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

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Key Words

Functional dyspepsia • Rome III • Acotiamide • Acetylcholinesterase inhibitor • Z-338 • Prokinetic agent

Abstract

Background: This long-term 48-week study of acotiamide was carried out to investigate the efficacy, safety and administration pattern in patients with functional dyspepsia (FD).

Methods: This was a multicenter, open-label, single-arm, long-term phase III study in which patients with FD were given acotiamide, 100 mg t.i.d., for 48 weeks. The two major efficacy endpoints were global overall treatment efficacy (OTE) and the elimination rate of three cardinal symptoms (i.e. postprandial fullness, early satiation and upper abdominal bloating), which were evaluated weekly and daily by the patients, respectively. The long-term administration patterns were investigated by following the patients based on cessation and readministration criteria. **Results:** Efficacy was analyzed in 405 patients. The OTE improvement rate was 26.1% at week 1 and increased with time. It was 60.6% at week 8 and subsequently maintained. Similarly, the symptom elimination rate increased up to week 8. Many patients who met the cessation criterion achieved remission of FD symptoms after experiencing dose interruption and read-

ministration. The incidence rate of adverse drug reactions was 11.5% and most of the adverse drug reactions were mild in severity except increased ALT in 1 patient. **Conclusion:** FD symptoms were controlled by intermittent administration of acotiamide even in patients with relapsing FD.

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Introduction

According to the Rome III consensus, functional dyspepsia (FD) is defined by the presence of symptoms thought to originate in the gastroduodenal region (postprandial fullness, early satiation, epigastric pain or burning), in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms [1]. Epidemiological surveys suggest that 20–30% of the general population experience dyspepsia over the course of a year, and this percentage is reasonably consistent around the world [2]. In Japan, approximately 25.6% of the population report dyspeptic symptoms [2, 3]. In most patients with FD, symptoms persist over a long period of time through remission and relapse [4]. Due to the high morbidity and prolonged duration of the disease, FD has been reported to have a substantial impact

on the patient's quality of life, medical cost and labor productivity [5].

The underlying pathophysiology in FD is incompletely understood, possibly because of the heterogeneous nature of the disorder [1, 6]. Based on a presumed relationship between symptom pattern and underlying pathophysiological mechanisms, the Rome III consensus subdivided FD into two subcategories: postprandial distress syndrome (PDS) and epigastric pain syndrome [1]. PDS, characterized by postprandial fullness and early satiation, is also referred to as meal-related FD and is thought to be caused by disturbed gastric motor function and impaired gastric accommodation [1, 6–8]. It has been suggested that this group of patients may respond to drugs that alter gastric motility, such as prokinetic and gastric fundus-relaxing drugs, but to date no drug has been approved for the treatment of FD or PDS [1, 6, 7].

Acotiamide (Z-338) is a first-in-class drug which exerts gastropromotor activity by enhancement of acetylcholine release [9]. It does so by acting as an antagonist on muscarinic autoreceptors in the enteric nervous system and by inhibiting cholinesterase activity [9, 10]. In addition, acotiamide may also act directly on the gut and indirectly on the central nervous system through the brain-gut axis [11]. In phase II trials in Europe, the USA and Japan, acotiamide has been shown to exert beneficial effects in FD, particularly for meal-related symptoms such as postprandial fullness, upper abdominal bloating and/or early satiation, without major adverse events [12–15]. Based on the Japanese and European studies, 100 mg t.i.d. was identified as the most effective dose [12, 13].

For Japanese phase III clinical trials of acotiamide, a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial and a multicenter, open-label, single-arm, long-term trial were performed. The primary endpoints of the placebo-controlled trial were a global assessment of overall treatment efficacy (OTE) and rate of elimination of the following three cardinal symptoms at the last survey point: postprandial fullness, upper abdominal bloating and early satiation (score 0). The results of the placebo-controlled trial in FD patients mainly with PDS (FD-PDS patients; ClinicalTrials.gov No. NCT00761358) demonstrated significant improvement of FD-PDS in the acotiamide group in comparison with the placebo group.

The open-label long-term trial was performed in order to explore long-term administration patterns and to examine the efficacy and safety of acotiamide. The results of the trial are presented in this report.

Methods

Patients

We recruited Japanese FD patients aged between 20 and 79 years, who had FD-PDS as defined by the Rome III classification [1].

Patients were required to have at least 1 of 4 symptoms (upper abdominal pain, upper abdominal discomfort, epigastric pain or epigastric burning) for at least 6 months before inclusion. Patients were also eligible if they experienced 2 or more of the following symptoms at a moderate or severe level within the previous 3 months: upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper abdominal bloating, early satiation, nausea, vomiting or excessive belching. Furthermore, the most bothersome symptom at the time of obtaining informed consent should be one of the following meal-related symptoms: postprandial fullness, upper abdominal bloating or early satiation.

All patients underwent upper abdominal endoscopy in the observation period. Those with any changes in the esophagus, stomach and duodenum were excluded. Patients who had experienced heartburn within 12 weeks prior to the baseline period were excluded. The following exclusion criteria were also applied: presence of any symptom indicating serious or malignant disease, drug or alcohol abuse, and severe abnormality in the electrocardiogram at rest or the clinical or laboratory examination during the observation period. Antisecretory medications, antacids, prokinetics, NSAIDs and antidepressants were not allowed after the observation period. Pregnant or breastfeeding women and those of childbearing age who were not using an approved method of contraception were also excluded.

Study Design

This multicenter, open-label, single-arm, long-term (48 weeks) phase III trial was conducted at 32 centers in Japan during a period of 17 months from August 2008 to December 2009. The trial was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and local laws and regulations. The protocol was reviewed and approved by the ethics committees of participating centers. Written informed consent was obtained from every patient.

The 48-week treatment period was preceded by an 8-day baseline period after the screening visit. The observation period consisted of an 8-day baseline period and the screening visit. The FD symptoms of the patients were evaluated weekly (for 48 weeks) and daily (the first 8 weeks) during the baseline period and treatment period (fig. 1).

Symptoms, Global Assessment and Safety

During the 48-week treatment period, patients completed a global assessment of an OTE questionnaire on a weekly basis. The question asked was, 'How were your gastric symptoms during the past week in comparison to the baseline period?' This was scored in the paper diaries on a 7-point Likert scale (1–7) ranging from 'extremely improved compared to the baseline period' to 'extremely aggravated compared to the baseline period', with 'not changed' as the middle score.

During the 8-day baseline period and until the first 8 weeks in the treatment period, patients rated each of nine symptoms (upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper abdominal bloating, early satiation, excessive belching, nausea, vomiting and heartburn) on a severity scale of 0–3 (none, mild, moderate and severe) using paper diaries.

The two efficacy endpoints were OTE and elimination rate of all three cardinal symptoms: postprandial fullness, upper abdominal bloating and early satiation (score 0) at every survey week. For evaluation of the OTE endpoint, patients who were ‘extremely improved’ or ‘improved’ on the OTE were considered responders, and responder rate was expressed as a percentage of the treated population.

Adverse events were reported for the treatment period.

The efficacy analysis was based on the full analysis set (FAS). Adverse events were evaluated in the population of the safety analysis set (SAF), which was defined as all patients who received at least one dose of trial medication.

Cessation and Readministration Criteria

In order to investigate clinical courses in treatment with acotiamide, the criteria for cessation and readministration were specified as follows. Cessation criterion: if a patient is assessed as a responder for 3 consecutive weeks at the time of a visit performed once every 4 weeks, dosing in the patient is interrupted until the next visit. Readministration criterion: if a patient is assessed as a nonresponder for 2 consecutive weeks during dose interruption at the time of a visit, treatment for the patient is resumed. Furthermore, if a dose interruption in a patient based on the cessation criterion continued for 12 weeks, the patient was assessed as having achieved remission and was discontinued from the study treatment. If OTE in a patient was assessed as ‘unchanged’ for 2 consecutive weeks at the time of a visit during the administration of the treatment period, the treatment for FD with acotiamide was regarded as having a ‘poor response’ and the patient was withdrawn from the trial.

Results

Study Population and Demographics

Of 582 outpatients screened, 170 patients were excluded from the trial during the observation period. Of the remaining 412 patients, 3 patients failed to receive the trial medication, 100 mg of acotiamide t.i.d. GCP violation was observed in 1 patient who was excluded from SAF and FAS. The remaining 408 patients were included in the SAF. Three patients were excluded from FAS due to failure to comply with the follow-up visits during the treatment period. The remaining 405 patients were included in the FAS.

Of the 409 patients who received the trial medication, 318 patients did not complete this treatment as shown by remission of FD symptoms, poor response to acotiamide according to the protocol criteria and adverse events, etc. Twenty-two patients completed this study at week 24 at their request and 69 patients completed this study at week

Fig. 1. Trial design. The criteria for cessation and readministration in the treatment period were specified in ‘Methods’.

Fig. 2. Flowchart of patients. GCP violation was observed in 1 patient who was excluded from SAF and FAS. 408 patients were included in the SAF. Three patients were excluded from FAS due to failure to comply with the follow-up visits during the treatment period. 405 patients were included in the FAS.

48. A flowchart of the patients is shown in figure 2. The baseline characteristics of the trial population are shown in table 1.

Efficacy

OTE improvement rates in the respective weeks during the treatment period are shown in figure 3. The improvement rate was 26.1% at week 1. It continued to increase and reached 60.6% at week 8. Thereafter, the improvement rate of around 60% was maintained.

Fig. 3. Global assessment of OTE improvement rates in the respective weeks during the treatment period.

Fig. 4. Elimination rate of the three cardinal symptoms (i.e. postprandial fullness, early satiation and upper abdominal bloating).

Figure 4 shows the rates of elimination of the three cardinal symptoms, postprandial fullness, upper abdominal bloating and early satiation, by week 8. Similarly to the OTE improvement rate, the symptom elimination rate increased up to week 8 with study treatment.

Cessation and Readministration

Table 2 shows the rate of patients who experienced dose interruption based on the cessation criterion, the

rate of patients for whom treatment was resumed based on the readministration criterion, the rate of patients who withdrew from the trial due to poor response to acotiamide and the rate of patients who discontinued the trial due to remission of FD symptoms. Based on the cessation criterion, dosing was interrupted in 304 patients (75.1%). Based on the readministration criterion, treatment was resumed in 167 of these 304 patients. Of the 167 patients in whom treatment was resumed based on the

Table 1. Demographic characteristics (FAS)

Item	Total (%)
Gender	
Male	152 (37.5)
Female	253 (62.5)
Age, year	
20–30	76 (18.8)
30–40	150 (37.0)
40–50	99 (24.4)
50–60	40 (9.9)
≥60	40 (9.9)
Weight, kg	
<50	106 (26.2)
50–60	135 (33.3)
60–70	93 (23.0)
70–80	44 (10.9)
≥80	27 (6.7)
BMI	
<18.5	46 (11.4)
18.5–25.0	292 (72.1)
25.0–30.0	57 (14.1)
30.0–40.0	10 (2.5)
≥40.0	0
Duration of illness	
6 months to 1 year	112 (27.7)
≥1 year	293 (72.3)
Chief complaint (observation period)	
Postprandial fullness	232 (57.3)
Bloating in the upper abdomen	94 (23.2)
Early satiation	79 (19.5)

readministration criterion, 128 patients experienced dose interruption more than once and 55 patients experienced it more than twice. Dosing was interrupted once in 43.5% of the patients (table 3). The highest frequency of dose interruption was 6, which was observed in 0.7% of the patients. Only a few patients experienced dose interruption more than 3 times.

During the treatment period, 55 patients (13.6%) were assessed as being withdrawn from the trial due to poor response to the study drug (table 2). This assessment was made at week 4 in nearly half of these patients. During the treatment period, 154 patients (38.0%) were assessed as being discontinued from the study due to remission of FD symptoms. The number of patients who met the criterion for remission of FD symptoms (a patient has a dose interruption based on the cessation criterion for 12 consecutive weeks without falling under the readministration criterion) increased over time from week 16 to week 48 (data not shown).

Table 2. Cessation rate, readministration rate, poor-response rate and remission rate

Item	Rate (%)
Cessation rate	304/405 (75.1)
Readministration rate	167/304 (54.9)
Poor-response rate	55/405 (13.6)
Remission rate	154/405 (38.0)

Cessation rate: rate of patients assessed as responders for 3 consecutive weeks at a visit performed every 4 weeks.

Readministration rate: rate of patients assessed as nonresponders for 2 consecutive weeks during dose interruption.

Poor-response rate: rate of patients in whom OTE was assessed as 'unchanged' for 2 consecutive weeks during the administration of treatment period.

Remission rate: rate of patients who experienced dose interruption based on the cessation criterion for 12 consecutive weeks.

As the most commonly observed administration pattern, patients had a dose interruption due to symptom improvement and were eventually discontinued from the study treatment following the remission of FD symptoms. As the second most commonly observed administration pattern, patients completed the trial while repeatedly experiencing dose interruption and readministration. Because of the dose interruptions and remission of symptoms observed in many patients, the mean overall duration of study drug administration was 102.9 days in this study (data not shown).

Safety

Adverse events occurred in 296 of 408 patients in the safety analysis set, for an incidence rate of 72.5%. Adverse drug reactions, for which a causal relationship to the study drug could not be ruled out, were observed in 47 patients, for an incidence rate of 11.5%. Table 4 shows adverse events with incidence rates of ≥4% and adverse drug reactions with incidence rates of ≥1%. Most of these events were mild. As a serious adverse drug reaction, increased ALT was observed in 1 patient (0.2%).

Discussion

In spite of the high prevalence of FD, treatment options for the disease are very limited. Systematic reviews of the available literature have indicated that antisecretory drugs and prokinetic agents may be more effective than placebo in relieving FD symptoms [16, 17], but these

Table 3. Number of cessation times

No cessation	1	2	3	4	5	6	≥7	Total
101 (24.9%)	176 (43.5%)	73 (18.0%)	42 (10.4%)	7 (1.7%)	3 (0.7%)	3 (0.7%)	0	405

Table 4. Frequency of adverse events (>4%) and adverse drug reactions (>1%)

Adverse events	Rate (%)	Adverse drug reaction	Rate (%)
Nasopharyngitis	105/408 (25.7)	constipation	9/408 (2.2)
TG increased	101/408 (24.8)	diarrhea	9/408 (2.2)
γGTP increased	30/408 (7.4)	ALT increased	6/408 (1.5)
WBC increased	27/408 (6.6)	blood prolactin increased	5/408 (1.2)
Diarrhea	26/408 (6.4)	γGTP increased	4/408 (1.0)
ALT increased	25/408 (6.1)		
T-Bil increased	17/408 (4.2)		

previous studies were hampered by flaws in patient selection and trial design [18–24]. To date, no approved therapies for FD have been established. Proton pump inhibitors are effective mainly in patients with symptoms of heartburn and FD. However, their efficacy is quite limited in comparison with that of placebo for symptoms that are not acid-related [18, 19, 25, 26]. Attempts have been made in vain to establish efficacy of prokinetic drugs in patients with FD. Mosapride, a 5-HT₄ receptor agonist, was not superior to placebo in a dose-finding trial in FD [27]. While positive results were obtained in a phase IIb trial with itopride, a dopamine-2 receptor antagonist with cholinesterase inhibitory properties, the drug was not superior to placebo in two phase III trials [28, 29]. Tegaserod, another 5-HT₄ agonist, showed some promise after phase II studies, but two phase III trials showed negative results [30, 31]. Therefore, there is a true unmet medical need for FD therapies. In this regard, many patients are turning to alternative therapies of unproven value [32].

Acotiamide is a first-in-class drug that was developed for the treatment of FD. Placebo-controlled phase II studies in Europe and Japan have shown beneficial effects of acotiamide on FD symptoms such as postprandial fullness, upper abdominal bloating and early satiation [12, 13].

In this current phase III trial of acotiamide, a multicenter, open-label, single-arm, long-term trial was performed. The objectives of the trial were to investigate

long-term administration patterns and to examine the efficacy and safety of acotiamide. The efficacy and safety observed in the trial were similar to those observed in another phase III randomized, 4-week placebo-controlled trial (ClinicalTrials.gov No. NCT00761358). The improvement rate increased over time, as well in the long-term administration. An excellent safety profile was also demonstrated. Just for reference, in another phase III, randomized, 4-week placebo-controlled trial, a significantly higher proportion of patients achieved the primary endpoint of being improved on the OTE in the acotiamide group compared to the placebo group.

First, patients who were discontinued due to remission of FD symptoms and those who were withdrawn due to poor response were evaluated. Many patients were assessed as being discontinued from the study treatment due to remission of FD symptoms at week 16 or later. Eventually, FD symptoms resolved in 38.0% of patients. The patients assessed as being discontinued from the study due to remission of symptoms at week 16 or later were those in whom dosing was interrupted after treatment for 4 weeks. FD symptoms may have improved at a relatively early stage of treatment. Therefore, acotiamide may be effective for improvement of subjective symptoms from an early stage of treatment and such an improvement effect may be maintained even after dose interruption. Meanwhile, 13.6% of the patients were assessed as being withdrawn from the study treatment due to poor response to the study drug. Such an assessment was made

at week 4 in about half of these patients. Therefore, those with poor response could have been detected at a relatively early stage of treatment.

Second, dose interruption based on the cessation criterion and readministration based on the readministration criterion were evaluated. Dose interruption based on the cessation criterion occurred once in 43.5%, twice in 18.0% and 3 times in 10.4% of the patients. It occurred up to 6 times. Considering that the mean duration of administration up to the first dose interruption based on the cessation criterion was 60.4 days, FD symptoms may have begun to improve at a relatively early stage of treatment and they may have improved to the extent of allowing dosing to be interrupted after about 8 weeks of treatment. The durations of the first, second and third dose interruption based on the cessation criterion were about 8 weeks, demonstrating that FD symptoms were unlikely to relapse immediately after dose interruption (data not shown).

As the most commonly observed administration pattern, patients had a dose interruption due to an improvement of FD symptoms after the start of study treatment and achieved remission of FD symptoms without readministration. These results demonstrated that remission of FD symptoms could be achieved by treatment with acotiamide. As the second most commonly observed administration pattern, patients completed the trial while

repeatedly experiencing dose interruption and readministration. This suggested that FD symptoms could be controlled by intermittent administration of acotiamide even in patients with relapsing FD.

Based on the above, it was suggested that FD symptoms started to improve from an early stage of treatment with acotiamide and that the improvement effect was maintained even after a dose interruption. There were many patients in whom FD symptoms resolved after a dose interruption. Even if FD symptoms relapsed after a dose interruption, symptoms could be improved again by resumption of treatment with acotiamide.

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Disclosure Statement

Dr. Matsueda has provided scientific advice to Astellas, Zeria, Ajinomoto and Abbott. Dr. Hongo has provided scientific advice to Astellas, Zeria, Takeda, Eisai, AstraZeneca and Sucampo. Mr. Ushijima and Mr. Akiho are employees of Astellas. The authors report no other potential conflicts of interest relevant to this article.

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