

A Pilot Study on Evaluating the Efficacy of Vonoprazan and Acotiamide in Patients with Functional Dyspepsia Overlapping Reflux Symptoms

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Abstract

Background: In Japan, novel gastric acid inhibitor vonoprazan and novel prokinetic drug acotiamide are available. Few studies have evaluated the efficacy of combined vonoprazan and acotiamide in patients with functional dyspepsia (FD) and gastroesophageal reflux disease (GERD).

Aims: To elucidate whether combined acotiamide and vonoprazan therapy will show greater improvement in clinical symptoms and satisfaction with treatment compared with monotherapy with proton pump inhibitors (PPIs).

Methods: In total, 120 consecutive patients presenting with typical symptoms of dyspepsia and reflux were enrolled. Patients were divided into four groups (PPI, vonoprazan, PPI + acotiamide, and vonoprazan + acotiamide). Symptoms were evaluated based on the patients' global assessment of overall treatment efficacy (OTE) and Izumo scale at 4 weeks after treatment.

Results: The OTE improvement rates in PPI, vonoprazan, PPI + acotiamide, and vonoprazan + acotiamide were 43.3%, 50.0%, 58.3%, and 63.3%, respectively. There was no statistically significant difference between vonoprazan + acotiamide and PPI monotherapy ($p = 0.120$). Only combination therapy of vonoprazan and acotiamide significantly reduced the total score and all symptom domains after 4 weeks (all, $p < 0.001$). The mean improvement degrees based on Izumo scale between baseline and after 4 weeks of therapy was the highest in the combined vonoprazan and acotiamide therapy, but did not differ significantly from PPI monotherapy ($p = 0.116$).

Conclusion: Although large-scale clinical studies are necessary, the combination therapy of vonoprazan and acotiamide has the possibility to be a new strategy for patients with FD and GERD.

Keywords: Vonoprazan; Acotiamide; Combination Therapy; Gastroesophageal Reflux Disease; Functional Dyspepsia

Introduction

Functional dyspepsia (FD) is prevalent gastrointestinal disorders and often affects patients during periods of activity, leading to a significant impairment of quality of life (QOL) [1]. It is generally assumed that functional dyspepsia (FD) is a heterogeneous condition. Visceral hypersensitivity in response to gastric distention [2], gastric acid, impaired meal accommodation [3] and delayed gastric emptying [4] have frequently been demonstrated. These common pathophysiological backgrounds should be the target of treatment in patients with FD. FD has been widely treated with acid inhibitors such as proton pump inhibitors (PPIs) [5,6] or prokinetic drugs such as mosapride [7], however, previous randomized controlled studies have suggested that the efficacy of these drugs are limited. It may be difficult to achieve a sufficient improvement in the symptoms of FD using a single agent therapy due to the pathophysiological complexity

of the conditions. Furthermore, clinicians have used a combination therapy of PPIs and prokinetic drugs; however, only few studies have showed significant improvements with such a combination therapy.

In Japan, the novel gastric acid inhibitor “vonoprazan” and novel prokinetic drug “acotiamide” are available. Acotiamide showed significant improvement in patients with postprandial distress syndrome (PDS) [8]. On the other hand, there are few studies evaluating the efficacy of vonoprazan monotherapy or combination therapy of these drugs in patients with FD. There is a much of interest on treatment for FD using these new drugs. Therefore, we conducted a pilot study to elucidate whether monotherapy of vonoprazan or combination therapy of acotiamide and vonoprazan could show greater improvement in clinical symptoms and satisfaction compared to PPI monotherapy.

Methods

This pilot study was a multicenter, randomized, open-label, and parallel groups study, which was conducted in the Saiseikai Nakatsu hospital and Fujita gastrointestinal hospital from July 2015 to March 2017. The study protocol and informed consent forms were reviewed and approved by the Ethics Committee of each hospital before the study was conducted. All participants provided informed written consents. The study was conducted in accordance with the principles and guidelines of the Declaration of Helsinki, the consolidated Good Clinical Practice guidelines, and the applicable regulatory requirements.

Participants

In total, 120 consecutive patients presenting with typical symptoms of dyspepsia were enrolled after upper gastrointestinal endoscopy was performed from July 2015 to March 2017. FD was diagnosed according to the guidelines of the Japanese Society of Gastroenterology (JSGE) [9] as a condition with chronic symptoms in the upper abdomen, such as early satiety, bothersome postprandial fullness, epigastric pain, or epigastric burning in the absence of any organic, systemic, or metabolic disease that can explain the symptoms. We defined the term “chronic symptoms” as symptoms persisting for more than 1 month in this study. Although this criterion is different from the Rome III criteria, which require that symptoms persist for at least 3 months, we could not apply the Rome III criteria to Japanese patients who have access to medical care through the national health insurance system. Symptomatic people in Japan often do not wait to see a doctor for duration of more than 3 months. Kinoshita, *et al.* [10] reported that only 12.3% of people in Japan with dyspepsia fulfill the Rome III criteria. Therefore, we used the JSGE criteria for Japanese patients. The diagnostic criteria for postprandial distress syndrome (PDS) included bothersome postprandial fullness occurring after ordinary-sizes meals and/or early satiety that prevented completion of a normal meal, with either symptom occurring at least several times a week. Diagnosis of epigastric pain syndrome (EPS) required all of the following: pain or burning that is intermittent, localized to the epigastrium, at least moderately severe, and occurring at least once a week. GERD symptom was defined as having reflux symptoms (heartburn and/or acid regurgitation) more than once a week without mucosal break noted on endoscopy. Patient profiles (age, gender, body mass index [BMI], alcohol intake, and smoking) and *Helicobacter pylori* (*H. pylori*) infection status were compared. *H. pylori* infection status was assessed based on the 13C-urea breath test and/or the presence of serum antibodies against *H. pylori*. Those who had peptic ulcers, gastric or esophageal malignancy, or undergone successful eradication of *H. pylori* within the previous 6 months or gastrectomy were excluded. Additionally, patients who were currently being treated with non-steroidal anti-inflammatory drugs and low-dose aspirin were excluded.

Efficacy Assessments

We used global assessment of overall treatment efficacy (OTE) questionnaires filled by the participants bi-weekly for the primary endpoint, which has been recommended by the Rome guidelines [11]. The question asked was ‘How were your reflux symptoms during

the last week in comparison to the baseline period? and was scored on a 7-point Likert scale as following: 1, extremely improved; 2, improved; 3, slightly improved; 4, unchanged; 5, slightly aggravated; 6, aggravated; and 7, extremely aggravated. Grades 1 or 2 meant the therapy was effective. We assessed OTE at 2 and 4 weeks after initiating the therapy.

We also evaluated each GI symptom using the Izumo scale [12], which includes 15 items, and has the following 5 domains, each evaluated by three questions: GERD (Q1 - 3), EPS (Q4 - 6), PDS (Q7 - 9), constipation (Q10 - 12), and diarrhea (Q13 - 15). Each question is rated on a 6-point Likert scale from 0 to 5 (0, not bothered; 1, not so bothered; 2, slightly bothered; 3, bothered; 4, strongly bothered, and 5, intolerably bothered). Domain specific scores range from 0 to 15. We calculated the changes in the scores from baseline to each survey point in each domain.

Study protocol

The participants were divided using the envelope method into the following four groups randomly: PPI monotherapy group (standard dose PPI once daily), vonoprazan monotherapy group (vonoprazan 20 mg once daily), PPI and acotiamide combination therapy group (standard dose PPI once daily and acotiamide 100 mg three times a day before meals), and vonoprazan and acotiamide combination therapy group (vonoprazan 20 mg once daily and acotiamide 100 mg three times a day before meals). The duration of each therapy was 4 weeks. The primary endpoint is the OTE improvement rate at 4 weeks after administration. Secondly endpoints were changes in the degree of improvement in the total score and in each symptom domain from baseline to the completion of the study.

Statistical analysis

Data are expressed as median ± standard error (S.E.). For statistical evaluation of group data, paired t-test was used for paired data and one-way analysis of variance (ANOVA) was used for comparisons among the groups. All tests were two-sided with a level of significance of $p < 0.05$. The statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Thirty participants were treated with each therapy for 4 weeks. Two participants in the vonoprazan monotherapy group and five in the combination therapy of PPI and acotiamide group were lost to follow up, and one in the combined PPIs and acotiamide therapy group

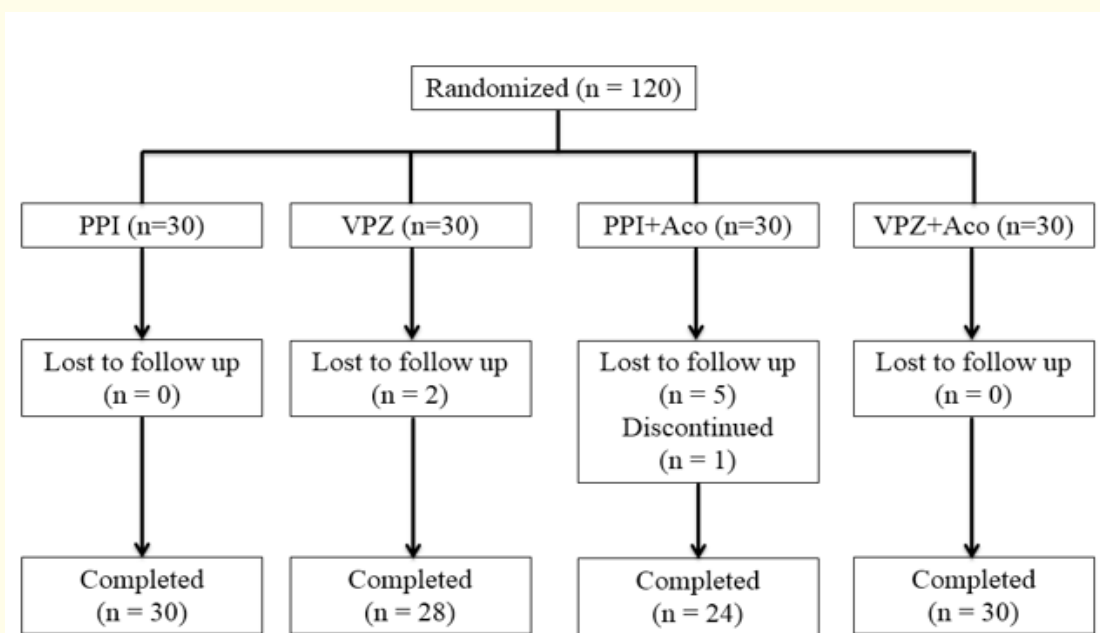


Figure 1: Summary of the study design. In the PPI and acotiamide combined group, one patient discontinued treatment due to diarrhea.

PPI: Proton Pump Inhibitors; VPZ: Vonoprazan; Aco: Acotiamide

		PPI (n = 30)	VPZ (n = 28)	PPI + Aco (n = 24)	VPZ + Aco (n = 30)	p value
Age (years) Mean ± SD		61.6 ± 17.0	53.5 ± 16.7	57.9 ± 15.3	58.3 ± 14.9	0.158
Gender	Male, n (%)	19 (63)	7 (25)	7 (29)	14 (46)	0.013
	Female, n (%)	11 (27)	21 (75)	17 (71)	16 (54)	
BMI (kg/m ²) Mean ± SD		22.3 ± 3.4	22.1 ± 3.6	23.6 ± 4.1	23.5 ± 7.8	0.666
<i>H. pylori</i> infection	Positive, n (%)	6 (20)	7 (25)	6 (25)	11 (36)	0.538
	Negative, n (%)	24 (80)	21 (75)	18 (75)	19 (64)	
Alcohol	Yes, n (%)	10 (33)	4 (14)	8 (33)	13 (43)	0.102
	No, n (%)	20 (67)	24 (86)	16 (67)	17 (57)	
Smoking	Yes, n (%)	2 (6)	2 (7)	2 (8)	5 (16)	0.597
	No, n (%)	28 (94)	26 (93)	22 (92)	25 (84)	
Izumo scale score Mean ± SD						
Total		22.7 ± 10.5	20.0 ± 9.6	20.6 ± 7.9	23.2 ± 9.7	0.714
GERD		5.3 ± 3.1	5.5 ± 2.9	5.2 ± 2.6	5.4 ± 2.6	0.585
EPS		4.7 ± 2.2	5.9 ± 3.4	5.5 ± 2.8	4.4 ± 2.7	0.231
PDS		4.8 ± 2.8	4.2 ± 2.4	4.9 ± 2.2	7.2 ± 2.1	< 0.001
Constipation		4.1 ± 3.7	2.3 ± 2.4	2.5 ± 2.7	3.0 ± 2.6	0.075
Diarrhea		3.7 ± 3.7	1.8 ± 2.2	2.4 ± 2.2	3.2 ± 3.5	< 0.001

Table 1: Baseline characteristics of the subjects in the full analysis set.

SD: Standard Deviation; PPIs: Proton Pump Inhibitors; VPZ: Vonoprazan; Aco: Acotiamide; GERD: Gastroesophageal Reflux Disease.

discontinued treatment, resulting in 112 participants available for analysis. The disposition of participants in each of the four treatment arms is shown in figure 1. The clinical characteristics of each group are summarized in table 1. The mean age, gender, BMI, prevalence of *H. pylori* infection, consumption of alcohol, and smoking did not differ statistically between the groups. There was a significant difference in the diarrhea among the groups.

Comparison of OTE among treatment groups

The improvement rates based on OTE compared with baseline in PPI, vonoprazan, PPI and acotiamide, and vonoprazan and acotiamide

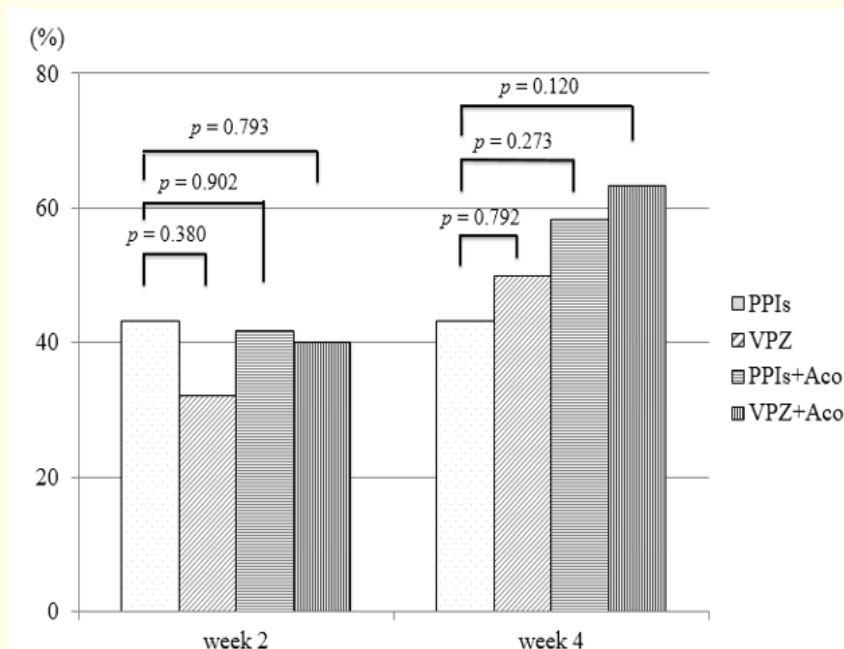


Figure 2: Improvement rates based on an overall treatment effect after 2 and 4 weeks of treatment are shown. The responder rate refers to the percentage of patients who were “extremely improved” or “improved” following treatment. Statistical significance was not found in any treatment group compared to PPI monotherapy. PPI: Proton Pump Inhibitors; VPZ: Vonoprazan; Aco: Acotiamide

groups were 43.3%, 32.1%, 41.7% and 40.0% after 2 weeks, and 43.3%, 50.0%, 58.3% and 63.3% after 4 weeks, respectively (Figure 2). The combination therapy of vonoprazan and acotiamide showed the highest OTE rates among the group at 4 weeks. In the comparison of improvement rates of OTE in vonoprazan, PPI and acotiamide, and vonoprazan and acotiamide compared with PPI monotherapy, there were no significant differences after 2 weeks and 4 weeks ($p = 0.380$, $p = 0.902$, and $p = 0.793$ after 2 weeks, respectively, and $p = 0.792$, $p = 0.273$, and $p = 0.120$ at 4 weeks, respectively).

Comparison of the degree of improvement score among the groups

	Total	GERD	EPS	PDS	Constipation	Diarrhea
PPIs (n = 30)						
Week 0	22.7 (10.5)	5.33 (3.19)	4.70 (2.23)	4.80 (2.87)	4.10 (3.77)	3.76 (3.75)
Week 4	11.9 (8.12)	2.73 (1.91)	2.13 (1.50)	3.56 (2.22)	2.16 (2.61)	1.73(1.68)
p value	< 0.001	< 0.001	< 0.001	0.058	< 0.001	0.003
VPZ (n = 28)						
Week 0	20.0 (9.64)	5.53 (2.99)	5.92 (3.43)	4.28 (2.49)	2.35 (2.40)	1.82 (2.21)
Week 4	9.75 (5.16)	2.42 (1.69)	2.10 (1.57)	2.57 (1.49)	1.67 (1.82)	1.00 (1.24)
p value	< 0.001	< 0.001	< 0.001	< 0.001	0.147	0.052
PPIs + Aco (n = 24)						
Week 0	20.6 (7.97)	5.21 (2.60)	5.50 (2.87)	4.95 (2.28)	2.58 (2.70)	2.45 (2.24)
Week 4	7.58 (6.78)	1.41 (1.50)	1.45 (1.64)	2.54 (2.12)	1.41 (1.95)	0.75 (1.32)
p value	< 0.001	< 0.001	< 0.001	< 0.001	0.062	< 0.001
VPZ + Aco (n = 30)						
Week 0	23.2 (9.76)	5.40 (2.69)	4.30 (2.70)	7.20 (2.17)	3.30 (2.67)	3.26 (3.56)
Week 4	9.53 (8.04)	2.13 (2.23)	1.66 (1.64)	2.70 (2.26)	1.63 (2.20)	1.30 (2.83)
p value	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001

Table 2: Change of clinical symptom score based on Izumo scale after 4 weeks.

Data are expressed as mean (standard deviation).

PPIs: Proton Pump Inhibitors; VPZ: Vonoprazan; Aco: Acotiamide; GERD: Gastroesophageal Reflux Disease; EPS: Epigastric Pain Syndrome; PDS: Postprandial Distress Syndrome.

Table 2 showed the median (SE) degree of improvement score based on Izumo scale from baseline to after 4 weeks for PPI, vonoprazan, PPI and acotiamide, and vonoprazan and acotiamide. In total score (question domain 1-5), these were 11.23 (8.14), 10.25 (9.45), 13.04 (7.45), and 14.63 (7.73), respectively. In GERD score, these were 2.70 (2.55), 3.14 (3.11), 3.75 (2.45), and 3.03 (2.49), respectively. In EPS score, these were 2.56 (1.87), 3.89 (3.72), 4.00 (2.62), and 2.70 (2.73), respectively. In PDS score, these were 1.66 (2.17), 1.89 (1.81), 2.54 (1.74), and 4.53 (2.55), respectively. In constipation score, these were 2.16 (2.49), 0.71 (1.19), 1.58 (2.46), and 1.63 (1.79), respectively. In diarrhea score these were 2.26 (3.21), 1.14 (1.54), 1.73 (1.89), and 2.07 (2.19), respectively.

Vonoprazan monotherapy, combination therapy of PPI and acotiamide, and combination therapy of vonoprazan and acotiamide could not show a significant effect compared with PPI in total score ($p = 0.692$, $p = 0.423$, and $p = 0.116$, respectively), in GERD score ($p = 0.557$,

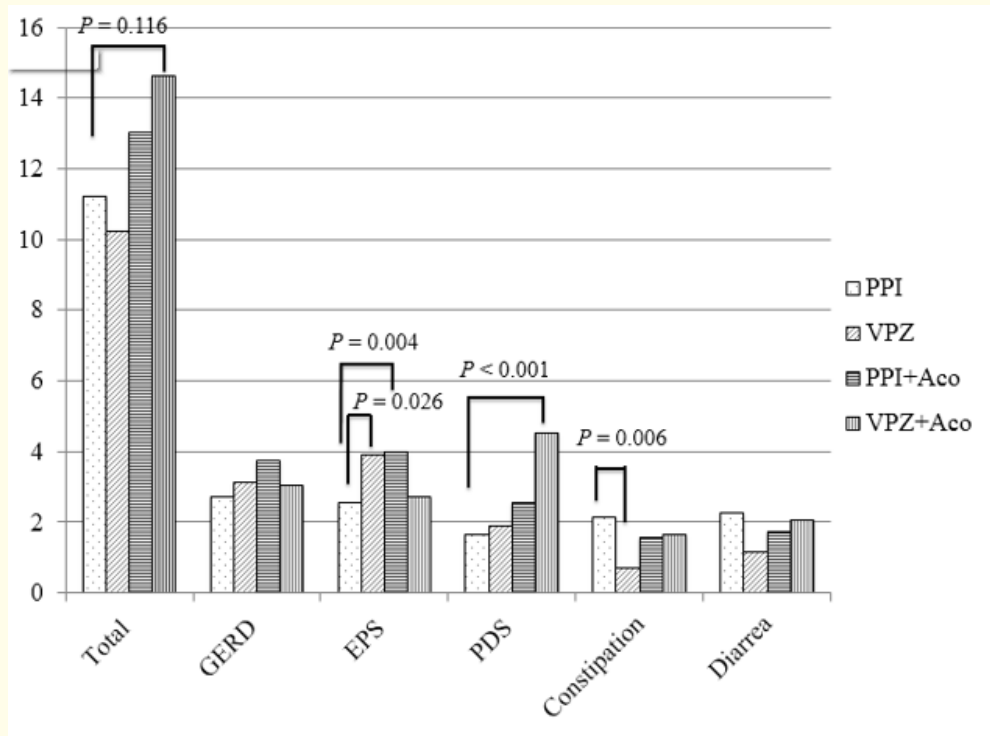


Figure 4: The mean changes on the Izumo scale from baseline to after 4 weeks for total scores and each domain. Treatment with vonoprazan monotherapy and combination therapy of PPI and acotiamide showed statistically significant change in the epigastric pain syndrome (EPS) symptom scores ($p = 0.004$, $p = 0.026$, respectively). Treatment for combination therapy of vonoprazan and acotiamide showed statistically significant change in the postprandial distress syndrome (PDS) symptom scores ($p < 0.001$).

PPI: Proton Pump Inhibitors; VPZ: Vonoprazan; Aco: Acotiamide; GERD: Gastroesophageal Reflux Disease

$p = 0.129$, and $p = 0.610$, respectively) and in diarrhea score ($p = 0.107$, $p = 0.465$, and $p = 0.778$, respectively). In EPS score, vonoprazan monotherapy and combination therapy of PPI and acotiamide had a statistically significant improvement ($p = 0.026$ and $p = 0.004$, respectively) but not in combination therapy of vonoprazan and acotiamide ($p = 0.360$) compared with PPI monotherapy. In PDS score, combination therapy of vonoprazan and acotiamide had a statistically significant improvement ($p < 0.001$) compared with PPIs but not with vonoprazan monotherapy and combination therapy of PPI and acotiamide ($p = 0.667$ and $p = 0.106$, respectively). The improvement was significantly low in vonoprazan therapy ($p = 0.006$) on constipation score compared with PPIs, but there was no significant difference in the combination therapies of PPI and acotiamide, and vonoprazan and acotiamide ($p = 0.394$, and $p = 0.341$, respectively).

Adverse events

An adverse effect found in two participants of the combined PPI and acotiamide therapy group and one patient of the combined vonoprazan and acotiamide therapy was diarrhea. One of them in the combined PPI and acotiamide therapy group subsequently withdrew from the study.

Discussion

The major findings of this clinical study are: 1) In participants who received combination therapy of vonoprazan and acotiamide, the OTE improvement rate was highest and there was a marginal tendency that OTE improvement rate was better compared with that of PPI monotherapy. 2) With regard to the degree of improvement of symptoms, combination therapy of vonoprazan and acotiamide was the highest among the treatment groups. 3) According to FD subtype, vonoprazan monotherapy and the combination therapy of PPI and acotiamide significantly improve EPS symptoms, and the combination therapy of vonoprazan and acotiamide significantly improve PDS symptoms. These findings indicate the possibility that vonoprazan and acotiamide would expect higher effectiveness than conventional PPI therapy.

Lee, *et al.* [13] reported excessive duodenal acidification increased sensitivity to gastric distention and inhibited gastric accommodation to a meal, resulting in dyspeptic symptoms. Therefore, gastric acid is considered one of the important factors of generating FD symptoms. Although, clinicians are used to prescribing PPIs for patients with FD, meta-analysis showed the statistical effectiveness of PPIs for FD symptoms compared to placebo [14], and the patient satisfaction is limited [15]. PPIs are known to have certain disadvantages, including being affected by genetic polymorphisms of CYP2C19 and the absence or presence of *H. pylori* infection [16]. There is a possibility that PPIs could not suppress enough gastric acid in the patients such as above mentioned. It has been reported that vonoprazan has a potent and long-lasting anti-secretory effect on H⁺/K⁺-ATPase due to its high accumulation and slow clearance from gastric tissue [17,18]. Previous studies showed that the efficacy of gastric acid suppression of vonoprazan is not affected by genetic polymorphisms of CYP2C19 and the absence or presence of *H. pylori* infection [19,20]. Kagami, *et al.* [19] indicated that vonoprazan showed significant higher gastric pH 4 holding time and mean gastric pH than those of PPIs. Taking these findings into consideration, using vonoprazan for FD treatment could contribute to improve symptoms more than PPIs. Indeed, the improvement degree of EPS was significantly higher than that in PPI monotherapy ($p = 0.026$). In addition, the combination therapy with vonoprazan and acotiamide showed the significant improvement degree in PDS score compared to PPI monotherapy. These findings may suggest better outcomes are expected from treatment including vonoprazan.

PPIs as well prokinetics have been proposed as first-line treatment and recommendations for specific initial pharmacotherapy were made with the Rome III subdivision of FD [21]. Thus, in EPS, PPI therapy is the initial treatment of choice, whereas in PDS a prokinetic drug is proposed as initial therapy. Acotiamide is a novel prokinetic agent developed in Japan, which inhibits the activity of acetylcholinesterase and enhances acetylcholine release by antagonizing muscarinic M1 and M2 receptors [8], resulting in better gastric empty [22] and gastric accommodation [23], and acotiamide has shown significant response to FD symptoms [8,22,23]. Furthermore, Seto, *et al.* [24] indicated that acotiamide improved stress-induced delayed gastric emptying by influencing the expression of neuromedin U in rats, and Nakamura, *et al.* [22] also reported that acotiamide improved not only FD symptoms but also anxiety score. Psychological factors have been thought to be an important factor in the development of symptoms in FD [25]. According to these reports, it is possible that acotiamide will act on gastric motility as stress modulator, which might be favorable for the improvement of dyspeptic symptoms.

Vanheel, *et al.* [26] investigated the prevalence of gastric sensorimotor dysfunction (gastric hypersensitivity, impaired gastric accommodation, and delayed gastric emptying) according to the FD subgroups, and reported that FD subgroups were not differently associated with putative pathophysiological mechanism. These findings suggest that the treatment for FD might need to cover several pathophysiological mechanisms, and using vonoprazan and acotiamide could improve patient satisfaction more than conventional monotherapy. There are only a few studies that have evaluated the effect of combination of acotiamide and acid-suppressive drugs in FD patients. Hojo,

et al. [27] evaluated the effect of combination therapy with famotidine and acotiamide using OTE and Izumo scale, and indicated that OTE improvement rate for combination therapy was 40.9%, which was lower than that of acotiamide monotherapy of 57.9%. Yamawaki, *et al.* [28] also evaluated the satisfaction with the combination of acotiamide and rabeprazole compared to acotiamide monotherapy or rabeprazole monotherapy, and reported that the combination therapy significantly improved the satisfaction with treatment compared to rabeprazole monotherapy. In the present study, we also reported the combination therapy with vonoprazan and acotiamide showed highest OTE improvement rates among the treatment groups and the significant higher improvement degree in PDS scores compared to PPI monotherapy. In addition, the combination therapy with PPI and acotiamide showed the significant higher improvement degree in EPS scores compared to PPI monotherapy. According to these findings, adding acotiamide to gastric acid inhibitors, especially vonoprazan, may be a more effective treatment that could achieve higher patient's satisfaction compared to PPI monotherapy.

We previously reported that acotiamide significantly decreased the number of TLESRs and reflux events [29]; therefore, we assumed that a treatment regime containing acotiamide would indicate better response to GERD symptoms than PPI monotherapy. However, no treatment regimens could show significant improvement of GERD symptoms compared with PPI monotherapy. We recruited patients complaining of heartburn or regurgitation without mucosal break in this study; as a result, there would be the possibility that patients with functional heartburn who are known to be often resistant to acid suppressive or prokinetic drugs might be included, which might affect the results. In a future study, it may be necessary to monitor the association between reflux and symptom using impedance-pH monitoring.

There are several limitations of this study. First, the sample size of each treatment group was small and the study design was that of an open-label study. Subgroup analysis based on individual CYP2C19 genotypes and *H. pylori* status could not be performed due to the small sample sizes. Second, NERD patients may include functional heartburn which tends to be refractory to treatment because we could not use impedance-pH monitoring for all participants in this study. However, our findings may serve as a hypothesis forming a guide for developing future study. Thus, high-quality research is required to assess the best treatment strategy for patients with overlapping FD and GERD.

Conclusion

The combination therapy of vonoprazan and acotiamide showed the highest OTE improvement rate among four treatment groups, but statistical significance was not found compared to PPI monotherapy. However, our findings do not necessarily negate a potential benefit of treatment with vonoprazan and acotiamide, because significant improvement was found in PDS score for treatment with vonoprazan and acotiamide, and in EPS score for treatment with vonoprazan compared to PPI monotherapy. Although further clinical studies with greater sample sizes are necessary, the treatment using vonoprazan for EPS and adding acotiamide to vonoprazan for PDS could expect better clinical outcomes compared to PPI monotherapy.

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