

# Adherence to an Acotiamide Therapeutic Regimen Improves Long-Term Outcomes in Patients with Functional Dyspepsia

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## ABSTRACT

**Background & Aims:** Long-term outcomes in patients with functional dyspepsia remain elusive. Acotiamide, a prokinetic drug, has been available in Japan since 2013. The aim of this study was to assess long-term outcomes in patients with functional dyspepsia treated with acotiamide.

**Methods:** We retrospectively reviewed 79 consecutive patients with functional dyspepsia whose symptoms improved with acotiamide therapy and who were followed for more than one year. All patients underwent esophagogastroduodenoscopy prior to acotiamide therapy. The mean follow-up was 1.9 (range, 1.0-3.3) years. We assessed the patients' symptom severity using the Izumo scale, which reflects changes in various abdominal symptoms.

**Results:** At one year, dyspepsia symptoms recurred in 25% (20/79) of the patients. In multivariate analysis, severe dyspepsia was significantly associated with increased recurrence (odds ratio [OR] 15.04, 95% confidence interval [CI] 1.73-130.47,  $p=0.013$ ). Continued use of acotiamide for one year diminished the recurrence of dyspepsia symptoms significantly (OR 0.16, 95%CI 0.04-0.61,  $p=0.006$ ). The influence of these significant predictors on long-term outcomes was analyzed using the Kaplan-Meier method. Patients with severe dyspepsia before starting acotiamide had significantly more recurrences than those with mild symptoms ( $p=0.004$ , log-rank test). Patients who continued acotiamide therapy throughout the follow-up period had significantly fewer recurrences than those who stopped therapy ( $p<0.001$ ).

**Conclusions:** Over the long-term, patients with functional dyspepsia have a considerable rate of recurrence of dyspepsia. Severe dyspepsia before treatment increases the recurrence rates, while adherence to an acotiamide therapeutic regimen decreases recurrence rate.

**Key words:** acotiamide – medication adherence – patient outcome assessment – dyspepsia.

**Abbreviations:** QOL: quality of life; EPS: epigastric pain syndrome; PDS: postprandial distress syndrome; EGD: esophagogastroduodenoscopy; GERD: gastroesophageal reflux disease.

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## INTRODUCTION

Although the worldwide prevalence of functional dyspepsia is considerable, there are few effective treatments [1]. Uncontrolled functional dyspepsia (FD) affects negatively the quality of life (QOL) and increases the social costs [2]. Acotiamide, a prokinetic drug, has been available in Japan since 2013. It was shown to improve dyspepsia symptoms by increasing both gastric

accommodation and gastric emptying in one clinical study [3]. It also improves delayed gastric emptying and feeding inhibition by stress-related hormone inhibition in a rat model [4]. A large Japanese randomized-controlled trial showed significant clinical effects on meal-related dyspepsia symptoms [5].

We previously reported short-term outcomes in patients with FD treated with acotiamide [6]. Although acotiamide is effective both for the relief of symptoms of epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS), PDS symptoms take longer to resolve than EPS symptoms during three months follow-up [6]. These results suggest the need to evaluate these symptoms over a long period of time because FD recurs frequently [7]. The aim of this study was to assess long-term outcomes in patients with FD treated with acotiamide.

## PATIENTS AND METHODS

### Study population

From April 2014 to June 2016, 133 consecutive patients with FD who improved following acotiamide therapy at Shinozaki Medical Clinic were included in this study. The diagnosis of FD was performed according to the guidelines of the Japanese Gastroenterology Society as previously described [1, 6]. We retrospectively reviewed the medical records and collected data, including medical history, endoscopic findings and the Izumo scale score. All patients underwent esophagogastroduodenoscopy (EGD) prior to acotiamide administration. We graded the degree of gastric atrophy endoscopically based on the Kimura-Takemoto classification, in which closed and open types correspond to mild and severe atrophy, respectively [8, 9]. The follow-up period was defined as the interval from starting acotiamide therapy until the last visit, when an Izumo scale score was recorded. Improvement within six months after starting acotiamide was defined as a decrease in the Izumo scale score of more than half. We excluded 48 patients who were followed for less than one year and 6 patients without improvement within 6 months. Consequently, 79 patients with long-term outcome data were included in the final cohort. The Institutional Review Board of the Shinozaki Medical Clinic approved this retrospective study.

### Patient reported outcome using Izumo scale

The Izumo scale, which assesses the severity of various abdominal symptoms, is fully validated and widely used in Japan [6, 10-12]. It has good internal consistency and correlation with the Gastrointestinal Symptom Rating Scale [11, 13]. It is based on a self-reported questionnaire including 15 items (Q1-15) in five domains: gastroesophageal reflux disease (GERD) (Q1-3), EPS (Q4-6), PDS (Q7-9), constipation (Q10-12) and diarrhea (Q13-15). Each item is scored from 0 to 5 on a Likert scale according to the degree of symptoms, as follows: 0 = not bothered, 1 = not so bothered, 2 = slightly bothered, 3 = bothered, 4 = strongly bothered and 5 = intolerably bothered. Each domain comprises three items. Therefore, each domain has a score from 0 to 15 points to evaluate the severity of symptoms, with higher scores meaning more severe symptoms. Since FD includes EPS and PDS, the dyspepsia score defined in this study was obtained by adding the EPS (Q4-6, 0 to 15 points) and PDS domain scores (Q7-9, 0 to 15 points). Severity of dyspepsia was evaluated with a total score ranging from 0 to 30 points. For GERD, constipation and diarrhea, a domain score of four or more points was considered as a "significant symptom". We routinely use the Izumo scale in clinical practice to assess various abdominal symptoms [14]. During the follow-up period, we evaluated the Izumo scale score at each clinic visit regardless of acotiamide intake, even if a patient did not complain of dyspepsia symptoms.

### Criteria for recurrence of dyspepsia symptoms

We defined "recurrence of dyspepsia symptoms" as one of the following conditions: (1) a dyspepsia score equal or higher than the value observed before starting acotiamide, (2) a six point increase in the dyspepsia score compared to the lowest score observed after starting acotiamide or (3) acotiamide was

resumed because of the patient's wishes. Since the physician in charge always encouraged patients to continue acotiamide therapy to prevent recurrence, acotiamide was stopped only at the patient's request.

### Statistical analysis

To analyze the predictive factors for recurrence of dyspepsia symptoms in a one-year period, we used univariate and multivariate logistic regression analysis. In multivariate analysis, factors were selected by a stepwise method using Statflex ver. 6.0 software (Artech Co. Ltd. Osaka, Japan). Long-term follow-up data were analyzed with the Kaplan-Meier method and the difference was evaluated by the log-rank test using BellCurve for Excel (Social Survey Research Information Co., Ltd. Tokyo, Japan). Differences were considered significant when  $P < 0.05$ .

## RESULTS

### Characteristics of the patients and follow-up

Demographic and follow-up data of 79 patients are shown in Table I. Sixty patients (76%) had at least one other gastrointestinal complaint such as GERD (acid reflux, heartburn and throat discomfort), constipation or diarrhea. All patients underwent EGD prior to acotiamide therapy, and 30% of the patients had severe gastric atrophy. In addition to EGD, abdominal ultrasound was conducted in 62/79 patients (78%), and colonoscopy was performed in 18/79 patients (23%) prior to acotiamide treatment. No other prokinetic agent was used throughout the study period. The mean follow-up period was  $1.9 \pm 0.5$  (range, 1-3.3) years. During the follow-up period,

**Table I.** Characteristics of the patients with functional dyspepsia treated with acotiamide

	n = 79
Age, years, mean $\pm$ SD	56.2 $\pm$ 15.1
Gender, male, n (%)	34 (43)
Body mass index, mean $\pm$ SD	22.2 $\pm$ 3.7
Current Smoker, n (%)	14 (18)
Alcohol use >20g/day, n (%)	14 (18)
Duration of dyspepsia symptom, years, mean $\pm$ SD	1.5 $\pm$ 3.5
Severity of dyspepsia, Izumo scale score, mean $\pm$ SD	11.0 $\pm$ 4.8
Combination use of proton pump inhibitor, n (%)	33 (42)
Other gastrointestinal symptoms, n (%)	
Gastroesophageal reflux disease	35 (44)
Constipation	34 (43)
Diarrhea	20 (25)
Gastric atrophy, n (%)	
Closed-type atrophy	27 (34)
Open-type atrophy	24 (30)
Continued use of acotiamide for one year, n (%)	35 (44)
Continued use of acotiamide throughout the follow-up period, n (%)	30 (38)
Follow-up period, years, mean $\pm$ SD (range)	1.9 $\pm$ 0.5 (1.0-3.3)

SD: Standard deviation

the physician in charge encouraged all patients to continue acotiamide to prevent recurrence. Consequently, 35 (44%) patients continued acotiamide for one year and 30 patients (38%) did throughout the follow-up period.

#### One-year outcomes of patients and predictive factors for recurrence of dyspepsia symptoms

Out of the 79 patients followed for one year, 20 (25%) had recurrent dyspepsia. We attempted to identify factors which predicted recurrence of dyspepsia symptoms (Table II). In the univariate analysis, alcohol use, severe dyspepsia ( $\geq 8$  points) and continued use of acotiamide for one year were significantly associated with recurrence of dyspepsia. In the multivariate analysis, severe dyspepsia was associated with a significantly increased rate of recurrence of dyspepsia symptoms, and continued use of acotiamide for one year was associated with a significantly decreased rate of recurrence of dyspepsia symptoms.

#### Long-term outcomes in patients with or without good medication adherence

We next analyzed long-term outcomes (more than one year) using the Kaplan-Meier method. Based on the results of multivariate analysis, we analyzed the influence of severe dyspepsia before starting acotiamide and of adherence to a therapeutic regimen on the recurrence of dyspepsia. The overall recurrence rate of dyspepsia was considerable (Fig. 1a). The recurrence-free rate of dyspepsia was significantly lower in patients with severe symptoms compared with patients with mild symptoms ( $p=0.004$ ) (Fig. 1b). The recurrence-free rate of dyspepsia symptoms was significantly higher in the continued treatment group than in that of the cessation group ( $p<0.001$ ) (Fig. 1c). The cessation group had a high recurrence rate, of 35%, one year after starting acotiamide, and the rate increased up to 68% at two years. Patients who continued acotiamide had low recurrence rates: 10% at one year and 14% at two years.

Adherence to a therapeutic regimen with acotiamide therapy improved long-term outcomes in patients with FD. No adverse events occurred throughout the follow-up period.

## DISCUSSION

Functional dyspepsia recurs frequently if treatment is stopped. In the present study, the recurrence rate of dyspepsia symptoms was considerable in patients with FD with follow-up for more than one year, but adherence to a therapeutic regimen was a significant predictor of decreased recurrence. To the best of our knowledge, this is the first report on the effect of adherence to a therapeutic regimen on the recurrence of dyspepsia symptoms based on long-term follow-up data. Severe dyspepsia before starting acotiamide therapy is a significant predictor of an increased rate of recurrence. Further, the follow-up period in this study is the longest among studies of acotiamide.

Functional dyspepsia is a chronic condition caused by impaired accommodation and delayed emptying of the stomach and it decreases the QOL [1]. Antisecretory drugs and prokinetic agents may be more effective than placebo in relieving dyspepsia symptoms [15, 16]. However, these symptoms recurred in 20% of the patients three months after cessation of proton pump inhibitors [17] and resumption of this drug was needed in 67% of patients due to aggravation of symptoms [18]. Likewise, a high rate of cessation and recurrence of dyspepsia symptoms was reported during six months or one year follow-up of acotiamide medication [19]. Therefore, adherence to a therapeutic regimen may largely influence chronic symptoms and longer follow-up data are necessary than those in previous studies. In the current study, the recurrence rate in the cessation group increased gradually and reached 68% within two years. These results suggest that the physician should manage carefully the patients with dyspepsia symptoms and inform them about the high recurrence rate of dyspepsia symptoms after the cessation of acotiamide.

**Table II.** Factors associated with recurrent dyspepsia symptoms during a one-year period

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	p-value	Odds ratio	95% confidence interval	p-value
Male gender	0.846	0.301 ~ 2.374	0.751			
Age, $\geq 60$ years	0.387	0.130 ~ 1.144	0.086			
Body mass index, $\geq 25$ kg/m <sup>2</sup>	0.484	0.097 ~ 2.404	0.375			
Alcohol use $>20$ g/day	4.000	1.191 ~ 13.429	0.024			
Current smoker	2.732	0.812 ~ 9.185	0.104			
Complications of GERD	1.360	0.491 ~ 3.761	0.553			
Complications of constipation	1.112	0.400 ~ 3.089	0.837			
Complications of diarrhea	0.435	0.112 ~ 1.682	0.228	0.272	0.062 ~ 1.200	0.085
Duration of dyspepsia symptoms, $\geq 1$ year	1.377	0.445 ~ 4.259	0.578			
Severe dyspepsia symptoms, $\geq 8$ points	9.743	1.214 ~ 78.138	0.032	15.045	1.735 ~ 130.472	0.013
Combination use of PPIs	0.683	0.238 ~ 1.958	0.478			
Open-type gastric atrophy	0.487	0.143 ~ 1.653	0.248			
Continued use of acotiamide for 1 year	0.225	0.067 ~ 0.756	0.015	0.165	0.045 ~ 0.610	0.006

GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor

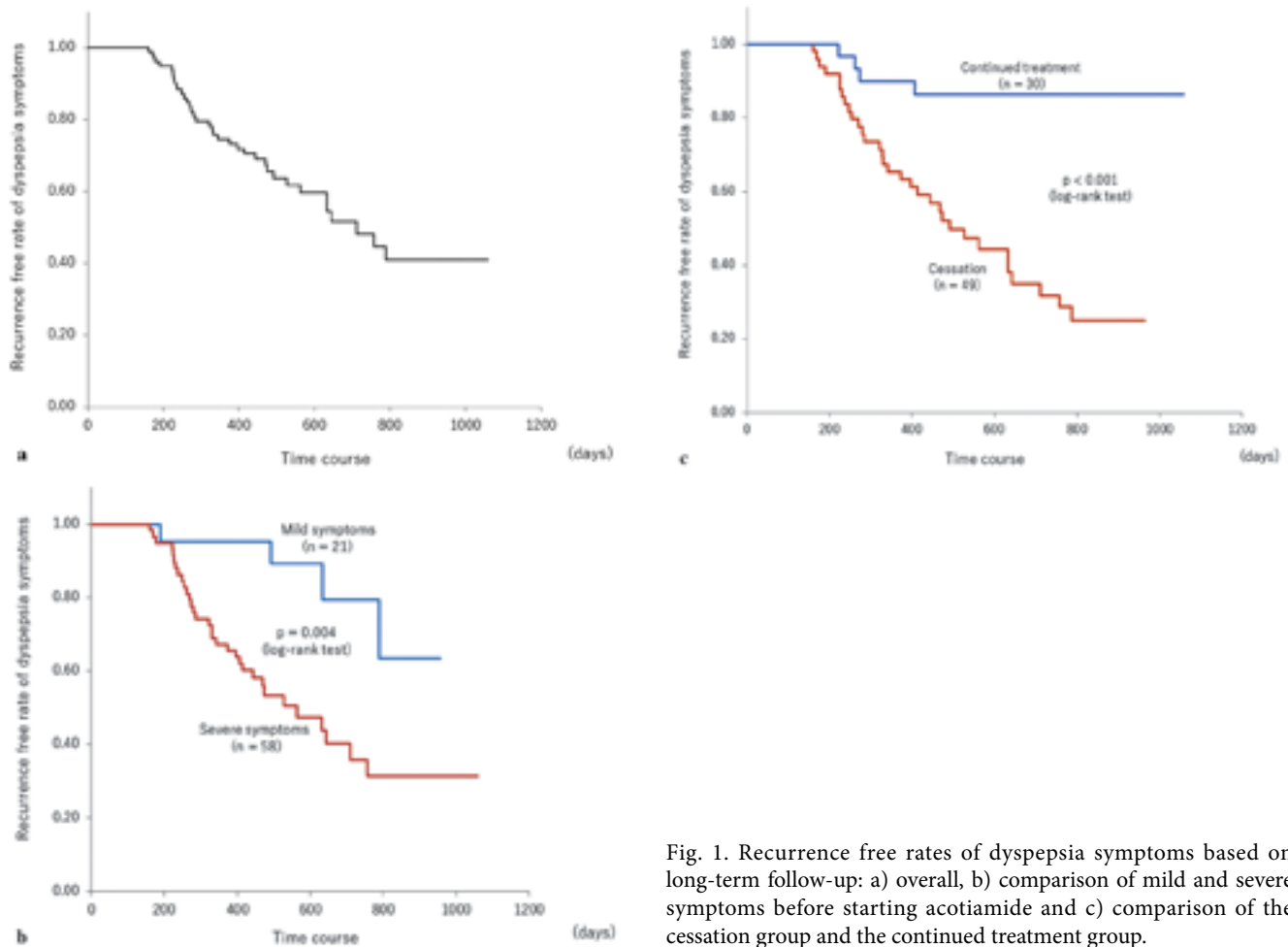


Fig. 1. Recurrence free rates of dyspepsia symptoms based on long-term follow-up: a) overall, b) comparison of mild and severe symptoms before starting acotiamide and c) comparison of the cessation group and the continued treatment group.

We previously reported that EPS symptoms improved after one month of treatment with acotiamide, but PDS symptoms improved gradually only after three months [6]. Considering the long-term outcomes of patients with PDS symptoms, it is important to elucidate whether the initial treatment should be continued or not. When patients with PDS symptoms resume acotiamide after cessation, they may need a longer time to obtain a satisfactory effect on PDS symptoms than on EPS symptoms. The current long-term data show that adherence to a therapeutic regimen with acotiamide decreased the recurrence of dyspepsia symptoms. Considering the high recurrence rates of dyspepsia symptoms, we believe that continuous therapy can result in a good QOL of patients with FD.

Multivariate analysis showed that continuation of acotiamide therapy was the significant predictor for decreased recurrence of dyspepsia symptoms. In a therapeutic trial with cisapride in patients with dyspepsia, symptom resolution during short-term treatment decreased the recurrence in the long-term follow up after cessation of cisapride [20]. It seems to be ideal to resolve symptoms during the initial treatment period. We always encourage patients to continue acotiamide to achieve symptom resolution and prevent recurrences. Adherence to a therapeutic regimen is important to treat effectively patients with dyspepsia symptoms for a long period of time. The importance of a good patient-doctor relationship for effective long-term outcomes was shown in an irritable bowel syndrome study [21]. In the present study, adherence

to the therapeutic regimen may in part result from a good patient-doctor relationship. Therefore, such a relationship might provide an additional effect beside the physiological effects of acotiamide.

Our previous short-term study reported that the severity before treatment was a significant negative predictive factor for resolution of dyspepsia symptoms at three months [6]. In the present long-term study, the severity of dyspepsia before treatment was a significant predictor of recurrence. Thus, we should give appropriate care to patients with severe dyspepsia. However, a previous long-term study using cisapride showed that symptom severity prior to treatment is not a significant factor [20]. Further investigations are required regarding this predictive factor.

It is well known that patients with fundic atrophy have delayed gastric emptying [22, 23]. In our previous short-term study, patients with gastric atrophy showed a negative trend toward resolution of dyspepsia symptoms after acotiamide therapy compared to those without atrophy, but the difference was not statistically significant [6]. In this long-term study, severe gastric atrophy did not influence the recurrence rate of dyspepsia symptoms. Further studies with a detailed evaluation of the degree of atrophy based on the Kimura-Takemoto classification may provide new insight.

There are some acknowledged limitations of this study, including: (1) the retrospective study design; (2) the patients and doctors were not blinded to the therapy used; (3) several

patients were not followed for more than one year. These patients might have a good clinical course, resulting in short follow-up, because voluntary clinic visits with scoring determined the follow-up period in this study; and (4) cessation of acotiamide therapy was strongly influenced by patient's wishes.

## CONCLUSION

The recurrence of dyspepsia symptoms is considerable in patients with FD with long-term follow up for more than one year. Severity of symptoms before treatment is a significant predictor of an increased rate of recurrence. Adherence to a therapeutic regimen is a significant predictor for decreased recurrence, and long-term use of acotiamide is safe and effective. Therefore, long-term maintenance therapy using acotiamide is recommended. Despite these important results, we do not conclude that all patients with FD should continue to take medication forever. Further studies are necessary to clarify the appropriate timing of cessation and the effect of resumption of acotiamide after recurrence.

**Conflicts of interest:** S.S. and H.O. have received honoraria from Zeria pharmaceutical Co, Ltd and Astellas Pharma Inc. Y.H. has received honoraria from Zeria pharmaceutical Co, Ltd. H.Y. has received honoraria from Zeria pharmaceutical and a research grant from Astellas Pharma Inc. Other authors declare no conflict of interest for this study. The funding source had no role in the design, practice or analysis of this study.

**Authors' contributions:** S.S. designed the study, performed the research and wrote the manuscript; H.O. designed the study, wrote the manuscript and supervised the study. Y. M. and H.Y. designed and supervised the study; H.S. and Y.H. analyzed the data. A.L. wrote the manuscript. All authors prepared and revised the manuscript, and agreed to the final version of the manuscript.

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