable erosive esophagitis on endoscopy are classified as non-erosive reflux disease (NERD) (about 70% of GERD patients), and those with both GERD symptoms and erosive esophagitis are classified as erosive reflux disease (ERD) (about 30% of GERD patients).[1]

For the treatment of GERD, life style modifications can initially be applied, but the mainstay of treatment is still proton pump inhibitors (PPIs). Other therapeutic measures include anti-reflux surgery and alternative acid suppressing medications such as antacids and histamine-2 receptor antagonists (H2RAs).[4] PPIs are effective in relieving GERD symptoms, healing erosive esophagitis, and preventing complications such as esophageal stricture. However, PPIs are not adequate for completely relieving the symptoms of patients with NERD.[5] In contrast to a response rate of 80% in patients with ERD, PPI responsiveness in NERD patients is estimated at about 50%.[6,7] Therefore, other treatment modalities are needed for those with NERD.

Significant treatment targets in NERD are recently identified important pathogenetic mechanism of NERD, microscopic mucosal abnormalities in the distal esophagus.[8,9] Investigators have found that the intercellular space between esophageal epithelial cells is dilated in NERD, and this dilation increases permeability, allowing gastric acid, bile, and pepsin to access submucosal nerve fibers and generate symptoms of heartburn.[10] In order to target these mucosal abnormalities, a combination treatment of acid suppressants with bio-adhesive formulations has been suggested,[11] while mucosal protectants such as sucralfate are also viewed as complementing the use of anti-secretory agents.[12] AlbisD is a type of acid-suppressive drug containing the mucosal protectant, sucralfate, as well as ranitidine and bismuth. The ranitidine inhibits histamine release from G cells of the gastric mucosa, while sucralfate (a sucrose sulfate-aluminum complex) acts as a mucosal protectant and acid buffer by promoting bicarbonate secretion. Therefore, a treatment including an acid suppressant and a mucosal protectant, may perhaps be as effective as a PPI in NERD. However, whether AlbisD is comparable to PPI in terms of its efficacy and safety for the treatment of NERD has not been evaluated. Therefore, we compared the efficacy and safety of AlbisD twice daily with omeprazole once daily, in a multicenter (5 centers), randomized, open-label, parallel-group, non-inferiority comparative study.

Materials and Methods

Patients

The enrolled patients were male and female adults aged between 20 and 80 years, who had a history of heartburn or regurgitation with a frequency of at least 2 episodes per week and more than moderate severity (> score 2) within the previous 6 months. The diagnosis of NERD was confirmed by the absence of any esophageal mucosal breaks on endoscopy at the time of screening.

Exclusion criteria were the presence of esophageal stricture or Barrett's esophagus, active peptic ulcer, malignancy, pancreatobiliary disorder, functional dyspepsia, previous gastric or major gastrointestinal surgery (except appendectomy, cholecystectomy, and hysterectomy), liver or kidney disease (increased levels of blood urea nitrogen, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase (> 1.5 times normal)), mental or psychiatric disorder. Pregnant, lactating or fertile women (not using contraceptive methods), those who took any forbidden medications or were hypersensitive to the study drug, and those who were regarded by the researcher as not being suitable participants, were also excluded.

Study Design

The study was a multicenter, randomized, open-label, parallel-group, non-inferiority comparative study. Five Korean hospitals were involved from February 2016 to August 2016. The study protocol was approved by the institutional review board of each study center and conducted in accordance with the ethical principles based on the Declaration of Helsinki and good clinical practice (IRB No. Hanyang University, 2015-11-008; Kangwon National University, 2015-11-004; Kyunghee University, 2015-12-204; Chonju Presbyterian Medical Center, 2015-11-044; Inje University, 129792-2015-133). Written informed consent was obtained from all patients before enrollment.

Following a screening period of 0-2 weeks, eligible patients were randomly assigned either to study drug (AlbisD; ranitidine hydrochloride 168 mg, sucralfate hydrate 600 mg, and tripotassium dicitrate bismuthate 200 mg) twice daily or to the control drug (Losec cap; omeprazole 20 mg) once daily. The duration of drug administration was 6 weeks (screening: 0 to 2 weeks, treatment period 4 weeks). Treatments were assigned by a computer-generated randomization schedule that was designed to allocate patients to the 2 treatment arms in a 1:1 ratio. The subjects were assigned to sequential allocation numbers at each site. Because it was an open-label study, the test and control drugs were not identical. Follow-up visits were scheduled on days 14 ± 2 and 28 ± 4 to assess drug compliance as well as efficacy and safety. Any medications targeting GERD or affecting the gastrointestinal system were forbidden except rescue medications for uncontrolled symptoms. Drug compliance was assessed at visit 3 and 4 by the participants' diaries and was considered good or bad if the compliance was more than or less than 80%, respectively.

Evaluation Variables

Efficacy

The primary efficacy variable was the cure rate of heartburn on the 4th week, complete resolution. Complete resolution was defined as absence of heartburn on each day (all daytime/nighttime) for the 7 days prior to evaluation at week 4, based on the patient's symptoms log. The secondary efficacy variables were: proportions of complete response, proportions of those whose symptoms of heartburn and acid reflux had completely disappeared over the 7 days of week 4; proportions of partial response, proportions of those who had symptoms of heartburn and acid reflux for ≤ 1 day over the 7 days of week 4; proportions of those with no acid reflux for the 7 consecutive days of week 4; proportions of days without heartburn or acid reflux during daytime or nighttime for 4 weeks; time to the first day without heartburn; time to the first day without acid reflux; none (no symptoms), mild (symptoms but not long lasting and easily tolerated), moderate (discomforting symptoms sufficient to cause daily life limitations), severe (significant restrictions on daily life due to symptoms), and very severe (severe and persistent life limitations due to symptoms).

Safety

The safety variable was monitoring of clinical adverse events (systemic symptoms and signs), vital signs (systolic and diastolic blood pressure, pulse rate), physical examination, and laboratory tests.

Statistical Methods

It was not necessary to calculate the sample size based on efficacy size and statistical power because this was an exploratory study to evaluate the efficacy and safety of AlbisD compared to omeprazole in NERD patients. We aimed to collect a total of 112 subjects assuming 50 in each group and a dropout rate of 10%, based on a previous study[13] where the control and study groups contained 48 and 50 individuals, respectively.

The efficacy variables were analysed based on the full analysis set (FAS) and a per-protocol set (PPS). The FAS was composed of all randomized patients who took at least one dose of study drug and had at least one post-baseline efficacy measurement. The PPS included all patients within the FAS population who took more than 50.0% of their assigned drugs and had no major protocol violations. The safety variables were analyzed in all the subjects who took at least one dose of study drug.

The test group was considered non-inferior to the control provided the lower limit of the 97.5% single-sided confidence interval exceeded the margin of inferiority of −15.0%. The margin of inferiority was conservatively set at 15.0% (lower than half the difference in effects between the two: 21.5%) based on a study determining the difference in efficacy between omeprazole 20 mg (48.0%) and placebo (5.0%) groups.[13]

Categorical variables were assessed by frequency and proportion for each group, and analyzed by Pearson's chi-square test or Fisher's exact test. Continuous variables were recorded as means ± standard deviation, medians, maxima and minima, and analyzed by 2-sample t tests or Wilcoxon's rank sum tests depending on whether normality was satisfied with respect to the differences between groups. The Kaplan-Meier method was used to estimate the time to the first day without each symptom. The log-rank test was used to assess difference between groups. A P-value of 0.05 was considered statistically significant. Statistical analyses were performed with SPSS for Windows version 11 (SPSS Inc, Chicago, IL, USA).

Results

Subjects

A total of 132 NERD patients were screened in the 5 centers involved in the study, and 113 of them were randomized to treatment: 57 and 56 in the AlbisD and omeprazole groups, respectively (Fig. 1). Of these, 6 were considered dropouts. There were no sta-
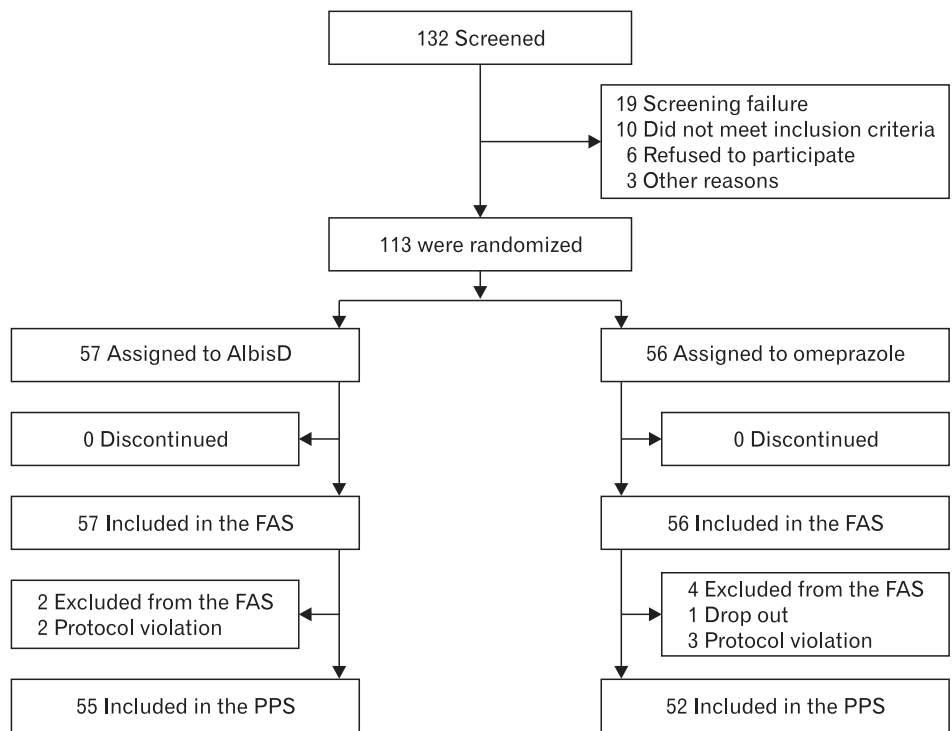
Figure 1. Enrolment, randomization, and follow-up in the study. FAS, full analysis set; PPS, per-protocol set.

Table 1. Demographic Characteristics of the Subjects With Non-erosive Esophageal Reflux Diseases

Variables		AlbisD (n = 57)	Omeprazole (n = 56)	P-value
Age (yr)	Mean ± SD	40.23 ± 12.71	40.95 ± 12.78	0.700[a]
	Median	37.00	39.50	
	Min, Max	20.00, 69.00	21.00, 74.00	
Age groups	20-29	12	12	0.853[b]
	30-39	20	16	
	40-49	8	12	
	50-59	15	13	
	60-69	2	2	
	70-80	0	1	
Sex (n [%])	Male	18 (31.6)	26 (46.5)	0.106[c]
	Female	39 (68.4)	30 (53.6)	
Height (cm)	Mean ± SD	164.26 ± 8.07	166.27 ± 9.05	0.216[d]
	Median	163.00	165.50	
	Min, Max	150.00, 180.00	151.00, 185.00	
Weight (kg)	Mean ± SD	61.61 ± 12.58	67.25 ± 13.26	0.011[a]
	Median	57.00	64.00	
	Min, Max	45.00, 108.80	45.00, 103.00	
BMI (kg/m^2)	Mean ± SD	22.69 ± 3.25	24.19 ± 3.45	0.010[a]
	Median	21.93	24.52	
	Min, Max	16.46, 34.34	16.96, 30.64	

[a]Wilcoxon's rank sum test.
[b]Fisher's exact test.
[c]Pearson's chi-square test.
[d]Two sample t test.

tistically significant differences in the baseline demographics and the clinical characteristics, between the 2 groups except for weight and body mass index (BMI) (Table 1). The drug compliance between the 2 groups was not different (98.0% vs 92.0%, $P = 0.206$). No subjects in the 2 groups reported to have experienced uncontrolled symptoms requiring any allowed rescue medications.

The primary efficacy variable, the proportion of patients with complete resolution of heartburn at week 4, was not different between the 2 groups (35.1% vs 32.1% in the AlbisD and omeprazole groups, respectively; $P = 0.740$) (Table 2). The one-sided confidence interval, 97.5% of the difference between the 2 groups, was −0.148 (−14.8%), which was within the non-inferiority tolerance limit of −15.0%, indicating that AlbisD is not inferior to omeprazole in cure rate of heartburn at week 4 (Fig. 2).

None of the secondary efficacy variables differed between the 2 groups (Table 2). The proportions of those who had no symptoms of heartburn and acid reflux for all of week 4 (29.8% vs 30.4% in the AlbisD and omeprazole groups, respectively), of those who had symptoms of heartburn and acid reflux for less than 1 day in week 4 (35.1% vs 42.9%), and of those whose had no acid reflux symptoms

in week 4 (45.6% vs 55.4%), were not significantly different in the 2 groups (all $P > 0.05$). The proportions of days when there were no symptoms of heartburn or acid reflux during daytime and night-
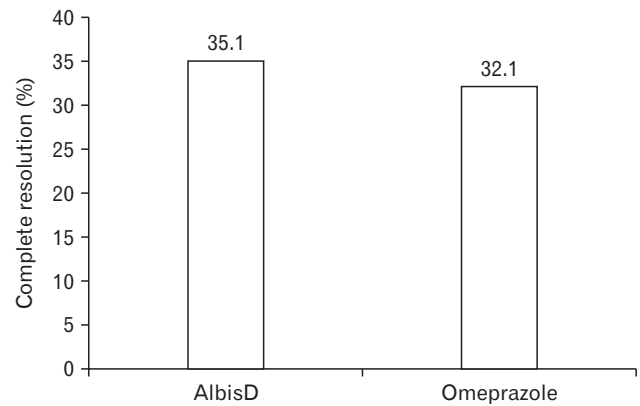

Figure 2. The primary outcome results of the study: Complete resolution, no heartburn on each day (both daytime and nighttime) for the 7 days at week 4. The one-sided confidence interval, 97.5% of the difference between the 2 groups, was −0.1480 (−14.8%), which was within the non-inferiority tolerance limit of −15.0%.

Table 2. Symptom Responses of Non-erosive Esophageal Reflux Disease Patients at Week 4

Outcome variables		AlbisD	Omeprazole	Difference [97.5% CI]	P-value[a]
FAS		n = 57	n = 56		
Complete resolution	Yes	20 (35.1)	18 (32.1)	[−0.148, ∞]	0.740
	No	37 (64.9)	38 (67.9)		
Complete response	Yes	17 (29.8)	17 (30.4)		0.951
	No	40 (70.2)	39 (69.6)		
Partial response	Yes	20 (35.1)	24 (42.9)		0.397
	No	37 (64.9)	32 (57.1)		
No acid reflux	Yes	26 (45.6)	31 (55.4)		0.300
	No	31 (54.4)	25 (44.6)		
PPS		n = 55	n = 52		
Complete resolution	Yes	20 (36.4)	16 (30.8)	[−0.134, ∞]	0.540
	No	35 (63.6)	36 (69.2)		
Complete response	Yes	17 (30.9)	15 (28.9)		0.816
	No	38 (69.1)	37 (71.1)		
Partial response	Yes	20 (36.4)	22 (42.3)		0.529
	No	35 (63.6)	30 (57.7)		
No acid reflux	Yes	26 (47.3)	27 (51.9)		0.631
	No	29 (52.7)	25 (48.1)		

[a]Pearson's chi-square test.
FAS, full analysis set; PPS, per-protocol set.
Complete resolution, no heartburn on each day (both daytime and nighttime) for the 7 days at week 4; Complete response, no heartburn and acid reflux on each day for the 7 days at week 4; Partial response, less than one day of heartburn and acid reflux for the 7 days at week 4; no acid reflux, No acid reflux on each day for the 7 days at week 4.
The one-sided confidence interval, 97.5% of the difference between the 2 groups, was −0.148 (−14.8%), which was within the non-inferiority tolerance limit of −15.0%.
Values are presented as n (%).

time for the 4 weeks were also not different in the 2 groups (Table 3).

There were no significant differences between the 2 groups in the remaining secondary variables. The median time to the first day without heartburn was 6 days in the AlbisD group and 7 days in the omeprazole group, and the median time to the first day without acid reflux were 4 days and 3 days in the AlbisD and omeprazole groups, respectively (Table 4). The severities of heartburn and acid reflux symptoms assessed by investigators also did not differ (Table 5),

and the results of FAS and PPS analyses were similar.

Safety

Adverse events were reported in 7 patients (8 cases, 12.3%) in the AlbisD group and 6 (7 cases, 10.7%) in the omeprazole group (Table 6). In terms of the causal relationship, none of the adverse events in the AlbisD group were related to the study drug, whereas one adverse event of constipation in the omeprazole group was

Table 3. Proportions of Days Without Heartburn or Acid Reflux During Daytime/Nitghttime for 4 Weeks (%)

Symptom	Time	AlbisD	Omeprazole	P-value[a]
FAS		n = 57	n = 56	
Heartburn	Daytime	54.2 ± 29.2	47.8 ± 32.3	0.295
	Nighttime	60.6 ± 28.3	55.7 ± 32.7	0.656
	Daytime and nighttime	47.6 ± 31.1	42.9 ± 32.9	0.478
Acid reflux	Daytime	66.7 ± 31.9	66.7 ± 31.9	0.341
	Nighttime	69.7 ± 32.1	72.9 ± 32.2	0.307
	Daytime and nighttime	60.0 ± 33.5	64.3 ± 34.6	0.303
PPS		n = 55	n = 52	
Heartburn	Daytime	53.7 ± 29.1	47.6 ± 30.7	0.309
	Nighttime	60.6 ± 28.1	55.8 ± 31.8	0.644
	Daytime and nighttime	47.4 ± 30.8	42.6 ± 31.7	0.475
Acid reflux	Daytime	67.4 ± 31.9	69.6 ± 32.1	0.463
	Nighttime	70.3 ± 32.4	72.1 ± 32.6	0.494
	Daytime and nighttime	60.7 ± 33.5	63.5 ± 34.6	0.444

[a]Wilcoxon's rank sum test.
FAS, full analysis set; PPS, per-protocol set.
Values (%) are presented as mean ± SD.

Table 4. The First Day When There Was No Heartburn or Acid Reflux on Each Day (Daytime and Nighttime)

Symptom	Parameter	AlbisD	Omeprazole	P-value[a]
FAS		n = 57	n = 56	
Heartburn	Event	52 (91.2)	48 (85.7)	0.316
	Censored	5 (8.8)	8 (14.3)	
	Time (day)	6	7	
Acid reflux	Event	52 (91.2)	51 (91.1)	0.357
	Censored	5 (8.8)	5 (8.9)	
	Time (day)	4	3	
PPS		n = 55	n = 52	
Heartburn	Event	50 (90.9)	45 (86.5)	0.422
	Censored	5 (9.1)	7 (13.5)	
	Time (day)	6	7	
Acid reflux	Event	50 (90.9)	47 (90.4)	0.374
	Censored	5 (9.1)	5 (9.6)	
	Time (day)	3	3	

[a]Log-rank test.
FAS, full analysis set; PPS, per-protocol set.
Event, proportions of patients with no heartburn or acid reflux more than one day during the study period; Censored, proportions of patients with no heartburn or acid reflux less than one day during the study period; Time, time to the first day without heartburn or acid reflux.
Values are presented as n (%).

Table 5. Severity of Heartburn and Acid Reflux at Week 4 Assessed by Investigators

Symptom	Severity	AlbisD	Omeprazole	*P*-value[a]
FAS		n = 57	n = 56	
Heartburn	None	23 (40.4)	21 (37.5)	0.246
	Mild	20 (35.1)	25 (44.6)	
	Moderate	14 (24.6)	8 (14.3)	
	Severe	0 (0.0)	2 (3.6)	
	Very severe	0 (0.0)	0 (0.0)	
Acid reflux	None	31 (54.4)	34 (60.7)	0.582
	Mild	17 (29.8)	17 (30.4)	
	Moderate	7 (12.3)	5 (8.9)	
	Severe	2 (3.5)	0 (0.0)	
	Very severe	0 (0.0)	0 (0.0)	
PPS		n = 55	n = 52	0.204
Heartburn	None	23 (41.8)	19 (36.5)	
	Mild	19 (34.6)	24 (46.2)	
	Moderate	13 (23.6)	7 (13.5)	
	Severe	0 (0.0)	2 (3.9)	
	Very severe	0 (0.0)	0 (0.0)	
Acid reflux	None	31 (56.4)	31 (59.6)	0.738
	Mild	16 (29.1)	16 (30.8)	
	Moderate	6 (10.9)	5 (9.6)	
	Severe	2 (3.6)	0 (0.0)	
	Very severe	0 (0.0)	0 (0.0)	

[a]Fisher's exact test.
FAS, full analysis set; PPS, per-protocol set.
None, no symptoms; Mild, symptoms but not long lasting and easily tolerated; Moderate, discomforting symptoms sufficient to cause daily life limitations; Severe, significant restrictions on daily life due to symptoms; Very severe, severe and persistent life limitations due to symptoms.
Values are presented as n (%).

Table 6. Adverse Events During the Study

Event	AlbisD (n = 57)	Omeprazole (n = 56)
Constipation	1 (1.8)	1 (1.8)
Colitis	0 (0.0)	1 (1.8)
Vomiting	1 (1.8)	0 (0.0)
Cystitis	1 (1.8)	0 (0.0)
Nasopharyngitis	0 (0.0)	1 (1.8)
Tonsillitis	1 (1.8)	0 (0.0)
Cough	0 (0.0)	1 (1.8)
Oropharyngeal pain	0 (0.0)	1 (1.8)
Hematuria	1 (1.8)	0 (0.0)
Pyuria	1 (1.8)	0 (0.0)
Musculoskeletal pain	1 (1.8)	0 (0.0)
Headache	0 (0.0)	1 (1.8)
Acute stress disorder	1 (1.8)	0 (0.0)
Menopausal symptoms	0 (0.0)	1 (1.8)
Total	8 (12.3)	7 (10.7)

No serious adverse events were reported.
Values are presented as n (%).

identified to have a cause and effect. However, there were no serious adverse events or serious adverse drug reactions in either group.

No clinically significant abnormal findings were encountered in the experimental tests carried out on either group ($P = 0.794$), and there were no significant changes in clinical aspects of vital signs and no statistically significant intra- or inter-group differences for any of the measurements of vital signs.

Discussion

This multicenter, randomized, open-label, pilot study demonstrates that AlbisD (combination of ranitidine, sucralfate, and bismuth) twice daily is effective and safe in improving the symptoms of NERD patients, and is not inferior to the standard dose of omeprazole once daily. Numbers of complete cures of heartburn after 4 week of treatment were not different in the patients receiving AlbisD and those receiving omeprazole. In addition, AlbisD was not inferior to omeprazole with respect to many secondary outcomes

evaluating typical GERD symptoms. Also, AlbisD was as safe as omeprazole, and serious adverse events or serious adverse drug reactions did not occur in either group.

The non-inferiority of AlbisD to omeprazole in improving NERD symptoms could be due to the combined effect of the 3 components of AlbisD. These 3 components have different mechanisms of action, namely, acid suppression, mucosal protection, and *Helicobacter pylori* inhibition. First, ranitidine is known to be less effective than PPIs for acid suppression, probably because PPIs directly block proton pumps while H2RAs inhibit acid secretion indirectly by blocking the histamine receptors of gastrin cells. It has been shown that the time that intragastric pH remains above 4 is longer for PPIs than for H2RAs.[14,15] A meta-analysis also showed that the healing rate of erosive esophagitis by PPIs was greater than by H2RAs.[16] Despite the superiority of PPIs to H2RAs for acid suppression, our results indicate that AlbisD is not inferior to omeprazole in improving the heartburn of NERD patients after 4 week of treatment. This may be because functional mechanism is involved in NERD.[17] A study of those with functional heartburn found that ranitidine was more effective than placebo in improving symptoms, implying that ranitidine may modulate visceral hypersensitivity.[18]

Second, the mucosal protectant, sucralfate may also have contributed to the non-inferiority of AlbisD. According to previous reports, intercellular space dilation is consistently evident in NERD patients with or without abnormal acid exposure. Sucralfate plays a role in mucosal protection by creating a physical barrier, healing the inflamed mucosae, and inhibiting aggressive factors. Sucralfate was reported to develop a physical barrier between the positively charged proteins in inflamed mucosa and the negatively charged sucralfate polyanions.[19] It also induces the production of fibroblast growth factors and prostaglandins in the mucosa.[20] It was also demonstrated to be more effective than placebo in improving GERD symptoms as well as endoscopic healing.[21] It is even as effective as H2RAs in improving GERD symptoms and healing erosive esophagitis.[22,23] Third, the other component of AlbisD, bismuth, can inhibit certain bacterial activities. However, its inhibitory effect on bacteria such as *H. pylori* may not have played an important role in improving the symptoms of the study patients, because GERD or NERD are not closely associated with *H. pylori* status.[24] Instead, bismuth seems to have mucosal protective effect that may have improved microscopic mucosal impairment in the NERD patients.

However, there were significant differences in weight and BMI between the 2 groups; average weight and BMI were slightly lower in the AlbisD group than the omeprazole group. Although weight and BMI are considered risk factors for NERD, it is not currently clear whether it is high or low BMI that is a risk factor for NERD. Some investigators have argued that BMI > 25 kg/m^2 is a risk factor,[25] but others that it is low BMI.[26] Furthermore, the range of BMIs in the present study subjects was from 18.50 kg/m^2 to 24.99 kg/m^2, which is within the normal range based on the World Health Organization criteria; therefore, we do not think the difference was clinically meaningful.

The efficacy of treatment seemed somewhat lower in our study than in other studies. Complete cure of heartburn in the present study was achieved in only about a third of the patients in the 2 groups. However, in a previous study comparing omeprazole 20 mg once daily with placebo for 4-week treatment, more than half of 209 patients in the omeprazole group became free of heartburn symptoms.[27] Also in a study of patients with NERD randomized to omeprazole 20 mg/day, omeprazole 10 mg/day, and placebo, complete relief of heartburn at week 4 was found in 46.0% of patients treated with omeprazole 20 mg/day, and in 31.0% treated with omeprazole 10 mg/day.[28] However, the response to PPIs is reportedly lower in NERD than ERD patients. Even the response to high-dose of PPIs is not satisfactory in patients with NERD, which may be related to a variety of factors such as weekly acid or alkali reflux, visceral hypersensitivity, or heterogeneity of enrolled subjects across trials. Thus, the pooled rate of PPI response was 36.7% in NERD patients but 55.5% in those with ERD.[29] Evidently, the proportions of responders in our study were consistent to the pooled data from many other studies.

This study has some limitations. First, we defined patients with NERD as those with typical reflux symptoms but without evident erosive esophagitis at endoscopy. This definition may have resulted in the inclusion of patients with reflux hypersensitivity or functional heartburn.[30] In order to exclude such patients we would have had to monitor impedance-pH. However, ambulatory impedance-pH monitoring is practically difficult to perform in primary medical institutions and furthermore causes patients considerable discomfort. Second, we may have included patients with ERD. Among the enrolled patients, there may have been some mistakenly regarded as having NERD who had erosive esophagitis that has been healed by previous PPI therapy. Erosive esophagitis has been reported to be found in 30.0% of PPI-naïve GERD patients but in only 10.0% of those previously treated with PPIs.[31] Third, eosinophilic esophagitis and esophageal motor disorders may not have been completely excluded, because we did not perform esophageal biopsy and manometry, which are not routinely performed in the primary health care system. Overall, although the study patients

with NERD were not well-defined, we can assume that the proportions of patients with true NERD, reflux hypersensitivity, functional heartburn, and previous ERD were similar in the 2 groups. Fourth, extraesophageal symptoms of GERD were not evaluated; extraesophageal symptoms of GERD such as chronic cough and hoarseness are also reported in NERD patients, and are known to be less responsive to PPIs than the typical symptoms. Instead, we evaluated typical GERD symptoms thoroughly along with a variety of secondary variables, and all the primary and secondary outcomes of typical GERD symptoms were improved by AlbisD as much as by omeprazole. Last, quality of life was not evaluated by validated questionnaires like GERD-Q.

However, to the best of our knowledge, this is the first study to show that AlbisD (H2RA combined with mucosal protectants) is as effective and safe for treating NERD as a standard dose of PPI over a period of 4 weeks. Although PPIs such as omeprazole have superior therapeutic effects to previous generations of antisecretory agents such as ranitidine, they have disadvantages: patients have to take the PPI about one hour before a meal to obtain the optimal effect, and there is inter-individual variation in efficacy due to differences in drug metabolism that are dependent on cytochrome P450 genotypes.[32]

In conclusion, oral administration of AlbisD twice daily is as effective as a once-daily dose of omeprazole 20 mg in improving typical symptoms of GERD in patients with NERD over a 4-week period. The safety and tolerability of AlbisD was very good and no clinically significant abnormalities were encountered. Therefore, we suggest that double-dose daily administration of AlbisD can be an effective alternative to PPI for treating symptoms in patients with NERD over a short period. Longer term and large-scale studies are needed.

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References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-1920.

2. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871-880.

3. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. J Neurogastroenterol Motil 2011;17:14-27.

4. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2010;11:CD002095.

5. Scarpignato C. Poor effectiveness of proton pump inhibitors in non-erosive reflux disease: the truth in the end! Neurogastroenterol Motil 2012;24:697-704.

6. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther 2005;22:79-94.

7. Hershcovici T, Fass R. Nonerosive reflux disease (NERD) - an update. J Neurogastroenterol Motil 2010;16:8-21.

8. Farré R, van Malenstein H, De Vos R, et al. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. Gut 2008;57:1366-1374.

9. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. Am J Gastroenterol 2005;100:543-548.

10. Weijenborg PW, Smout AJ, Verseijden C, et al. Hypersensitivity to acid is associated with impaired esophageal mucosal integrity in patients with gastroesophageal reflux disease with and without esophagitis. Am J Physiol Gastrointest Liver Physiol 2014;307:G323-G329.

11. Savarino V, Pace F, Scarpignato C;Esoxx Study Group. Randomised clinical trial: mucosal protection combined with acid suppression in the treatment of non-erosive reflux disease - efficacy of Esoxx, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation. Aliment Pharmacol Ther 2017;45:631-642.

12. Surdea-Blaga T, Băncilă I, Dobru D, et al. Mucosal protective compounds in the treatment of gastroesophageal reflux disease. a apsition paper based on evidence of the romanian society of neurogastroenterology. J Gastrointestin Liver Dis 2016;25:537-546.

13. Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. Arch Intern Med 2000;160:1810-1816.

14. Houben GM, Hooi J, Hameeteman W, Stockbrügger RW. Twenty-four-hour intragastric acidity: 300 mg ranitidine b.d., 20 mg omeprazole o.m., 40 mg omeprazole o.m. vs. placebo. Aliment Pharmacol Ther

data.

1995;9:649-654.

15. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997;112:1798-1810.

16. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol 2005;11:4067-4077.

17. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. Gastroenterology 2016;150:1368-1379.

18. Rodriguez-Stanley S, Ciociola AA, Zubaidi S, Proskin HM, Miner PB Jr. A single dose of ranitidine 150 mg modulates oesophageal acid sensitivity in patients with functional heartburn. Aliment Pharmacol Ther 2004;20:975-982.

19. Gorget C. [Sucralfate: development of a new concept of anti-ulcer treatment. Review of its pharmacodynamic properties]. Rev Med Interne 1985;6:313-319.[French]

20. Candelli M, Carloni E, Armuzzi A, et al. Role of sucralfate in gastrointestinal diseases. Panminerva Med 2000;42:55-59.

21. Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1996;10:441-446.

22. Bremner CG, Marks IN, Segal I, Simjee A. Reflux esophagitis therapy: sucralfate versus ranitidine in a double blind multicenter trial. Am J Med 1991;91(2A):119S-122S.

23. Vermeijden JR, Tytgat GN, Schotborgh RH, et al. Combination therapy of sucralfate and ranitidine, compared with sucralfate monotherapy, in patients with peptic reflux esophagitis. Scand J Gastroenterol 1992;27:81-84.

24. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the maastricht III consensus report. Gut 2007;56:772-781.

25. Savarino E, Zentilin P, Marabotto E, et al. Overweight is a risk factor for both erosive and non-erosive reflux disease. Dig Liver Dis 2011;43:940-945.

26. Fujiwara Y, Higuchi K, Shiba M, et al. Differences in clinical characteristics between patients with endoscopy-negative reflux disease and erosive esophagitis in Japan. Am J Gastroenterol 2005;100:754-758.

27. Bate CM, Griffin SM, Keeling PW, et al. Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. Aliment Pharmacol Ther 1996;10:547-555.

28. Lind T, Havelund T, Carlsson R, et al. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 1997;32:974-979.

29. Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004;2:656-664.

30. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol 2013;10:371-380.

31. Poh CH, Gasiorowska A, Navarro-Rodriguez T, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointest Endosc 2010;71:28-34.

32. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet 2005;20:153-167.