Original Article

Influence of acotiamide on ^{13}C-urea breath test for *Helicobacter pylori* diagnosis

Kazuhiro Mizukami,[1,*] Makoto Katsuta,[2] Kazuhisa Okamoto,[1] Kensuke Fukuda,[1] Ryo Ogawa,[1] Yoshinari Kawahara,[1] Yuka Hirashita,[1] Yuto Sato,[1] Masahide Fukuda,[1] Tadayoshi Okimoto,[1] Masaaki Kodama,[1] Toshio Fujioka,[2] and Kazunari Murakami[1]

[1]Department of Gastroenterology, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama, Yufu, Oita 879-5593, Japan
[2]Department of Internal Medicine, Takada Chuo Hospital, 1176-1 Shinchi, Bungotakada, Oita 879-0627, Japan

(Received 7 February, 2020; Accepted 31 March, 2020; Published online 30 June, 2020)

The *Helicobacter pylori* infection and functional dyspepsia are often coexisted. The effect of acotiamide, a drug for functional dyspepsia, on the result of *Helicobacter pylori* diagnosis has yet to be studied. We evaluated the influence of acotiamide on the results of *Helicobacter pylori* diagnosis in the ^{13}C-urea breath test. Twenty patients with *Helicobacter pylori*-positive functional dyspepsia were treated with 100 mg of acotiamide three times a day for two weeks. Changes in ^{13}C-urea breath test were investigated before and after administration, and two weeks after administration as the follow-up period. The ^{13}C-urea breath test and the medical questionnaire of modified frequency scale for the symptoms of gastroesophageal reflux disease were conducted at every period. Nineteen patients were included for analysis. No patients showed negative in ^{13}C-urea breath test at Weeks 2 and 4. On the symptom scale, dyspepsia and total scores decreased from Week 0 to Week 2 and increased from Week 2 to Week 4, and the improvement rates of the dyspepsia score at Week 2 was 63%. In conclusion, we confirmed that acotiamide is unlikely to influence the result of ^{13}C-urea breath test and it may improve the symptoms of functional dyspepsia during *Helicobacter pylori* eradication treatment.

***Key Words*: acotiamide, bacteriostatic effect, functional dyspepsia, *Helicobacter pylori*, urea breath test**

In recent years, the comprehensive disease concept of chronic gastritis has been subdivided systematically, in which *Helicobacter pylori* (*H. pylori*)-infected gastritis and functional dyspepsia (FD) are now treated as independent diseases. Recent reports indicate that *H. pylori* is not only associated with gastric cancer, but also affects patient nutrition, and further research is ongoing.[1] On the other hands, Clinical FD diagnosis is irrelevant to whether *H. pylori* infection is seen or not. Even if a patient tests positive for *H. pylori*, he/she will be diagnosed with FD if one or more of the following symptoms are present: bothersome postprandial fullness, early satiation, and epigastric pain or burning. And there are no organic lesions that may cause these symptoms.[2,3]

For the treatment of dyspepsia, the use of gastric acid secretion inhibitors, such as proton pump inhibitors (PPIs) and H_2 receptor antagonists, is recommended.[4,5] However, it is known that bacteriostatic drugs effective against *H. pylori* interfere with the results of urea breath test (UBT), which is simple yet highly reliable for detecting *H. pylori* infection. Thus, during eradication therapy, there is a need to temporarily discontinue the administration of PPIs, H_2 receptor antagonists, mucosa protective agents, antimicrobial agents, and the like until determining whether the bacteria have been eliminated.[6–8] This means that when treating patients with *H. pylori*-positive FD, drugs for improving dyspepsia without affecting the infection test results are required for the period until determining whether the bacteria have been eradicated with the eradication method used.

While FD is divided into following syndromes, the postprandial distress syndrome (PDS), exhibiting a strong feeling of postprandial fullness or early satiation, and the epigastric pain syndrome (EPS), whose main symptom is stomachache, not a few patients present both PDS and EPS.[3,9–11] Especially, many patients with PDS display reduced stomach antrum movement and delayed gastric emptying.[12,13] Therefore, it is thought that the acceleration of gastrointestinal motility and the improvement of abnormal gastrointestinal motility are useful for the treatment of FD.

Acotiamide hydrochloride hydrate (acotiamide), which is used for the treatment of FD, accelerates gastric movements by inhibiting acetylcholinesterase (AChE), resulting in improvement of the symptoms of dyspepsia, mainly PDS. Although there are only a few reports on the actual clinical use of acotiamide, it has been shown to have a high efficacy and safety profile both inside and outside Japan.[14–17] However, no studies have been conducted to investigate whether FD can be improved without affecting the results of *H. pylori* eradication judgment in patients with both *H. pylori*-infected gastritis and FD. In this study, the influence of a two-week treatment with acotiamide in patients with *H. pylori*-positive FD was investigated using the UBT. At the same time, the improvements achieved in the symptoms of dyspepsia were also evaluated.

Methods

Study design. This was a single arm, prospective intervention open study conducted at two facilities in Japan. Between October 2016 and January 2018, 20 patients with *H. pylori*-positive FD, who provided written consent, were enrolled. A dose of 100 mg of acotiamide (Acofide® tablet) was orally administered three times a day for two weeks, and changes in ^{13}C in the breath as well as changes in the abdominal symptoms were investigated before and after administration. This study was performed in compliance with the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects, and was conducted after receiving an approval for the protocol and informed consent form from the General Clinical Research Center, Oita University Hospital (UMIN-CTR ID: UMIN000023886).

Patients. Out of those with FD defined according to the Rome III criteria[2] who provided written consent to participate in the study, outpatients between 20–80 years of age meeting the

*To whom correspondence should be addressed.
E-mail: mizkaz0809@oita-u.ac.jp

doi: 10.3164/jcbn.20-17

following criteria were enrolled in the study: (1) the patient has shown at least one of the following symptoms for more than one month: postprandial fullness, upper abdominal bloating, and early satiation; (2) the modified frequency scale for the symptoms of gastroesophageal reflux disease (mFSSG) for more than one question corresponding to the symptoms of PDS is 3 (frequency: "often") or higher; (3) no organic diseases causing the symptoms were found in the upper gastrointestinal endoscopy performed within six months before the consent; and (4) the patient tested positive for *H. pylori* in the UBT that was performed prior to the administration of the study drug (UBT value ≥2.5‰, 20 min after taking Ubit® tablets). The following patients were excluded: (1) those complaining mainly of heartburn or epigastric pain, (2) those requiring treatment for irritable bowel symptoms, (3) those who took PPIs, antibacterials, antiprotozoal drugs, bismuth drugs, or ecabet sodium hydrate and the like with an anti-urease activity, within two weeks prior to providing the written consent, (4) those with a history of severe drug allergies and hypersensitivity to the drugs used in the study; and (5) pregnant women, breastfeeding women, or women wishing to become pregnant during the study period.

Treatment and evaluation method. UBT and the mFSSG medical questionnaire were conducted at the start of acotiamide treatment (baseline) and two weeks after the baseline (Week 2). A two-week follow-up period was set after the completion of administration, and tests based on UBT and the mFSSG medical questionnaire were conducted again at the end of the follow-up period, which was four weeks from the baseline. Throughout the study period, the patients were checked for adverse events.

The diagnosis of *H. pylori* infection was determined using the UBT. Prior to the test, breaths were sampled and then 100 mg of ^{13}C-urea (Ubit® tablets) was administered on an empty stomach. The patients were then asked to lie on their left side for 5 min and then to sit upright to sample breath 20 min after administration of ^{13}C-urea in order to measure the ^{13}C-CO_2 amount before and after administration and calculate Δ^{13}C (‰). The results were considered positive for UBT values of ≥2.5‰ 20 min after administering the Ubit® tablets (100 mg).

In order to prevent the influence on drug efficacy evaluation of acotiamide and the effects of bacteriostasis on *H. pylori*, the combined use of the following was prohibited: prokinetic agents other than acotiamide, PPIs, H_2 receptor antagonists, gastroprotective drugs, antibacterials, antiprotozoal drugs, bismuth drugs, drugs with an antiurease activity, drugs with anticholinergic effects, choline activators, and AChE inhibitors. The integrity of the patient's medication was confirmed in the examination for each period.

The primary endpoint of this study was the changes in the UBT value before and after the administration of acotiamide. As the secondary endpoint, changes in the mFSSG medical questionnaire score were evaluated.

mFSSG medical questionnaire. In this study, an evaluation using the mFSSG medical questionnaire was conducted in order to investigate the clinical effects of acotiamide on the symptoms of dyspepsia (Table 1). The medical questionnaire consisted of a total of 14 questions. The higher the score of the answers, the more frequent the symptoms of dyspepsia. Moreover, the 14 questions were divided into seven reflux-related questions and seven dyspepsia-related questions. The one with the higher total score was considered the main symptom of the patient.

Statistical analysis. In this study, patients completed the entire study period were included for analysis. SAS 9.4® software (SAS Institute Inc., Cary, NC) was used for the analysis. The confidence interval (CI) for differences were provided. The improvement rate was calculated from the scores of the mFSSG medical questionnaire between Week 0 and Week 2 using the following equation:

Table 1. mFSSG

No.	Question
1	Do you get heartburn?
2	Does your stomach bloated?
3	Does your stomach ever feel heavy after meals?
4	Do you sometimes subconsciously rub your chest with your hand?
5	Do you ever feel sick after meals?
6	Do you get heartburn after meal?
7	Do you have an unusual (burning) sensation in your throat?
8	Do you feel full while eating meals?
9	Do some things get stuck when you swallow?
10	Do you get bitter liquid (acid) coming up into your throat?
11	Do you burp a lot?
12	Do you get heartburn if you bent over?
13	Do you get epigastric pain (burning) after meals?
14	Do you get epigastric pain (burning) before meals?

mFSSG: modified frequency scale for the symptoms of gastroesophageal reflux disease. Scoring: Never, 0; Occasionally, 1; Sometimes, 2; Often, 3; Always, 4.

$$\text{Improvement rate} = \frac{\text{Number of patients with a decreased score before administration}}{\text{Total number of patients}} \times 100.$$

Results

Patient demographics. The study drug was administered to a total of 20 patients (4 males, 16 females), who all provided written informed consent. One patient was found to be *H. pylori*-positive in the UBT (Δ^{13}C, ‰) that was performed before the administration of the study drug. However, *H. pylori* could not be proven in the detailed tests (culture and histopathology) conducted later, and the patient was excluded from the analysis. No patients were withdrawn from the study throughout the study period. The mean age was 51.2 ± 17.6 years, and the mean weight was

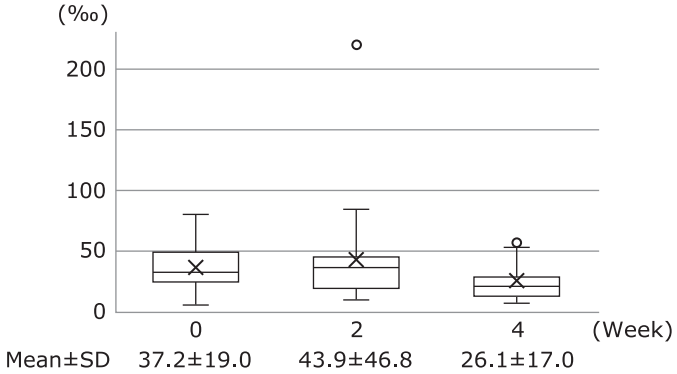

Fig. 1. Box-and-whisker plots at Weeks 0, 2, and 4 of the UBT levels. The boxes of each week extend from the 25th percentile to the 75th [$X_{[75]}$, i.e., the interquartile range (IQ)] percentile. The lines inside the boxes represent the median values, and the X-marks of each week indicate the average values. The lines emerging from the boxes extend to the upper and lower adjacent values. The upper adjacent value is defined as the largest data point $\leq X_{[75]} + 1.5$ X IQ, and the lower adjacent value is defined as the smallest data point $\geq X_{[25]} - 1.5$ X IQ. The observed values more extreme than the adjacent values are individually plotted (circle).

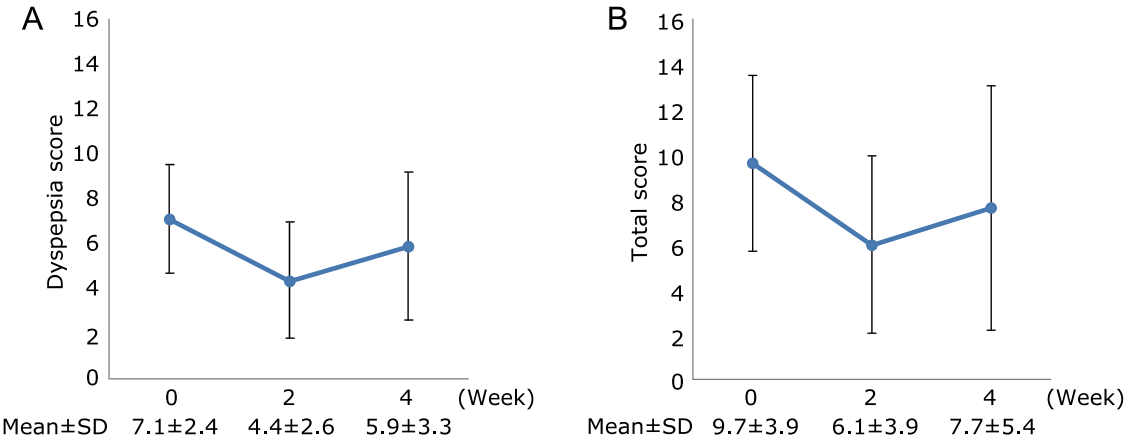

Fig. 2. Dyspepsia score and total score in mFSSG. (A) Change in the dyspepsia score of mFSSG from the baseline. (B) Change in the total score of mFSSG from the baseline.

54.4 ± 9.7 kg. Eight patients (42.1%) had complications before participating in this study, and one patient (5.3%) had a history of small intestine cancer and transverse colon cancer. The acotiamide compliance rate during the treatment period was more than 75% among all patients (100%: 15 patients, 75–99%: 4 patients).

UBT and mFSSG medical questionnaire. The mean UBT ($\Delta^{13}C$, ‰) value ± SD was 37.2 ± 19.0‰ at Week 0, 43.9 ± 46.8‰ at Week 2, and 26.1 ± 17.0‰ at Week 4 (Fig. 1, $n = 19$). The changes from Week 0 were 6.7‰ (95% CI: –14.8 to 28.2) at Week 2, and –11.1‰ (95% CI: –20.3 to –1.9) at Week 4. No patients became negative at Weeks 2 and 4.

Dyspepsia score in the mFSSG medical questionnaire was 7.1 ± 2.4, 4.4 ± 2.6, and 5.9 ± 3.3 at Weeks 0, 2, and 4, respectively (Fig. 2A), and the total score combining the dyspepsia score and the reflux score was 9.7 ± 3.9, 6.1 ± 3.9, and 7.7 ± 5.4, respectively (Fig. 2B). The improvement rates of the dyspepsia score and the total score at Week 2 were 63% (12/19 patients). The patients with deteriorated scores after administration included two (10.5%) shown by score of dyspepsia and one (5.3%) shown by total score.

As a result of comparing the number of dyspepsia questions scoring 3 (often) or more, all patients answered frequency of more than "often" for at least one question at Week 0, while 68.4% (13/19 patients) and 57.9% (11/19 patients) replied that none of the questions were of a frequency higher than "often", at Week 2 immediately after the end of administration and at Week 4 after the follow-up period, respectively. For the questions "Does your stomach bloated?," "Does your stomach ever feel heavy after meals?," "Do you burp a lot?," and "Do you feel full while eating meals?," the number of patients who provided an answer higher than "often" decreased from Week 0 to Week 2 and maintained (Fig. 3A) or increased mildly (Fig. 3B–D) from Week 2 to Week 4 thereafter. With regard to safety, no adverse events or adverse drug reactions were observed during this study.

Discussion

In this study, all patients who were treated with acotiamide for two weeks were found to be positive in the UBT at Weeks 2 and 4. There were no patients suspected to be false negatives. To date, numerous studies have been conducted on the bacteriostatic effect of peptic ulcer treatment drugs on *H. pylori*, as one of the factors affecting the bacteria eradication results of UBT.[6–8,18–24] PPIs are thought to have a bacteriostatic effect against *H. pylori* owing to their strong antacid action. Omeprazole and lansoprazole reduce the growth of *H. pylori* and the urease activity in the gastric mucosa.[20,21] H_2 receptor antagonists are known to increase the pH in the stomach and to decrease the urease activity of *H. pylori*, resulting in false negatives in the UBT.[22] Chey *et al.*[23] found that subjects who were false negative in the UBT after taking PPIs and H_2 receptor antagonists showed further reduced gastric acid secretion compared to positive subjects, causing false-negative results for gastric pH dependence. These results suggest that *H. pylori* and its enzymic activities depend considerably on the gastric pH. Vonoprazan, a new pharmacological PPI that has recently emerged, has also been shown to inhibit acid secretion faster and more strongly than conventional PPIs such as lansoprazole and esomeprazole, and it is suggested that it may affect UBT results.[25,26] On the other hand, pantoprazole, a type of PPI, is reported to have the same antacid mechanism as other PPIs. However, it does not affect the UBT results.[24] Another possible cause is the mutual actions of the bacterial count and distribution of *H. pylori* inside the stomach,[22] suggesting that gastric acid secretion is not the only mechanism causing false-negative UBT results.

Acotiamide is a prokinetic agent whose pharmacological actions inhibit AChE and increase the ACh amount in the synaptic cleft, thereby improving weak gastric movements and improving the gastric emptying functions. It has not been found that acotiamide has direct actions on gastric acid secretion. In a non-clinical pharmacological study that was conducted during the development of acotiamide to evaluate its influence on basal gastric acid secretion in rats, the subcutaneous administration of acotiamide (1 and 10 mg/kg) did not affect the basal gastric acid secretion in rats.[27]

Interestingly, in a study on drugs which may cause false negatives in the UBT eradication results, the mean UBT value after the discontinuation of therapy was found to be similar with the levels before treatment.[18,19] In this study, the mean UBT value at Week 4 (after the two-week follow-up period) decreased compared to the value at the start of the study. Regarding the reasons for the decrease in the mean UBT value at two weeks after the completion of acotiamide treatment, the possibility of factors other than the gastric pH environment having some kind of influence could not be excluded in this study. As a result of studying the influence of acotiamide on the UBT results for the first time in this study, no patients were negative in the tests that were performed after the administration. Thus, there was no evidence that acotiamide had a bacteriostatic effect on *H. pylori*.

The dyspepsia score and the total score in the mFSSG medical questionnaire decreased from Week 0 immediately after the end of the two week of administration, confirming an improvement in the frequency of dyspepsia occurrence. However, after the follow-up

doi: 10.3164/jcbn.20-17

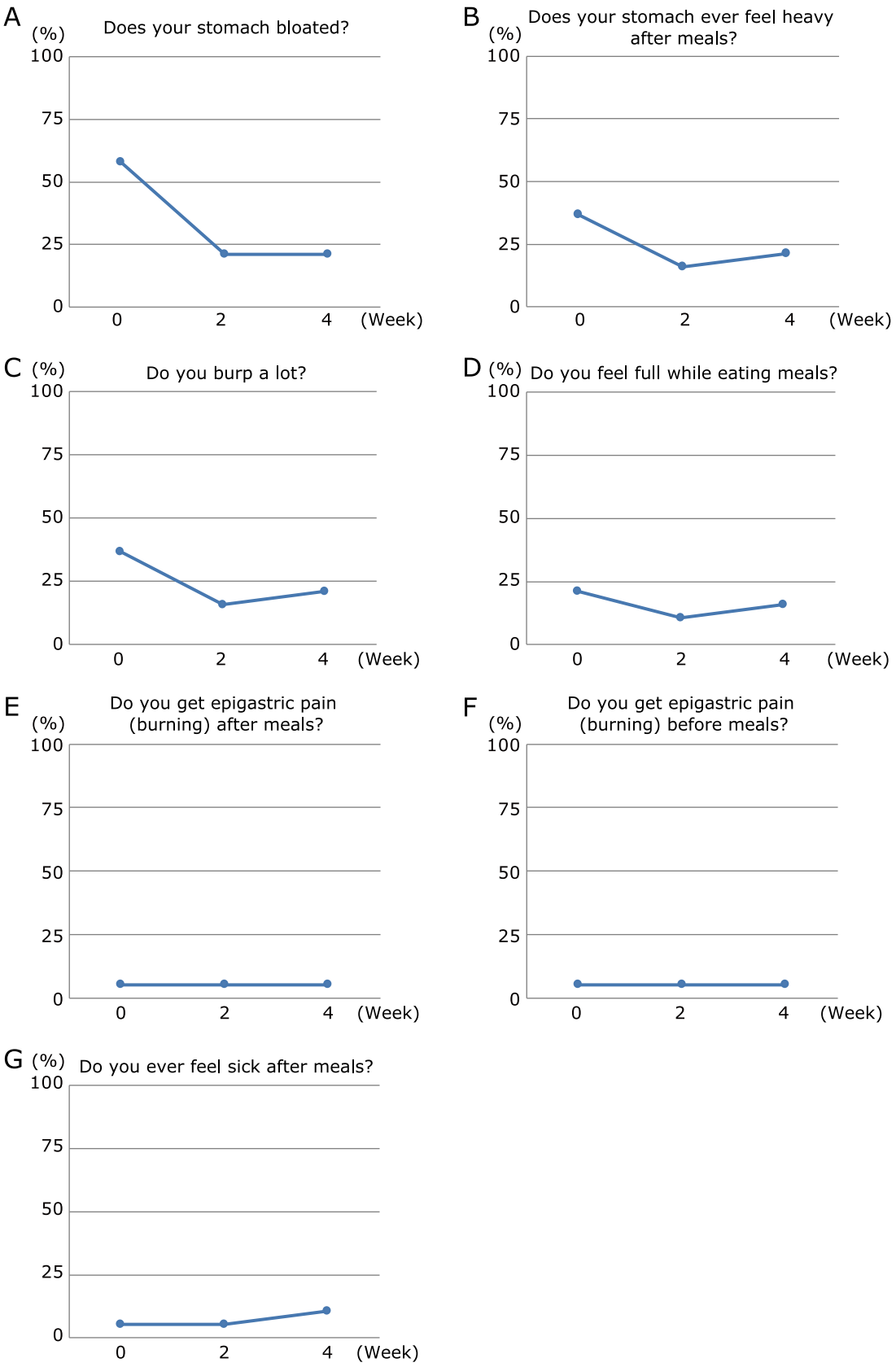

Fig. 3. Changes in the percentage of patients from the baseline who chose a score above 3 (often) in each questionnaire on dyspepsia. The total number of patients was 19. (A) The numbers of patients were 10 at Week 0, 3 at Week 2, and 3 at Week 4. (B) The numbers of patients were 6 at Week 0, 2 at Week 2, and 3 at Week 4. (C) The numbers of patients were 6 at Week 0, 2 at Week 2, and 3 at Week 4. (D) The numbers of patients were 3 at Week 0, 1 at Week 2, and 2 at Week 4. (E) and (F) The numbers of patients were 0 at Week 0, 2, and 4. (G) The numbers of patients were 0 at Week 0, 0 at Week 2, and 1 at Week 4.

period, the score showed a tendency to approach the levels at baseline (Fig. 2). Matsueda *et al.*[14] pointed out that the results of the Phase III tests for acotiamide confirmed that the improvements achieved by administering acotiamide for four weeks consecutively appeared at a relatively early stage at Week 2. Even after the administration was stopped, there was no sudden recurrence or aggravation of symptoms, and the improvement effects were maintained. Given that a two-week treatment with acotiamide led to an improvement rate of 63% even in this study, it was confirmed that the improvement effects for the symptoms of dyspepsia appear at a relatively early stage. With regard to the sustenance of the improvement effects of acotiamide after the completion of administration, dyspepsia symptoms (Fig. 3) for which the frequency of occurrence above "often" increased at Week 4 compared to baseline were "Do you ever feel sick after meals?" (Fig. 3G) only. For all other questions, the symptoms reduced to a certain extent even after the administration was completed. In addition, only one patient showed deterioration of the total score at Week 4 compared to that of the baseline. All the other patients maintained their improvement up to Week 4. In this study, as the follow-up period was set as two weeks after the completion of administration, there is a need to study the accurate sustenance period of the improvement effects of acotiamide in more detail in future investigations. No sudden recurrence of symptoms was seen after the end of administration, supporting the previous report on the sustenance of effects.[14]

In this study, the two weeks of administration period of acotiamide was shorter than those in other studies.[14] Given that this was an open label study on functional gastrointestinal disorders, the bias in the self-evaluation by the patients in the mFSSG medical questionnaire after the end of the two-week administration period may have worked negatively. In reality, the placebo effects that occur during the evaluation of FD drug treatments are substantial, and this is considered a limitation in the study design.

There was no evidence that acotiamide had a bacteriostatic effect on *H. pylori* after the completion of acotiamide treatment. We confirmed that acotiamide is unlikely to have effects on the UBT results and that it may improve the symptoms of FD during treatment.

Author Contributions

KMizukami: study concept and design, acquisition of data, analysis and interpretion of data, statistical analysis and drafting of the manuscript. MK, KO, KF, RO, YK, and TO: acquisition of data and interpretion of data. YH, YS, and MF: interpretation of data, critical revision of the manuscript. MK, TF, and KMurakami: study concept and design, interpretation of data, critical revision of the manuscript and study supervision.

Acknowledgments

This study was supported by a research grant from Astellas Pharma Inc. (Tokyo, Japan).

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article. The sponsor had no role in the study design; collection, analysis, and interpretation of data; writing of the manuscript; or the decision to submit the manuscript for publication.

References

1 Ichikawa H, Sugimoto M, Sakao Y, *et al*. Eradication therapy for *Helicobacter pylori* infection improves nutrition status in Japanese hemodialysis patients: a pilot study. *J Clin Biochem Nutr* 2019; **64**: 91–95.
2 Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; **130**: 1377–1390.
3 Tack J, Talley NJ, Camilleri M, *et al*. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466–1479.
4 Moay.yedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006; **(4)**: CD001960.
5 Talley NJ, Meineche-Schmidt V, Paré P, *et al*. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998; **12**: 1055–1065.
6 Logan RP, Walker MM, Misiewicz JJ, Gummett PA, Karim QN, Baron JH. Changes in the intragastric distribution of *Helicobacter pylori* during treatment with omeprazole. *Gut* 1995; **36**: 12–16.
7 Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB. Effect of proton-pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. *Ann Intern Med* 1998; **129**: 547–550.
8 Graham DY, Opekun AR, Hammoud F, *et al*. Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol* 2003; **98**: 1005–1009.
9 Matsuzaki J, Suzuki H, Asakura K, *et al*. Classification of functional dyspepsia based on concomitant bowel symptoms. *Neurogastroenterol Motil* 2012; **24**: 325–e164.
10 Manabe N, Haruma K, Hata J, *et al*. Clinical characteristics of Japanese dyspeptic patients: is the Rome III classification applicable? *Scand J Gastroenterol* 2010; **45**: 567–572.
11 Tack J, Talley NJ. Functional dyspepsia—symptoms, definitions and validity of the Rome III criteria. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 134–141.
12 Quartero AO, de Wit NJ, Lodder AC, Numans ME, Smout AJ, Hoes AW. Disturbed solid-phase gastric emptying in functional dyspepsia: a meta-analysis. *Dig Dis Sci* 1998; **43**: 2028–2033.
13 Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986; **91**: 94–99.
14 Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* 2012; **61**: 821–828.
15 Tack J, Pokrotnieks J, Urbonas G, *et al*. Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)—results from the European phase 3 open-label safety trial. *Neurogastroenterol Motil* 2018; **30**: e13284.
16 Ueda M, Iwasaki E, Suzuki H. Profile of acotiamide in the treatment of functional dyspepsia. *Clin Exp Gastroenterol* 2016; **9**: 83–88.
17 Matsueda K, Hongo M, Ushijima S, Akiho H. A long-term study of acotiamide in patients with functional dyspepsia: results from an open-label phase III trial in Japan on efficacy, safety and pattern of administration. *Digestion* 2011; **84**: 261–268.
18 Murakami K, Sato R, Okimoto T, *et al*. Influence of anti-ulcer drugs used in Japan on the result of ^{13}C-urea breath test for the diagnosis of *Helicobacter pylori* infection. *J Gastroenterol* 2003; **38**: 937–941.
19 Savarino V, Bisso G, Pivari M, *et al*. Effect of gastric acid suppression on ^{13}C-urea breath test: comparison of ranitidine with omeprazole. *Aliment Pharmacol Ther* 2000; **14**: 291–297.
20 Connor SJ, Seow F, Ngu MC, Katelaris PH. The effect of dosing with omeprazole on the accuracy of the ^{13}C-urea breath test in *Helicobacter pylori*-infected subjects. *Aliment Pharmacol Ther* 1999; **13**: 1287–1293.
21 Nagata K, Satoh H, Iwahi T, Shimoyama T, Tamura T. Potent inhibitory action of the gastric proton pump inhibitor lansoprazole against urease activity of *Helicobacter pylori*: unique action selective for *H. pylori* cells. *Antimicrob Agents Chemother* 1993; **37**: 769–774.
22 Graham DY, Opekun AR, Jogi M, *et al*. False negative urea breath tests with H2-receptor antagonists: interactions between *Helicobacter pylori* density and pH. *Helicobacter* 2004; **9**: 17–27.
23 Chey WD, Woods M, Scheiman JM, Nostrant TT, DelValle J. Lansoprazole and ranitidine affect the accuracy of the ^{14}C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997; **92**: 446–450.

doi: 10.3164/jcbn.20-17

24 Parente F, Sainaghi M, Sangaletti O, *et al*. Different effects of short-term omeprazole, lansoprazole or pantoprazole on the accuracy of the ^{13}C-urea breath test. *Aliment Pharmacol Ther* 2002; **16**: 553–557.
25 Sakurai Y, Mori Y, Okamoto H, *et al*. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. *Aliment Pharmacol Ther* 2015; **42**: 719–730.
26 Ohkuma K, Iida H, Inoh Y, *et al*. Comparison of the early effects of vonoprazan, lansoprazole and famotidine on intragastric pH: a three-way crossover study. *J Clin Biochem Nutr* 2018; **63**: 80–83.
27 Astellas Pharma Inc. Acofide® Tablets 100 mg Interview form. Revised: Jun 2014 (Ver. 5).