〈Regular Article〉

Comparison of Efficacy and Safety between Mosapride and Acotiamide for Japanese patients with Functional Dyspepsia

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ABSTRACT **Background**: 5-HT4 agonists (mosapride) and acetylcholine esterase inhibitor (acotiamide) are prokinetics used to treat functional dyspepsia (FD). However, to date, there has been no direct comparative study between them. The aim of this study was to compare the drugs' efficacy and safety and to determine their predictive biomarkers.

Methods: The present study was a prospective, randomized, open-labeled, and crossover trial in Japanese FD patients. FD was diagnosed using Rome IV. We performed upper gastrointestinal (GI) endoscopy, GI symptom rating scale, and 8-item Short-Form Health Survey to evaluate the presence of GI disorders, GI symptoms, and quality of life (QOL), respectively. Responders were defined when reporting at least a 40% improvement of the GSRS scores from their baseline.

Results: In total, 60 Japanese FD patients were randomly assigned to the acotiamide preceding group (n = 30) or mosapride preceding group (n = 30), and 51 patients were finally analyzed. Following treatment with both mosapride and acotiamide, GI symptoms and QOL scores improved significantly. The responder rates of mosapride and acotiamide were 37% and 33%, respectively. No severe adverse clinical event developed. The prevalence of *H. pylori* eradication history was significantly lower in the mosapride responder group than in the non-responder group (45.9% vs. 14.2%, $p = 0.03$).

Discussion: Mosapride and acotiamide had similar effects on GI symptoms in FD patients in the absence of severe adverse events. *H. pylori* infection might impact in the pathogenesis of functional dyspepsia. Further investigation is needed to clarify the difference between mosapride and acotiamide. doi：10.11482/KMJ-E201945015 *(Accepted on May 28, 2019)*

Key words：Functional Dyspepsia, Mosapride, Acotiamide

INTRODUCTION

Prokinetic agents are a drug category that enhances gastrointestinal (GI) motility. They are predominantly prescribed for functional GI disorders

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(FGIDs) and functionally derived symptoms such as abdominal discomfort, bloating, and constipation[1]. Functional dyspepsia (FD) is among the most recognized FGIDs and target of prokinetic agents. FD patients tend to have postprandial fullness, early satiation, epigastric pain, and epigastric burning in the absence of abnormal findings after routine evaluations[2]. FD's pathogenesis includes gastric dysmotility. Therefore, prokinetics represent one of the key therapeutic options for FD patients[3].

Mosapride is a derivative of benzamide and selective serotonin type 4 (5-HT4) receptor agonist[4]. Unlike other 5-HT4 receptor agonists such as cisapride, it has little effect on the K+ channel. Consequently, it causes QT prolongation and cardiovascular events[5]. It is known that the 5-HT4 receptor plays a key role in gastric motility such as gastric emptying. Therefore, mosapride has been primarily used as a treatment for FD patients in Japan and other Asian countries[6]. A previous multi-center study for Japanese FD patients reported adequate efficacy and safety of mosapride[7]. On the contrary, in a meta-analysis on FD patients in Eastern and Western countries, no significant effect due to mosapride was observed[8].

Acotiamide inhibits acetylcholine esterase (AchE) and blocks M1 and M2 muscarinic receptors, resulting in acetylcholine release enhancement at the neuromuscular junction[9, 10]. Various placebo-controlled trials have demonstrated significant efficacy of acotiamide on clinical symptoms and gastric motility in Japanese FD patients (e.g., accommodation and gastric emptying)[11–13]. Of note, GI symptoms long-term safety and clinical improvement in FD patients were also confirmed in European countries[14].

Based on these results, prokinetics such as acotiamide and mosapride represent front-line therapy in Japanese clinical guidelines for FD patients[15]. Although only acotiamide is covered by Japanese national insurance, other prokinetics in particular mosapride are still frequentry selected[16]. The choice of prokinetics is based on the physicians' preferences. This is due to the fact that to date, no direct head-to-head comparative trial between prokinetics has been conducted. Furthermore, little is known about predicting factors for the effectiveness of prokinetics. However, it has been reported that atrophic gastritis has been related to the effectiveness of acotiamide[17].

The purposes of this study were to compare the efficacy and safety between mosapride and acotiamide for FD patients and to investigate biomarkers to predict the effectiveness of both medicines.

SUBJECTS AND METHODS

This study was a prospective, randomized, open-labeled, and crossover trial conducted in Kawasaki Medical School. The study was performed between December 2016 and February 2018. The ethical committee approved this trial (IRB No.2584). Additionally, the trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000024049). Written informed consent was obtained from all the participants.

Subjects

Patients with FD and irritable bowel syndrome (IBS) were diagnosed and subtyped according to the Rome IV criteria[18, 19]. Gastroesophageal reflux disease (GERD) was diagnosed based on reflux-related symptoms or by means of endoscopic findings of esophagitis[20]. With reference to the Rome IV criteria, we excluded patients based on the following characteristics: the presence of *Helicobacter pylori* infection, any malignant disease, ulcerative disease, systemic inflammatory diseases, >85 years old or <15 years of age. Furthermore, we excluded from the study patients with a history of treatment with mosapride or acotiamide within

a year, hypersensitivity to both medicines, various diseases affecting GI motility (e.g., severe diabetes, severe mental disorders, and Parkinson disease).

Endoscopic examination and h. pylori infection

All patients underwent an upper GI endoscopy before treatment. Reflux esophagitis (RE) was diagnosed and classified using the Los Angeles Classification[20]. Atrophic gastritis was assessed based on the Kimura–Takemoto classification[21]. Specifically, we classified the closed type as mild atrophic gastritis (C1–C3) and the open type as severe atrophic gastritis (O1–O3).

The status of negative *H. pylori* infection was determined through a less than the cut-off value of serum IgG antibodies (E plate test, Eiken Kagaku, Inc., Toyo Japan) or ^{13}C-Urea breath test.

Treatment randomization

We performed a prospective, randomized, open-labeled, and crossover trial comparing mosapride and acotiamide. Patients received mosapride, 5 mg three times/day[7], or acotiamide, 100 mg three times/day[13]. Patient selection was based on a computer-generated randomization code. Individuals were administered each medicine and vice versa after the 2 weeks of treatment. Fig. 1 summarizes the trial flow.

Study endpoints and outcome measurements

The GI symptom rating scale (GSRS) is composed of 15 questions. These generate five components including GERD, abdominal pain, indigestion, diarrhea, and constipation. Each item was rated according to severity, on a scale from 1 (no discomfort at all) to 7 (very severe discomfort)[22]. An 8-item Short-Form Health Survey (SF-8; Japanese translation) was used to evaluate the quality of life (QOL) scores[23]. The questionnaires were answered before and after each administration. Patients were defined as responders when reporting at least a 40% improvement of the GSRS scores from their baseline[24]. We set the primary endpoint to be the comparison of acotiamide and mosapride's effects based on the GSRS scores. Secondary endpoints were to compare adverse events and to investigate the predictive clinical factors for responders.

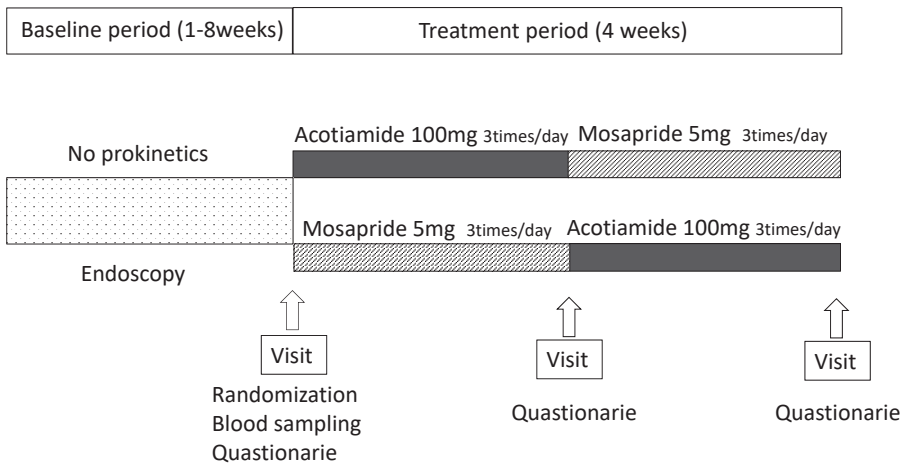

Fig. 1. Patients flow. After enrollment, patients received upper endoscopy and blood sampling prior to treatment. Subjects were treated for a total of 4 weeks. Half of them were treated with acotiamide and the remaining were given mosapride as an initial treatment, for 2 weeks. Following the initial 2 weeks of treatment, patients were administered the other medication for 2 weeks. Questionnaires were performed at baseline, then after 2 and 4 weeks.

Statistical analysis

We calculated the appropriate sample size to be at least 47 patients, based on earlier studies[13, 25]. We set α as 0.05 and 1-βas 0.803. We showed in mean and standard deviation continuous and distributed data including the following: age, body mass index, and GSRS scores. We presented in percentage the categorical data such as sex, prevalence of GERD, or IBS. We performed comparisons between two groups by using chi-square test (frequencies), student t-test (distributed continuous variables), and paired t-test. We considered as statistically significant a p-Value < 0.05. Statistical computations were processed using the SPSS statistical software (version 24.0; IBM Corp, Armonk, NY, USA).

RESULTS

Enrollment and baseline characteristics

We enrolled 64 patients with a suspected diagnosis of FD. Of these, 4 patients were excluded prior to treatment because of the following reasons: unwillingness for treatment, gastric cancer, and *H. pylori* infection. The remaining 60 patients were randomly assigned to the acotiamide preceding group (n = 30) or mosapride preceding group (n = 30). A total of 9 patients have not completed protocol due to: adverse events (n = 1), withdrawal (n = 1), or missing data (n = 7). Therefore, 51 patients were finally analyzed (Fig. 2). Table 1 shows demographics and the clinical characteristics at the base line. No significant difference was observed between the two groups.

Comparison of improvement in GI symptom and QOL scores

Both medicines were similarly effective, indicating significant improvement, except for diarrhea scores, after 2 weeks of treatment from baseline scores (Fig. 3, Table 2). Similar improvements were observed between the mosapride preceding group (from 2.53 to 2.01, $p < 0.01$) and the acotiamide preceding group (from 2.87 to 2.14, $p = 0.01$). The improvements were maintained 2 weeks after switching the medicine. Additionally, we found that

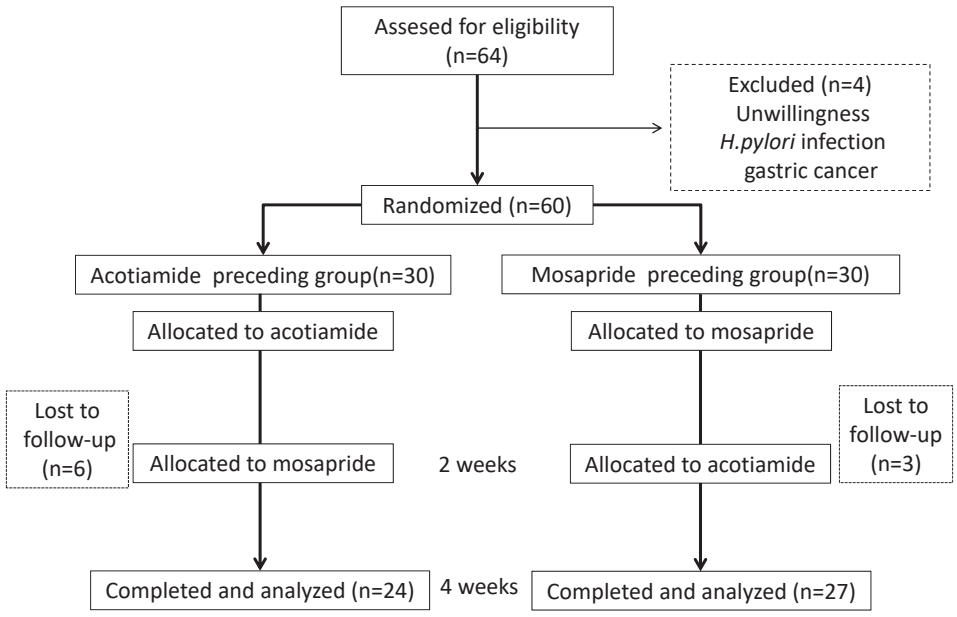

Fig. 2. Flow diagram. Eligibility was assessed in 64 FD patients. Of those patients, 4 were excluded and 60 were randomly treated with acotiamide or mosapride. Finally, 51 patients were analyzed.

Table 1. Comparison of demographic, clinical and serological characteristics at baseline between mosapride and acotiamide preceding group

Variables	Mosaprido preceding group (n = 27)	Acotiamido preceding group (n = 24)	*p*
Age mean (SD)	55.1 (20.7)	51.5 (18.6)	0.31[a]
Sex men (%)	6 (22.2)	7 (29.1)	0.74[b]
BMI mean (SD)	21.9 (3.3)	24.1 (5.2)	0.11[a]
Subtypes			
PDS (%)	14 (51.8)	10 (41.7)	
EPS (%)	9 (33.3)	9 (37.5)	0.74[b]
Overlap (%)	4 (14.8)	5 (20.8)	
GERD (%)	14 (51.9)	14 (58.3)	0.40[b]
RE (%)	5 (18.5)	4 (16.7)	0.58[b]
IBS	11 (40.7)	7 (29.1)	
IBS-C	11 (40.7)	6 (25.0)	0.31[b]
IBS-D	0 (0)	1 (4.1)	
H.pylori eradication (%)	10 (37.0)	10 (41.7)	0.77[b]
Atrophic gastritis (%)	14 (51.8)	12 (50.0)	0.98[b]
Mild	9 (33.3)	8 (29.6)	
Severe	5 (18.5)	4 (16.7)	
Anti-acids users (%)	7 (25.9)	7 (29.1)	0.79[b]

SD, standard deviation; BMI, body mass index; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; GERD, gastroesophageal reflux disease; RE, reflux esophagitis; IBS-D, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8. *p* value was calculated by the student T-test(a), Chi-squared test (b).

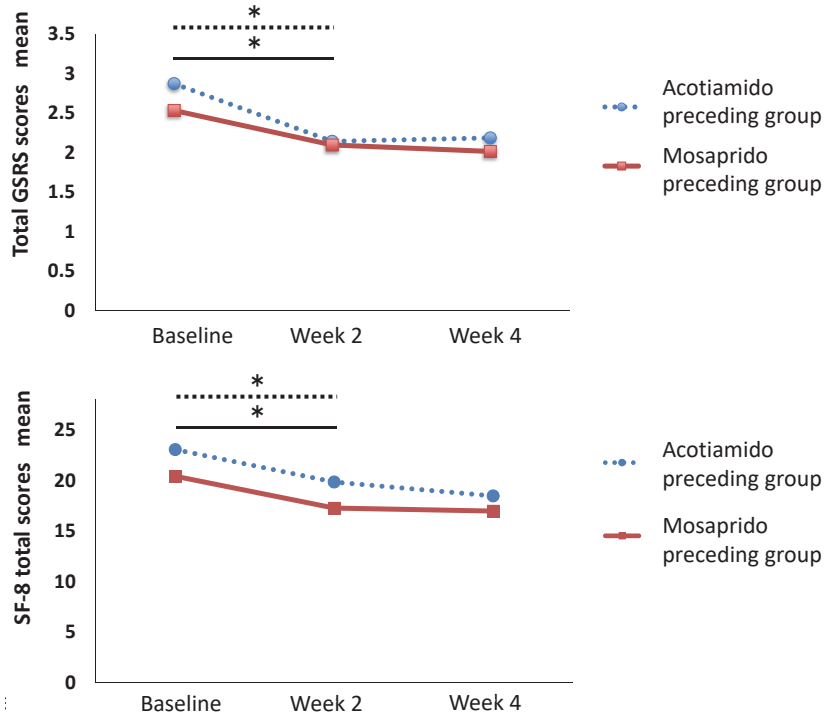

Fig. 3. GSRS scored over the trial period. Scores are expressed as mean. A significant difference was observed between baseline and post-medication scores. * $p < 0.05$.
GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8

Table 2. Score shift of GSRS and SF-8 after treatment

Score mean (SD)	Mosapride preceding group			Acotiamide preceding group		
	Baseline	2 weeks	4 weeks	Baseline	2 weeks	4 weeks
GSRS Total	2.53 (0.8)	2.01 (0.6)*	2.09 (0.9)#	2.87 (0.9)	2.14 (0.6)*	2.18 (0.8)#
Reflux	2.6 (1.2)	2.2 (0.9)*	2.3 (1.1)#	3.3 (1.3)	2.4 (1.2)*	2.5 (1.6)
Abdominal pain	2.9 (1.1)	2.0 (0.9)*	1.9 (1.1)#	3.2 (1.3)	2.3 (0.8)*	2.1 (1.2)#
Indigestion	2.7 (1.1)	2.0 (0.6)*	2.0 (0.7)#	2.7 (1.1)	2.0 (0.6)*	2.0 (0.7)#
Diarrhea	1.8 (0.8)	1.5 (0.6)	1.6 (0.8)	2.4 (1.3)	2.0 (1.4)	1.9 (0.9)
Constipation	2.8 (1.4)	2.0 (0.9)*	2.2 (1.0)	2.8 (1.4)	2.0 (0.9)*	2.2 (1.0)
SF-8 total (SD)	20.4 (6.3)	17.3 (7.1)*	17.0 (5.8)#	23.0 (6.1)	19.8 (6.4)*	18.4 (7.1)#

SD, standard deviation; GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8. *p* value was calculated by the paired T-test.
*: $p < 0.05$ Baseline vs. 2 weeks. #: $p < 0.05$ Baseline vs. 4 weeks

Table 3. Clinical adverse event during treatment period

Adverse event	Mosaprido preceding group(n = 30)		Acotiamido preceding group(n = 30)	
	Mosaprido (N = 30)	Acotiamido (N = 27)	Mosaprido (N = 25)	Acotiamido (N = 30)
Nausea (%)	1 (3.3)	1 (3.7)	0 (0)	0 (0)
Vomiting (%)	0 (0)	0 (0)	0 (0)	0 (0)
Heartburn (%)	0 (0)	0 (0)	1 (4.0)	1 (3.3)
Diarrhea (%)	0 (0)	1 (3.7)	0 (0)	1 (3.3)
Skin rash (%)	0 (0)	0 (0)	0 (0)	0 (0)

improvement of GSRS sub-scores and SF-8 scores were similar between both medicines (Table 2).

Safety

In 6 patients, several clinical adverse events were reported during medication (Table 3). Respectively, nausea and heartburn occurred in each patient taking mosapride. Nausea and heartburn occurred in one of each patient and diarrhea developed in both cases taking acotiamide. Of note, all symptoms were mild and no serious adverse event requiring hospitalization was observed.

Comparison between responder and non-responder on mosapride and acotiamide treatment

The prevalence of *H. pylori* eradication history was significantly lower in the mosapride responder group than in the non-responder group considering total GSRS scores (45.9% vs. 14.2%, $p = 0.03$). However, no other clinical factors associated with the responder of each treatment were found (Table 4).

DISCUSSION

Our study demonstrates that efficacy and safety do not differ between mosapride and acotiamide for Japanese FD patients. To the best of our knowledge, this is the first clinical comparative trial between acotiamide and other prokinetics in FD patients. There have been earlier studies on the efficacy of acotiamide vs. placebo effect[12]. However, to date, there has been no published study indicating mosapride's effects attenuating GI symptoms vs. placebo effect[8]. Contrary to our expectations, we did not confirm a difference in the effectiveness of either of the two drugs for FD symptoms. FD has heterogeneous pathophysiology. It includes symptoms such as abnormal gastric motility, hypersensitivity for extension or acid stimuli, and mental impairment including anxiety or depression[2]. Earlier studies have shown that both mosapride and acotiamide improve gastric emptying and accommodation[6, 11]. Both drugs have shown to improve reflux symptoms through increasing esophageal motility[26, 27]. In our trial, reflux

Table 4. Comparison of demographic and clinical characteristics between responder and non-responder on mosapride and acotiamide using total GSRS score

Variables	Mosaprido			Acotiamido		
	Non-Responder (n = 37)	Responder (n = 14)	*p*	Non-Responder (n = 38)	Responder (n = 13)	*p*
Age mean (SD)	52.9 (19.7)	54.7 (20.2)	0.77[a]	53.7 (20.0)	52.4 (19.3)	0.83[a]
Sex men (%)	7 (17.9)	2 (14.2)	0.70b	9 (23.6)	4 (30.7)	0.61[b]
BMI mean (SD)	22.7 (4.1)	23.6 (5.6)	0.65[a]	22.3 (4.1)	25.4 (4.8)	0.11[a]
Subtypes						
PDS (%)	16 (43.2)	8 (57.1)		18 (47.3)	6 (46.1)	
EPS (%)	14 (37.8)	4 (28.4)	0.67[b]	13 (34.2)	5 (38.4)	0.95[b]
Overlap (%)	7 (17.9)	2 (14.2)		7 (18.4)	2 (15.4)	
GERD (%)	20 (54.1)	8 (57.1)	0.84[b]	20 (52.6)	8 (61.5)	0.57[b]
RE (%)	7 (17.9)	2 (14.2)	0.69[b]	6 (15.7)	3 (23.0)	0.55[b]
IBS	12 (32.4)	6 (46.1)		13 (34.2)	5 (38.4)	
IBS-C	11 (29.7)	6 (46.1)	0.58[b]	12 (31.5)	5 (38.4)	0.77[b]
IBS-D	1 (2.7)	0 (0)		1 (2.6)	0 (0)	
H.pylori eradication (%)	17 (45.9)	2 (14.2)	0.03[b]	16 (42.1)	3 (23.1)	0.19[b]
Atrophic gastritis (%)	21 (56.7)	5 (35.7)		20 (52.6)	6 (46.1)	
Mild	13 (35.1)	4 (28.4)	0.32[b]	12 (31.5)	5 (38.4)	0.55[b]
Severe	8 (21.6)	1 (7.1)		8 (21.1)	1 (7.6)	
Antacids (%)	12 (32.4)	2 (14.2)	0.19[b]	11 (28.9)	3 (23.1)	0.68[b]
GSRS Total mean (SD)	2.62 (0.7)	2.87 (1.1)	0.35[a]	2.61 (0.7)	2.95 (1.0)	0.20[a]
Reflux	2.8 (1.2)	3.1 (1.3)	0.57[a]	2.8 (1.2)	3.1 (1.4)	0.52[a]
Abdominal pain	2.9 (1.0)	3.3 (1.4)	0.26[a]	3.0 (1.1)	3.3 (1.3)	0.40[a]
Indigestion	2.6 (0.9)	3.0 (1.6)	0.27[a]	2.6 (1.0)	3.1 (1.4)	0.16[a]
Diarrhea	2.1 (1.0)	2.2 (1.2)	0.78[a]	2.0 (1.0)	2.3 (1.2)	0.34[a]
Constipation	2.8 (1.4)	2.6 (1.4)	0.76[a]	2.7 (1.4)	2.7 (1.3)	0.99[a]
SF-8 mean (SD)	21.7 (6.4)	21.3 (6.0)	0.84[a]	21.1 (6.4)	22.9 (6.0)	0.41[a]

SD, standard deviation; BMI, body mass index; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; GERD, gastroesophageal reflux disease; RE, reflux esophagitis; IBS-D, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8; *p* value was calculated by the student T-test(a), Chi-squared test (b).

symptoms were improved after each treatment. Furthermore, both drugs were previously reported to be effective for treatment of hypersensitivity. Of note, mosapride attenuated visceral hypersensitivity in acetic acid- or zymosan-induced animal model[28]. Tack *et al.*[29] clarified that acotiamide ameliorated hypersensitivity to distension in a human gastric barostat study. We confirmed that abdominal pain scores were significantly decreased by oral administration of both drugs. The declined hypersensitivity and improvement of constipation might result in these improved scores of abdominal pain. Although racial effects should be carefully considered, at least for Japanese FD patients, both past studies[6, 7] and our results suggest that mosapride and acotiamide have similar effects in improving GI symptoms.

Regarding QOL, FD patients have impaired QOL and social problems[30]. It is known that GI and psychiatric symptoms influence each other bi-directionally, through the brain–gut axis[31]. Indeed, the improvement of GI symptoms brings recovery to mental malaise[32]. It has been shown that mosapride[7] and acotiamide have positive therapeutic effects on QOL, evaluated through Hospital Anxiety and Depression scale anxiety score[13]. Similar to past studies, our results demonstrate that both drugs improved patients' QOL as evaluated by using SF-8.

In terms of safety, in accordance with our results, past reports have shown mild adverse events including diarrhea during mosapride and acotiamide

treatment[11, 12, 33]. Nausea occurred in one patient, who had moderate nausea at baseline, and worsened during both mosapride and acotiamide medication periods. Therefore, we believe that nausea might originate from the disease progression rather than the side effects of the drugs.

Interestingly, we additionally observed that a history of *H. pylori* eradication was associated with the efficacy of mosapride. Of note, we found that the prevalence of *H. pylori* eradication history was lower in the mosapride responders. Recovery of esophagitis and dyspeptic syndrome due to gastric acid secretion can occur following *H. pylori* eradication[34, 35]. Such patients should be treated mainly by antacids rather than prokinetics. In the present trial, patients were not treated with antacids and checking intra-gastric acidity and gastric emptying. Mosapride improves GERD symptoms[27]. Thus, mosapride could be effective for improving GERD scores of GSRS in patients with history of *H. pylori* eradication. Taking data from past studies and ours together, there may be different pathogenesis between post-*H. pylori* infectious FD and FD without any history of *H. pylori* infection. Actually, composition of microbiome in post-*H. pylori* infectious FD and FD without any history of *H. pylori* infection were reported to be different[36]. A more detailed trial should be performed in order to elucidate the relationship between *H. pylori* eradication and the efficacy of mosapride.

Our study has some limitations. This trial was an open-labeled and not blind trial containing possibility of placebo effects and selection bias. To minimize subject-expectancy effect and bias, we endeavored a crossover design including sufficient individuals only in the initial treatment (at least 24 patients in each treatment). Since our aim was to compare the efficacy between the two medicines, we designed the trial as an active control trial rather than a placebo-controlled one. Moreover, half of the total number of subjects enrolled in this study had the first contact with the gastroenterology center, and the demographics and clinical characteristics of the enrolled patients matched previously reported epidemiological data on Japanese FD patients[37]. Thus, we believe that the evidence presented here is adoptive and meaningful for Japanese clinical practices. Difference of races affects pathogenesis and efficacy of treatment for FD patients. Nevertheless, this single race study provides reasonable evidence as an initial step. Another limitation is lacking washout period between the treatments, and carry-over effect should be considered. However, the drugs' half-life times are sufficiently short[38, 39], and some patients' symptoms deteriorated following the second phase indicating that drug efficacy did not always carry over. Moreover, the treatment periods was only two weeks and might be too short to evaluate the efficacy. However, we detected significant improvement of GI symptoms after two weeks, and past multi-center trial adopted two weeks as treatment periods[7]. Lastly, evaluation of GI symptoms was based on subjective data, and additional studies investigating other measurements such as ultrasonography, gastric scintigraphy, pH-impedance, and high-resolution manometry are needed to reveal the mechanisms of prokinetics at the basis of the efficacy. However, our measurements and endpoints were clinically relevant, as the most important target of FGIDs is the patient's subjective and self-reported outcomes[40].

In conclusions, our study demonstrated that mosapride and acotiamide were both effective and tolerated in FD patients without significant side effects. History of *H. pylori* infection was linked with the improvement of GI symptoms by taking mosapride. Further studies with an increased number of subjects are required in order to confirm the results.

ACKNOWLEDGEMENTS

The authors appreciate Ms. Miho Miyata and Mayumi Naoshima for their technical help and advice. The authors would like to thank Enago (www.enago.jp) for English language review.

FUNDING

The study was supported by a grant from the Kawasaki Medical School Project Grant (30- 大 -003).

CONFLICTS OF INTEREST

The authors have no conflict of interests.

AUTHORS' CONTRIBUTION

RK, HM, YH & AS performed the clinical trial.

MI & AS designed the study protocol.

RK wrote the paper.

KG & SF provided advice on statistical analysis.

TM and MF performed GI endoscopy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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