

## ORIGINAL

# The effect of acotiamide on epigastric pain syndrome and postprandial distress syndrome in patients with functional dyspepsia

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**Abstract :** The effect of acotiamide on gastrointestinal symptoms is undefined. The aim of this study is to evaluate the effect of acotiamide on abdominal symptoms in patients with functional dyspepsia. We retrospectively reviewed 51 patients treated with acotiamide. We evaluated patient quality of life using the Izumo scale that detects changes in quality of life caused by abdominal symptoms. Acotiamide ameliorated the symptoms of functional dyspepsia at one and three months (improved : 61% vs 80%,  $p=0.029$  and resolved : 17% vs 33%,  $p=0.069$ ). We then evaluated the effect of acotiamide on epigastric pain syndrome (EPS) ( $n=33$ ) and postprandial distress syndrome (PDS) ( $n=41$ ). Acotiamide treatment showed an early effect on rates of improvement (63%) and resolution (42%) of EPS symptoms at one month, maintained up to three months (69% and 39%, respectively). Both rates of improvement and resolution of PDS symptoms showed a significant increase from one month to three months (56% vs 78%,  $p=0.021$  and 17% vs 46%,  $p=0.004$ , respectively). The severity of functional dyspepsia symptoms before treatment was significantly associated with failed resolution of functional dyspepsia symptoms ( $p=0.013$ ). Acotiamide improves and resolves EPS symptoms as well as PDS symptoms. PDS symptoms take longer to resolve than EPS symptoms. *J. Med. Invest.* 63 : 230-235, August, 2016

**Keywords :** functional dyspepsia, acotiamide, gastroesophageal reflux, epigastric pain syndrome, postprandial distress syndrome

## INTRODUCTION

The prevalence of functional dyspepsia (FD) is high throughout the world, however few effective treatments are available (1). Approximately 10% of the population has FD in Japan (2). FD leads to a decreased quality of life and productivity resulting in high social costs and absenteeism (3). Therefore, it is important to develop effective treatments for this common condition. There are few articles about the effects of acotiamide on upper and lower gastrointestinal (GI) symptoms despite the fact that FD frequently overlaps with gastroesophageal reflux disease (GERD) and irritable bowel syndrome (2).

Acotiamide, a novel GI motility modulator, was made available in Japan in June 2013. Its main pharmacological effect is to increase the release of the acetylcholine ligand from cholinergic nerve terminals by the inhibition of acetylcholine esterase (4). It also antagonizes M1 and M2 muscarinic receptors that modulate acetylcholine release (5). A recent randomized controlled study showed that acotiamide improves impaired gastric accommodation and delayed gastric emptying (6). The effect of acotiamide on the brain-gut axis was reported in a rat model and showed improvement of delayed gastric emptying and feeding inhibition (7).

FD is divided into two categories : epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). The effect of acotiamide on PDS has been described regarding postprandial fullness, upper abdominal bloating and early satiety following randomized

controlled studies (8, 9). However, the effect of acotiamide on EPS has not been clarified and its effect on other GI symptoms has not been reported. Based on the modulation of motility, acotiamide may be effective in relieving other GI symptoms by modulating GI motility. The aim of this study is to evaluate the effect of acotiamide on upper and lower GI symptoms in patients with FD.

## PATIENTS AND METHODS

Eighty-eight patients with FD were treated with acotiamide (300 mg per day) from May 2014 to September 2015. The Izumo scale (10) (Figure 1), commonly used in clinical practice, was used to evaluate patient quality of life. This scale was designed to detect changes of quality of life caused by abdominal symptoms frequently noted by Japanese patients. We retrospectively reviewed the clinical findings, medical history, endoscopic findings, *Helicobacter pylori* (*H. pylori*) infection status and Izumo scale scores for patients treated with acotiamide. Of all patients treated, 36 were excluded from the study because they lacked three months of follow-up. Consequently, 51 patients with FD treated with acotiamide were included in the final study cohort. The Institutional Review Board approved this retrospective review.

### Diagnosis of FD

FD was diagnosed according to the guidelines of the Japanese Society of Gastroenterology (JSGE) (11) as a condition with chronic symptoms centered in the upper abdomen, such as epigastric pain or discomfort, in the absence of any organic, systemic, or metabolic disease likely to explain the symptoms. According to the guidelines, symptom severity and degree of quality of life for six months or more in the Roma III criteria are not different from those for less

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Izumo scale for abdominal symptom-related QOL		Please check <input checked="" type="checkbox"/> the most appropriate box for each question based on your most recent one-week daily activities.					
		Not bothered	Not so bothered	Slightly bothered	Bothered	Strongly bothered	Intolerably bothered
Q1	Are you bothered by acid reflux?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q2	Are you bothered by heartburn centered in the anterior chest?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q3	Are you bothered by throat discomfort?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q4	Are you bothered by epigastric pain?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q5	Are you bothered by hunger epigastric pain?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q6	Are you bothered by an epigastric burning sensation?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q7	Are you bothered by early satiation?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q8	Are you bothered by post-prandial long-lasting epigastric fullness or nausea?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q9	Are you bothered by epigastric bloating?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q10	Are you bothered by a feeling of incomplete defecation?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q11	Are you bothered by constipation or hard stools?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q12	Are you bothered by stress-related constipation?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q13	Are you bothered by fecal urgency?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q14	Are you bothered by diarrhea or soft stools?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
Q15	Are you bothered by stress-related diarrhea?	<input type="checkbox"/> <sub>0</sub>	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

Figure 1. The Izumo scale, designed to evaluate abdominal symptom-related quality of life impairment. (Cited from ref (10).)

than one month in Japanese patients (11, 12). Therefore, we defined the term “chronic symptoms” as symptoms continuing for more than one month in this study. Although this criterion is different from the Rome III criteria requiring at least a three-month duration of symptoms, we could not apply the Rome III criteria to Japanese patients who have access to medical care through the national health insurance system. Generally, symptomatic people in Japan do not wait to see a doctor for more than three months, and the duration of symptoms when treatment is initiated is relatively short. Kinoshita *et al.* reported that only 12.3% of people in Japan with dyspepsia fulfill the Rome III criteria (12). All 53 patients underwent esophagogastroduodenoscopy (EGD) prior to acotiamide administration, eliminating any endoscopic findings to explain the symptoms in all patients. Therefore, the diagnosis of FD was established after EGD.

*Criteria for improvement and resolution of symptoms*

We evaluated each GI symptom using the Izumo scale (10) (Figure 1) which includes 15 items, and has the following five domains, each evaluated by three questions: GERD (Q1-3), EPS (Q4-6), PDS (Q7-9), constipation (Q10-12) and diarrhea (Q13-15). Domain-specific scores range from zero to 15. In this study, four or more domain-specific scores were considered “significant

symptoms”. We assessed the Izumo scale before, then at one and three months after starting acotiamide. Since FD comprises EPS and PDS, we added the scores of the EPS (Q4-6, zero to 15 points) and PDS domains (Q7-9, zero to 15 points) to evaluate the severity of FD, with the total score ranging from zero to 30 points. Higher scores indicate worse symptoms. We defined “improvement of symptoms” as a score which decreased by 50% or more, “resolution of symptoms” as a score decreased to one or zero, and “aggravation of symptoms” as a score increased by three or more points from the initial score.

*Additional investigations*

In addition to EGD, patients underwent further evaluation. Abdominal ultrasound was performed in 43/51 patients (84%), and colonoscopy was performed 11/51 patients (22%). All studies were performed before the starting acotiamide and did not reveal pathology to explain the symptoms.

*Statistical analysis*

Data were analyzed with StatFlex ver. 6.0 software (Artech Co., Ltd. Osaka, Japan). Categorical data were compared using the chi-square test. Predictive factors for successful acotiamide treatment were evaluated with multiple logistic regression analysis. Differences

between variables with  $p < 0.05$  are considered significant.

RESULTS

Baseline characteristics of patients

We retrospectively reviewed the clinical data of 51 outpatients with FD treated with acotiamide. Demographic data for the 51 patients in the study are shown in Table 1. Symptoms of GERD complicated the clinical presentation in more than one-half of the patients. In about one-half of the patients, a proton pump inhibitor was administered for at least one month prior to starting acotiamide, for the treatment of GERD. Acotiamide was given in addition to the previously administered proton pump inhibitor. Three patients were treated with anti-depressants or anti-anxiety medications, which were continued after starting acotiamide therapy. Only one patient was treated with mosapride and it was changed to acotiamide. No additional medications for FD were prescribed during the three-month study period. EGD showed gastric atrophy in two-thirds of the patients, but no gastric cancers or ulcers were found. No adverse events occurred.

The effect of acotiamide on FD symptoms

The effect of acotiamide on patients with FD was evaluated (n=51) (Figure 2). At one month, the rate of improvement of FD symptoms was 61% (31/51), and the rate of resolution of symptoms was 17% (9/51). At three months, the rate of improvement of symptoms was increased to 80% (41/51) and the rate of resolution of symptoms

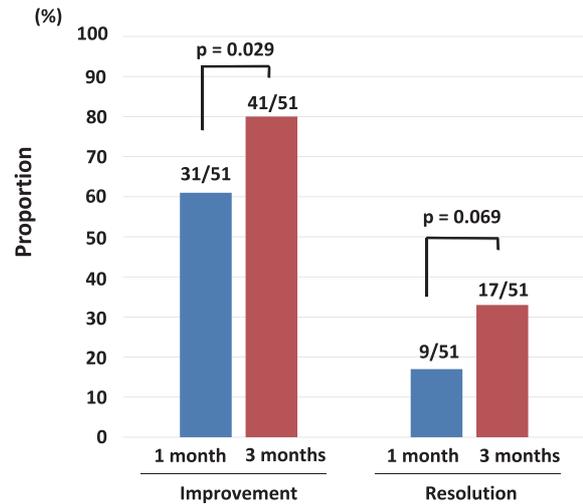


Figure 2. Improvement and resolution of symptoms of functional dyspepsia associated with acotiamide therapy.

was 33% (17/51).

We next evaluated changes in EPS (n=33) and PDS (n=41) symptoms in patients with FD (Figure 3). EPS symptoms improved in about 60-70% of patients taking acotiamide, and about 40% of patients showed resolution of EPS symptoms, but there was no significant

Table 1. Characteristics of 51 patients with functional dyspepsia

Gender (male), n (%)	23 (45%)
Age (mean±SD), years	55.7±16.3
Body Mass Index (mean±SD) kg/m <sup>2</sup>	22.3±4.0
Alcohol use (> 20 g/day), n	9 (18%)
Smoking, n	8 (16%)
Duration of functional dyspepsia, days, median (range)	92 (32-7680)
Comorbidities, n	
Hypertension	14 (27%)
Diabetes Mellitus	2 (4%)
Hyperlipidemia	14 (27%)
Depression	3 (6%)
Functional dyspepsia symptoms, n	
Epigastric pain syndrome	33 (70%)
Postprandial distress syndrome	41 (79%)
Functional dyspepsia (diagnosed by Rome III criteria), n	18 (35%)
Other gastrointestinal symptoms, n	
Gastroesophageal Reflux Disease	29 (57%)
Constipation	19 (37%)
Diarrhea	12 (24%)
Prior proton pump inhibitor use, n	28 (55%)
<i>Helicobacter pylori</i> infection, n	
Infected	15 (29%)
Not infected without eradication	31 (61%)
Not infected after eradication	5 (10%)
Endoscopic findings, n	
Gastric atrophy	36 (69%)
Regurgitation esophagitis, LA grade (N/M/A/B/C/D)	30/18/1/2/0/0
Hiatal hernia	1 (2%)
Duodenal ulcer scar	1 (2%)

SD : Standard deviation, LA : Los Angeles

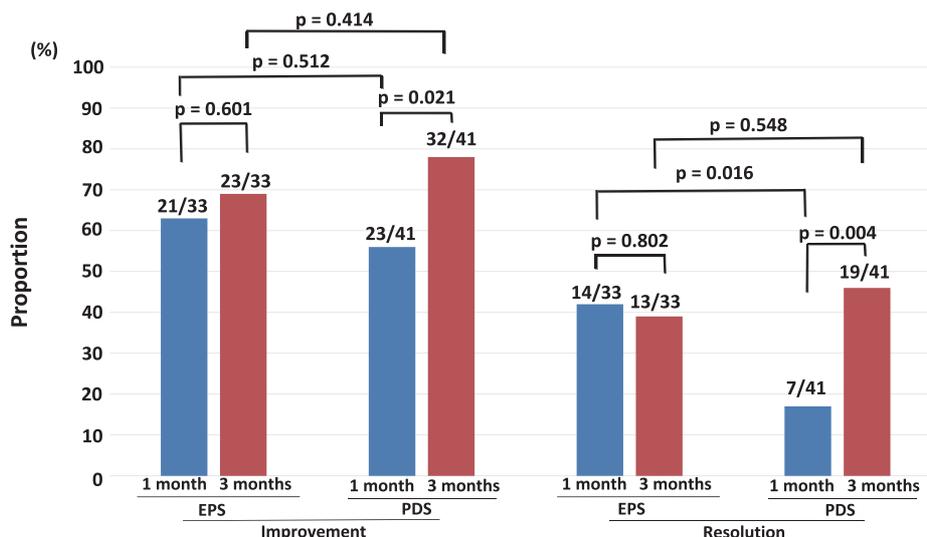


Figure 3. The effects of acotiamide on symptoms of epigastric pain syndrome and postprandial distress syndrome at one and three months. EPS : epigastric pain syndrome, PDS : postprandial distress syndrome.

difference at one and three months. In contrast, there was a significant difference in the rate of improvement and resolution of PDS symptoms at one and three months after starting acotiamide therapy (p=0.021 and p=0.004, respectively).

Comparing EPS and PDS symptoms, the rates of improvement were almost the same at one and three months after starting acotiamide therapy (Figure 3). However, the rate of resolution of EPS symptoms was significantly higher than PDS symptoms at one month (14/33 [42%] vs 7/41 [17%], p=0.016). At three months, the rates were similar because of the amelioration of PDS symptoms (13/33 [39%] vs 19/41 [46%], p=0.548). No patient reported worsening of EPS or PDS symptoms in comparison with symptoms before treatment. The time to improvement in PDS symptoms took longer than that for EPS after starting acotiamide therapy.

Predictive factors associated with the effects of acotiamide

We attempted to identify a factor which predicts the effect of acotiamide on FD symptoms at three months after starting acotiamide therapy (Table 2). We evaluated gender, age, body mass index, alcohol habits, smoking habits, disease duration, complication of GERD, constipation and diarrhea, H. pylori status, gastric atrophy and severity of FD symptoms using Izumo scale scores before

treatment. Age, body mass index, disease duration and severity of FD symptoms before treatment were evaluated as continuous variables. Based on this analysis, the severity of FD symptoms before treatment was significantly associated with failed acotiamide therapy (p=0.013).

Acotiamide effect on other GI symptoms

We next evaluated the effects of acotiamide on other GI symptoms including GERD, constipation and diarrhea (Figure 4). The rate of improvement of GERD was higher than that for constipation and diarrhea. None of the symptoms were aggravated at three months after starting treatment.

DISCUSSION

The present study reviews outcomes at both one and three months for patients with FD receiving acotiamide therapy regarding symptoms including EPS, PDS, GERD, constipation and diarrhea. Acotiamide improved and resolved more apparently the symptoms of FD at three months than at one month. The rates of improvement and resolution of EPS symptoms increased at one

Table 2. Factors predictive of successful acotiamide therapy for symptoms of functional dyspepsia

	Odds ratio	95% confidence interval	p-value
Male gender	0.466	0.078 ~ 2.764	0.401
Age	0.977	0.918 ~ 1.040	0.476
Body mass index	0.907	0.725 ~ 1.136	0.398
Alcohol use (> 20 g/day)	0.334	0.018 ~ 5.895	0.454
Current smoking	0.371	0.019 ~ 7.103	0.510
Disease duration	1.000	0.999 ~ 1.000	0.258
Complication of GERD	0.823	0.614 ~ 1.103	0.192
Complication of constipation	0.794	0.547 ~ 1.151	0.223
Complication of diarrhea	1.157	0.884 ~ 1.515	0.285
Helicobacter pylori infection	2.838	0.363 ~ 22.19	0.320
Gastric atrophy	0.231	0.026 ~ 2.023	0.186
Severity of functional dyspepsia	0.678	0.498 ~ 0.923	0.013

GERD : gastroesophageal reflux disease

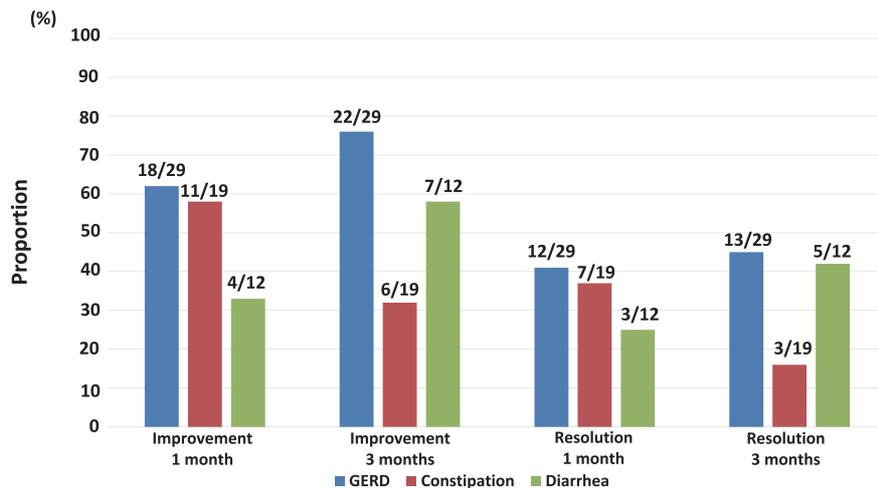


Figure 4. The effect of acotiamide on symptoms of gastroesophageal reflux disease, constipation and diarrhea. GERD : gastroesophageal reflux disease.

month, maintained up to three months, but symptoms of PDS were significantly improved at three months compared with one month.

At one month, the rate of resolution of symptoms of PDS in patients taking acotiamide in this study was similar to that reported in a previous study (8). The resolution of symptoms of EPS (42%) showed a rapid increase after starting treatment and was significantly greater than that for symptoms of PDS (17%) and was sustained at three months. Acotiamide has the potential to be the drug of choice for patients with EPS, although a treatment algorithm including acid suppressive therapy was suggested as the first choice for patients with EPS (13). However, the effect of acotiamide on EPS symptoms remained less defined in a meta-analysis (14). Therefore, prospective studies are necessary to clarify the effect of acotiamide on symptoms of EPS.

Acotiamide had a high rate of improvement and resolution of symptoms of FD at three months than at one month in this study. This trend is interesting because previous studies have focused on short-term outcomes (6,15). The rates of improvement and resolution of symptoms of EPS did not change comparing one and three months, but PDS symptoms at three months were significantly improved compared to results at one month. The improvement in symptoms of PDS took longer to improve than those of EPS, although the detailed mechanism remains unknown. Therefore, the effect of acotiamide on EPS can be evaluated at one month after starting treatment, but at least three months is necessary to determine the effects on symptoms of PDS.

Matsueda *et al.* reported that the improvement rate of global overall treatment efficacy (OTE) showed a rapid increase at one week, reaching 60% at eight weeks and was subsequently maintained. However, their data showed a gradual increase in the rate of resolution of PDS symptoms up to eight weeks (9). Therefore, the global OTE and PDS scores may not be related when evaluating the rapidity with which symptoms are improved. This dissociation may be explained by our data, showing a rapid improvement in symptoms of EPS at one month followed by a gradual improvement of symptoms of PDS up to three months. The rate of improvement in symptoms of EPS may influence the overall symptom score especially early in the treatment course with acotiamide. Therefore, it may be meaningful to add an evaluation of EPS symptoms, as shown in our data, to an overall evaluation of FD, although the Izumo scales used in our study are different from the OTE scores used to assess FD symptoms.

We attempted to identify factors which predict the outcomes

with acotiamide treatment. A less favorable response with the use of prokinetic drugs was reported in patients with a long duration of symptoms of FD (16). In the present study, symptom duration did not affect the efficacy of acotiamide to relieve symptoms. The severity of symptoms of FD was a significant factor for failed resolution of FD symptoms at three months. Additional treatment should be considered for such patients.

In this study, acotiamide improved symptoms of GERD, constipation and diarrhea in 30-70% of patients. The favorable trend for relief of GERD symptoms may be explained by the improved gastric emptying time as a result of acotiamide treatment. Overlap with lower GI symptoms is well recognized in patients with symptoms of FD, and about half of patients with FD also have lower GI symptoms in the present study similar to that reported in previous studies (2, 17). Since many patients have both upper GI symptoms of FD and lower GI symptoms, it is important to elucidate the influence of FD treatment on lower GI symptoms. Acotiamide increases release of the acetylcholine, and relief from constipation may be partially explained by increased intestinal motility. It is difficult to explain the reported improvement in diarrhea. FD is highly influenced by stress-induced factors (7). One possible explanation is an acotiamide effect on stress-related genes that may result in improvement of lower GI symptoms (7). In this study, the overlap of FD and lower GI symptoms did not affect the effect of acotiamide on FD symptoms (Table 2). The number of patients with diarrhea was comparatively small in this study (n=12). Thus, caution must be exercised when interpreting these results showing a favorable effect of acotiamide on lower GI symptoms. Placebo-like effects of acotiamide may be partially responsible. In this study, acotiamide was used to treat patients with FD symptoms, and not lower GI symptoms. Therefore, we have clarified at least, that acotiamide treatment shows a favorable trend of improvement of constipation or diarrhea.

We recognize the limitations of this study, including that it is a retrospective study evaluating the effect of acotiamide, given before treatment and at one and three months after. A large number of patients in a controlled prospective study is necessary to determine the efficacy of acotiamide for functional GI disorders and their long-term outcomes.

In conclusion, acotiamide significantly improves the symptoms of EPS as well as PDS at three months. The improvement in symptoms of PDS takes longer than that for EPS. Although the effect of acotiamide on EPS can be determined at one month after beginning

treatment, at least three months is needed to determine the effect on symptoms of PDS. A favorite trend of improvement of symptoms exists in GERD, constipation or diarrhea. Acotiamide has the potential to be a first-line therapy for patients with EPS as well as PDS.

## CONFLICT OF INTEREST

S.S. has received honoraria from Zeria pharmaceutical Co, Ltd and Astellas Pharma Inc. H.O. has received honoraria from Zeria pharmaceutical Co, Ltd. Other authors declare no conflict of interests for this article. The funding source had no role in the design, practice or analysis of this study.

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