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Uncontrolled, Open-Label Pre-Dinner Administration of Elobixibat in Japanese Adults with Chronic Constipation: A Retrospective Chart Review

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ABSTRACT

Background: Elobixibat has been approved as a new therapeutic drug for chronic constipation. Only the pharmacological efficacy and safety profile of pre-breakfast administration of elobixibat had been previously demonstrated.
Objective: We evaluated the efficacy and safety profile of pre-dinner administration of elobixibat in patients with functional constipation in a retrospective observational study.
Methods: Patients aged 20 years or older diagnosed with functional constipation by the Rome IV criteria from June 1, 2018, to January 17, 2019. The evaluation time points were at the start and 1, 2, 4, and 8 weeks after treatment. The primary end point was frequency of spontaneous bowel movements per week. The secondary end points were changes in Bristol Stool Form Scale score, onset time required for spontaneous defecation after administration, percent of patients with spontaneous defecation within 24 hours and 48 hours after the first administration, improvement of abdominal pain or abdominal bloating evaluated by a visual analog scale, and total score and each subscore of the Japanese-Translated Version of Patient Assessment of Constipation Quality of Life Questionnaire.
Results: Pre-dinner administration of elobixibat was associated with significantly increased frequency of spontaneous bowel movements and improved Bristol Stool Form Scale score at 1, 2, 4, and 8 weeks after treatment. The mean onset time until spontaneous defecation after treatment was 4 to 5 hours, which was earlier than that by conventional constipation treatment drugs and almost constant within an individual during the treatment period. Spontaneous defecation was achieved by 85.4% within 24 hours and 90.2% within 48 hours after the first administration. Elobixibat also improved patients' quality of life, which was evaluated by the Japanese-Translated Version of Patient Assessment of Constipation Quality of Life Questionnaire without adverse events.
Conclusions: Pre-dinner administration of elobixibat improved constipation, abdominal pain and bloating, and patient quality of life by management of fixed defecation. (*Curr Ther Res Clin Exp.* 2020; 81:XXX–XXX)

Introduction

Chronic constipation is a syndrome characterized by defecation disorders and abnormal symptoms. Patients with chronic constipation have poor quality of life (QOL) both physically and psychosocially.[1,2] Chronic constipation is classified into 2 types: organic constipation and functional constipation. Functional constipation is most common, and its diagnosis is academically defined by the Rome IV criteria.[3,4] According to an Internet survey conducted in Japan, 28.4% of respondents determined on their own that they have constipation, with functional constipation accounting for about 50% of them.[5] On the basis of clinical symptoms, constipation is classified into 2 types: 1 is reduction of defecation frequency and the other is difficulty in defecation. In pathophysiology, it is classified into 3 types: normal colonic transit time, delayed colonic transit time, and fecal discharge disorder.[4] Thus, chronic constipation is clinically diverse and complex. Patients with organic constipation were not considered for this trial.

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Recently, several newer treatment options have appeared. Lubiprostone activates type 2 chloride channels on intestinal epithelial cells, secreting water and softening the stool to promote defection.[6] Linaclotide activates guanylyl cyclase C receptors and promotes water secretion into the intestinal tract,[7] thereby improving bowel movements. Different from the pharmacologic functions of these drugs, elobixibat exhibits another function. Elobixibat was approved as a new treatment drug for chronic constipation in January 2018 in Japan. It is an oral small molecule drug that specifically inhibits a bile acid transporter (apical sodium-dependent/ileal bile acid transporter) expressed on the terminal ileum and suppresses the reabsorption of bile acids.[8] Bile acids activate transmembrane G protein-coupled receptor 5 present on the enterocytes and activate cystic fibrosis transmembrane conductance regulator. Thereby, bile acids increase chloride secretion and water into the colon. Bile acids also act transmembrane G protein-coupled receptor 5 present on enterochromaffin (EC) cells, stimulating a release of 5-HT. Thus, elobixibat induces colonic peristalsis, leading to a strong and fast defecation-promoting effect mediated by the above dual functions.[9–11] In the Japanese Phase III study of patients with chronic constipation, pre-breakfast administration of elobixibat improved spontaneous defecation frequency and Bristol Stool Form Scale (BSFS) scores compared with placebo. Furthermore, long-term sustainability of the effect has been confirmed for 52 weeks in long-term administration studies.[12,13] Thus, elobixibat has been reported to have excellent effects in clinical trials. Therefore, expectation for this novel agent has been higher in a clinical field.

Because bile acid is rapidly excreted into the duodenum by food intake, after-meal administration of elobixibat is not sufficiently effective. Therefore, the effects of pre-breakfast administration of elobixibat have been examined in previous clinical trials. However, patients with functional constipation, including most workers and students, are busy particularly in the morning due to their jobs and school lessons. As a result, its pharmacologic effects on promotion of defecation may be preferable during the evening until sleep because patients are adequately calm and spending time in their own home. However, its efficacy in accordance with the daily lifestyle of patients has not been sufficiently clarified because it has only recently appeared in general medical practice. In addition, although the Phase III study and the long-term administration study evaluated the number of bowel movements and BSFS scores or QOL, respectively, these studies did not evaluate whether elobixibat can beneficially or adversely influence subjective symptoms such as abdominal pain and bloating during treatment.

In the present study, to examine the efficacy and safety profile of pre-dinner administration of elobixibat, we analyzed the accumulated data regarding the treatment of functional constipation as outpatient care in our clinic.

Patients and Methods

This study was conducted as a retrospective observational study to examine data about defecation before and after treatment with elobixibat from the medical records of this clinic after the observation period with the approval of the Adachi Kyosai Hospital Second Clinical Trial Review Board, and complied with the ethical guidelines for medical research on humans (revised on December 27, 2018). Because this study was retrospective, we did not obtain informed consent from the patients. However, we provided patients an opportunity to refuse use of their medical records for this study by releasing information of this research as opt-out. This study was performed after registration with the University Hospital Medical Information Network Center (registration No.: UMIN000036163).

In this retrospective study, the survey period was from June 1, 2018, to January 17, 2019, and the enrolment period was from June 4, 2018, to December 3, 2018. The selection criteria was as follows: men and women aged 20 years or older, patients who were diagnosed with functional constipation by the Rome IV criteria in our clinic before taking elobixibat, patients who had fewer than 3 bowel movements per week, and patients who had received elobixibat before dinner during the study period. The exclusion criteria were: patients with suspected organic constipation; patients who were taking oral medication related to constipation or defecation (eg, magnesium oxide, stimulant laxative, epithelial function modifier, gastrointestinal motility enhancer, or herbal medicine); and patients who had a history of taking psychotropic, antidepressant, or anxiolytic drugs for mental illness. There were no selection or exclusion criteria other than those for this study.

Patients who met the above eligibility criteria and did not violate the exclusion criteria were evaluated for efficacy. The primary end point was frequency of spontaneous bowel movements (SBM) per week at each point for 8 weeks (baseline, 1, 2, 4, and 8 weeks) compared with that at the start of treatment. Stool form is scored from type 1 to type 7 by BSFS every day, and its average score was calculated per week at each measurement time point (baseline, 1, 2, 4, and 8 weeks). The secondary end points included the BSFS score, the onset time required for spontaneous defecation after treatment, the percentage of patients with spontaneous defecation within 24 hours and 48 hours after treatment (1, 2, 4, and 8 weeks), and total score and each subscale (physical discomfort, psychosocial discomfort, worries/concerns, and satisfaction) of the Validated Japanese-Translated Version of Patient Assessment of Constipation Quality of Life Questionnaire (JPAC-QOL)[14] at baseline, 4, and 8 weeks. In addition, for patients with abdominal pain or abdominal bloating concomitant with constipation at the start of administration, the intensity of these symptoms was evaluated by a visual analog scale (VAS) that ranged from −100 (complete remission) to +100 (maximal pain or bloating) completed at 4 and 8 weeks.

From the patients enrolled in this study, those to whom elobixibat was administered at least once were included in the analysis group for safety profile evaluation (eg, incidence of adverse events). The demographic characteristics of the patients, including age, gender, height, weight, and presence of complications were obtained.

At each evaluation time point, comparison with the values before the start to each point was performed using a paired *t* test. The significance level was 5% on both sides. Continuous variables are shown as mean (SD) and nominal variables were shown as the number of cases (%). The statistical analyses were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study flow diagram of the present study

Figure 1 shows the change in the number of patients at each measurement time point. The study evaluated 41 patients to whom 10 mg elobixibat was administered at the beginning. There were 5 noncontinuing patients who took elobixibat for 4 weeks and 36 patients administered elobixibat for 8 weeks. However, 4 patients reduced their elobixibat dose to 5 mg during the study. In noncontinuing patients, 2 patients did not come to our clinic and 3 patients stopped taking elobixibat. The 3 patients who stopped taking the drug developed watery stools and abdominal pain (not severe). We considered that the large intestine of these patients had a high sensitivity to bile acids.

The baseline demographic characteristics of the patients (total, reduced, and discontinued) are shown in the Table 1. Among the total cohort, the mean (SD) age was 49.1 (8.8) years, women made

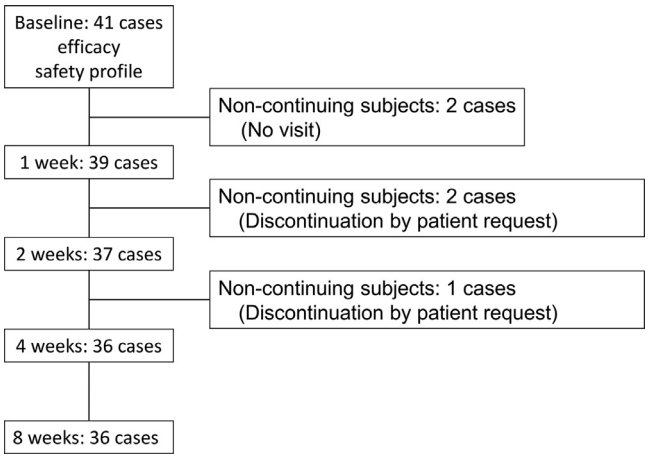

Figure 1. Study flow diagram of the present study.

Table 1
Overview of the baseline demographic characteristics of the patients.

Characteristic	Total (n = 41)	Reduced (n = 4)	Discontinued (n = 5)
Age*, y	49.1 (8.8)	43.5 (6.1)	45.0 (9.6)
Gender†			
Male	13 (31.7)	1 (25.0)	2 (40.0)
Female	28 (68.3)	3 (75.0)	3 (60.0)
Height*, cm	162.6 (8.2)	162.0 (10.6)	164.4 (10.7)
Weight*, kg	61.5 (9.9)	60.8 (14.1)	60.2 (13.4)
Complication†	22 (53.7)	1 (25.0)	2 (40.0)

* Values are presented as mean (standard deviation).
† Values are presented as n (%).

up 68.3%, mean (SD) height was 162.6 (8.2 cm), and mean (SD) weight was 61.5 (9.9) kg. There were no patients with fat-soluble vitamin deficiencies. The demographic characteristics of patients who discontinued and patients who reduced their dose were almost the same.

SBM frequency during the treatment period

Mean (SD) SBM frequency was 2.0 (0.8) times/week at the start of treatment. This was increased to 6.9 (1.3) times/week after 4 weeks of treatment ($P < 0.001$). SBM frequency was also increased at the other time points (7.1–8.3 times/week), which was significant compared with the start of treatment ($P < 0.001$ at 1, 2, and 8 weeks) (Figure 2). In those whose dose of elobixibat was reduced to 5 mg (4 of 36 cases), mean (SD) frequency of spontaneous defecation was 2.3 (0.5) times/week before the start of treatment and increased to 13.8 (2.2) times/week after 1 week, and decreased to between 5.3 and 6.3 times/week after 2 weeks of dose reduction (data not shown). The patient still had loose stools a few times a day even after the dose of elobixibat was reduced to 5 mg. However, it was not terribly watery stool, and there were no symptoms such as abdominal pain and borborygmus. It was considered that the large intestine of this patient had a high sensitivity to bile acids. As a result, the large intestinal motility promotion effect and the water secretion effect were strongly exerted. In the 3 other patients, elobixibat doses were reduced for a similar reason (loose stools).

BSFS at each time point

Mean (SD) BSFS was 1.8 (0.7) points at the start of treatment. BSFS was increased to about 4 points after 1 week of treatment and maintained throughout the entire treatment period (Figure 3).

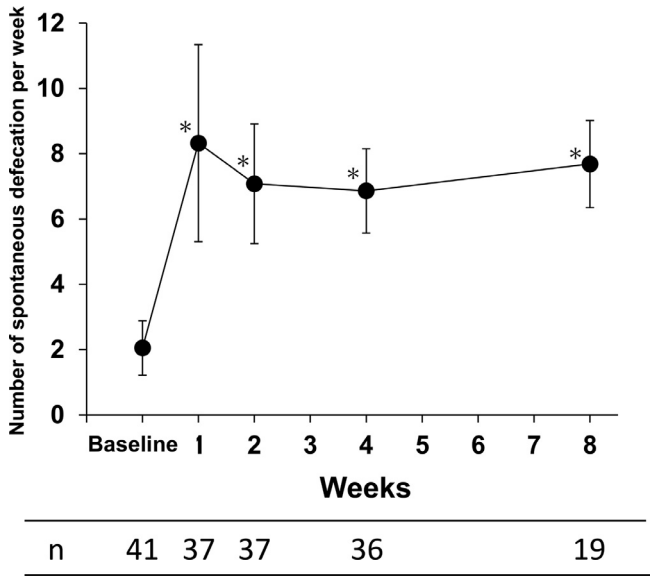

Figure 2. Changes in spontaneous bowel movement (SBM) frequency during treatment period. SBM frequency was expressed as mean (SD) at each time point. The numbers below the graph indicate the number of cases with data. *$P < 0.001$, paired t test (comparison with those at the start of treatment)

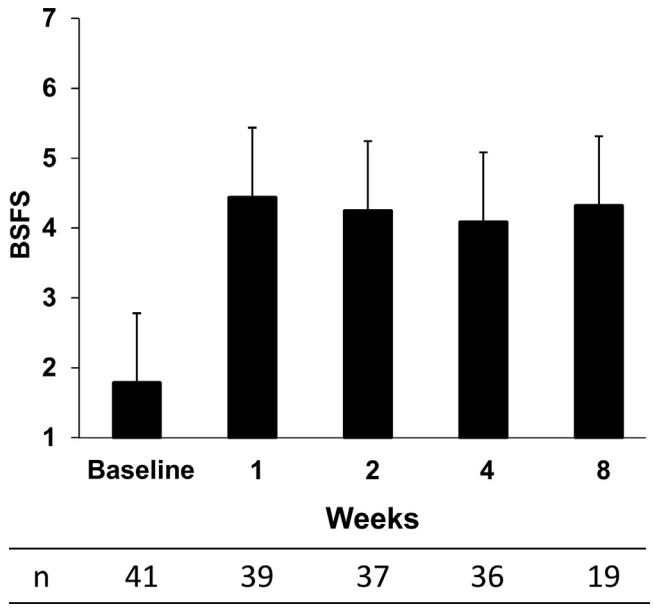

Figure 3. Changes in Bristol Stool Form Scale (BSFS) at each examined time point. BSFS was expressed as mean (SD). The numbers below the graph indicate the number of cases with data.

Change in time until the onset of spontaneous defecation

The mean (SD) values of spontaneous defecation were expressed as 4.2 hours after 1 week, 5.4 hours after 2 weeks, 5.4 hours after 4 weeks, and 5.1 hours after 8 weeks of treatment (Figure 4A). Figure 4B shows the changes in time (median) until the onset of spontaneous defecation after administration in individual patients (n = 15) who continued administration of elobixibat for 8 weeks. Although the time to defecation was slightly varied among these patients, it was kept in a range from 3.3 hours to 6.7 hours (median = 4.8 hours) at 4 weeks and a range from 4.0 hours to 7.0 hours (median = 5.0 hours) at 8 weeks. However, the time was almost constant within each patient throughout the treatment period. Percentages of spontaneous defecation were 85.4% within 24 hours and 90.2% within 48 hours after the first administration.

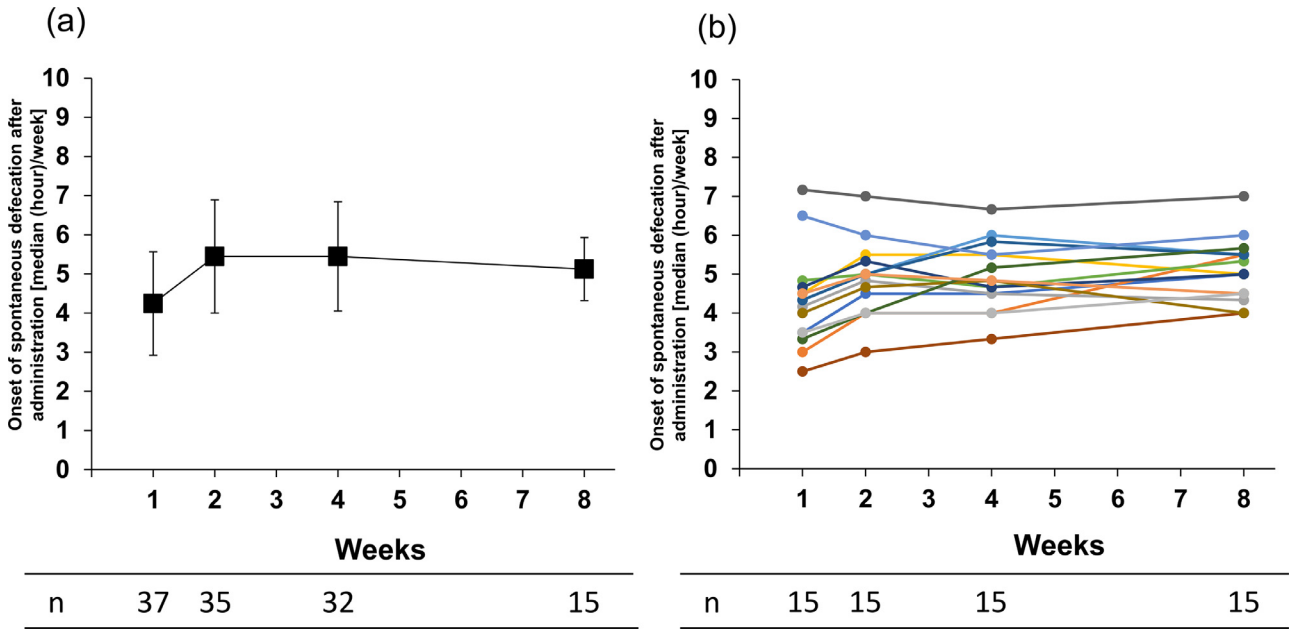

Figure 4. Changes in the time (median) until the first spontaneous defecation after oral administration. The mean values of spontaneous defecation were expressed as mean (SD). The numbers below the graph indicate the number of cases with data. (A) Changes in all patients. (B) Changes in individuals over 8 weeks of treatment.

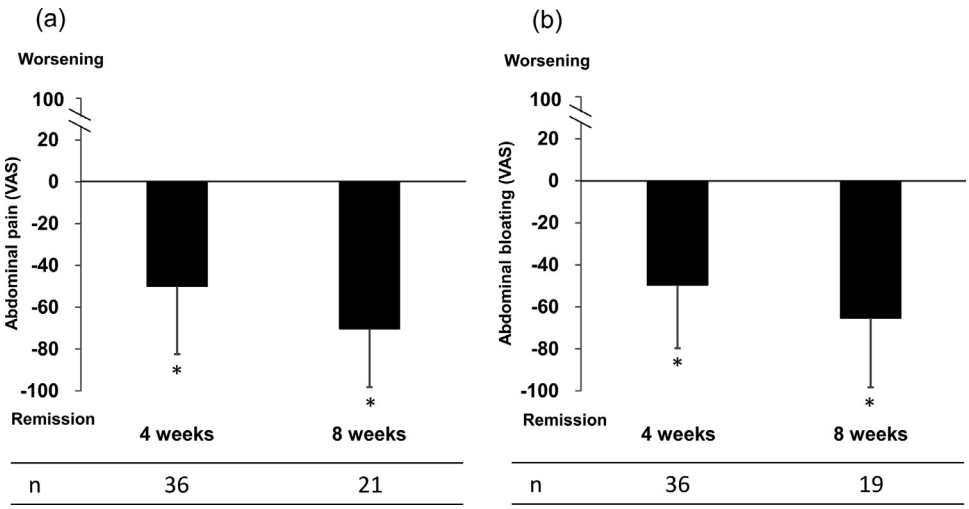

Figure 5. Changes in visual analog scale (VAS) of abdominal pain and bloating at 4 weeks and 8 weeks. The mean values of VAS scores changes were expressed as mean (SD). The numbers below the graph indicate the number of cases with data. (A) abdominal pain. (B) abdominal bloating. $^{*}P < 0.001$, paired t test (comparison with those at the start of treatment).

Changes in abdominal pain and bloating VAS score

Changes in the VAS score of abdominal pain and bloating concomitant with constipation from the start to the 4-week and 8-week treatment visits are shown in Figures 5A and B. Significant improvements in abdominal pain and bloating were observed at 4 weeks (abdominal pain decreased by 50.0% and bloating decreased by 49.7%) and at 8 weeks (abdominal pain decreased by 70.4% and bloating decreased by 65.4%) after treatment.

Total scores and each subscale (physical discomfort, psychosocial discomfort, worries/concerns, and satisfaction) score of the JPAC-QOL and safety profile

Mean (SD) total scores at baseline, 4 weeks, and 8 weeks were 2.2 (0.4), 1.1 (0.5), and 0.7 (0.3), respectively. There was a significant decrease between baseline and 4 weeks (or 8 weeks). Moreover, there was also a significant decrease in the comparison between 4 and 8 weeks. Thus, total score was associated with significantly improved over time (Figure 6A). The 4 subscales—physical discomfort, psychosocial discomfort, worries/concerns, and satisfaction—were also significantly decreased over time compared with the start of treatment (Figures 6B–E). No adverse effects were observed throughout the treatment period (data not shown).

Discussion

Until a few years ago, the drugs used to treat constipation in Japan were mainly osmotic laxatives represented by magnesium oxide and irritant laxatives of the anthraquinone and diphenyl groups. These 2 types of drugs alone cannot sufficiently improve diverse and complex chronic constipation. As a result, patient satisfaction remains low even when treated.[15] Recently, several new agents such as lubiprostone, linaclotide, and elobixibat have been developed and become available for constipation therapy. Different

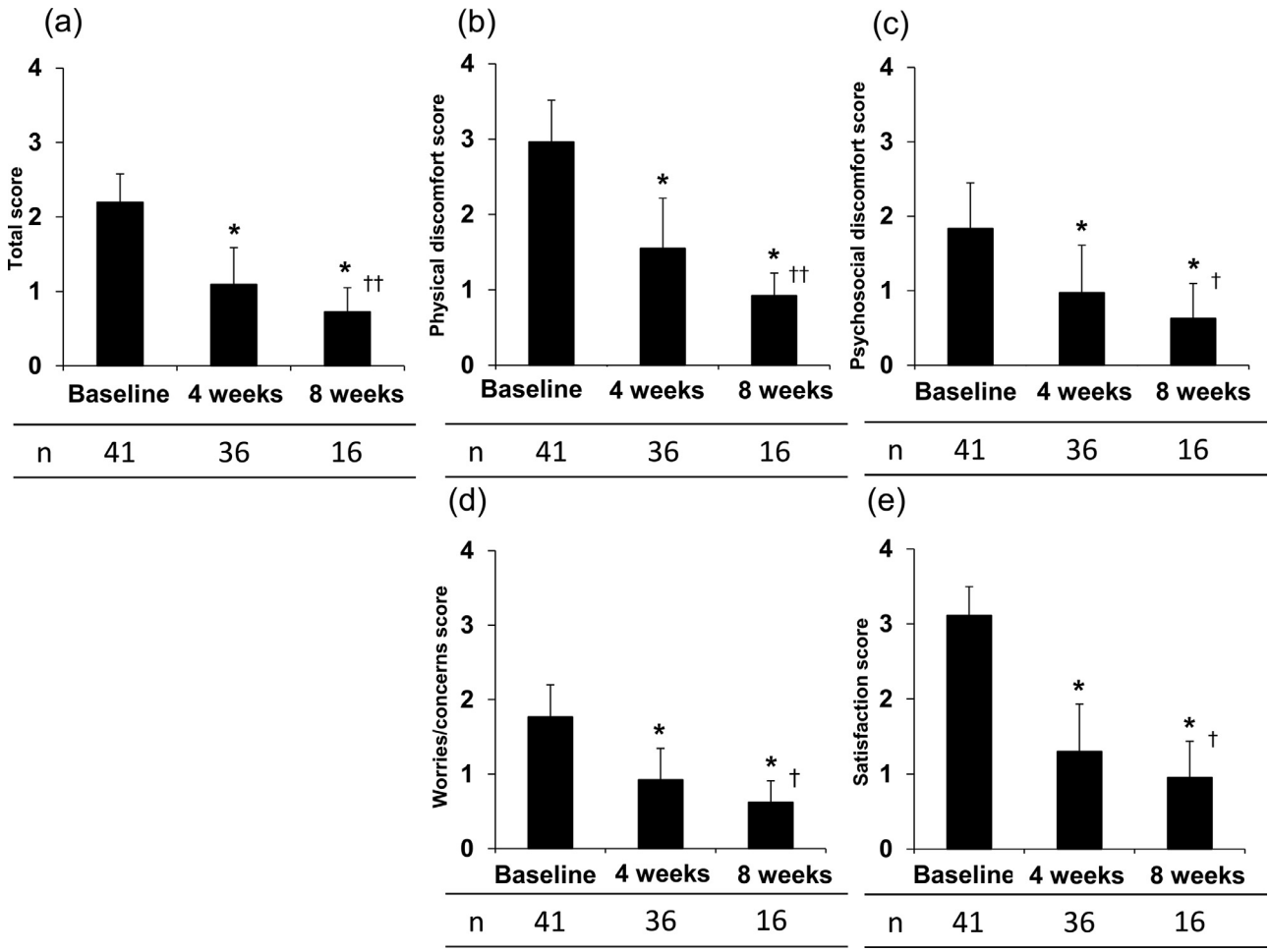

Figure 6. Total scores and each subscale scores of Japanese-Translated Version of Patient Assessment of Constipation Quality of Life Questionnaire (JPAC-QOL) at 4 weeks and 8 weeks. The mean values of JPAC-QOL scores were expressed as mean (SD). The numbers below the graph indicate the number of cases with data. (A) Total. (B) Physical discomfort. (C) Phycological discomfort. (D) Worries/concerns. (E) Satisfaction. $^{*}P < 0.001$, paired t test (comparison with those at the start of treatment). $^{\dagger}P < 0.01$ (comparison with those at 4 weeks of treatment). $^{\dagger\dagger}P < 0.001$ (comparison with those at 4 weeks of treatment).

from the pharmacological functions of other drugs, elobixibat increases bile acid concentration in the colonic lumen via suppression of the reabsorption of bile acids. Bile acids can induce water secretion in the colonic lumen via increased osmotic pressure. Additionally, bile acids can activate transmembrane G protein-coupled receptor 5 present on EC cells and stimulate a release of 5-HT followed by induction of colonic peristalsis. Thus, elobixibat has dual functions for colonic peristalsis via an increase in bile acids in the colonic lumen. However, there has been no report whether different timing such as pre-dinner administration of elobixibat exhibits the similar effects to those in a Japanese Phase III study.[12] Recently, a guanylate cyclase agonist, plecanatide, was approved in the United States. However, it is still unapproved in Japan.

In the present study, we first evaluated whether there are any differences or not in the efficacy of pre-dinner administration of elobixibat for the SBM frequency compared with the conventional administration method. Change in SBM frequency (6.3 times per week, a change from 2.0 to 8.3 times per week) at the first week of pre-dinner administration of elobixibat was similar to that shown in the Phase III study (6.4 times per week, a change from 1.8 to 8.2 times per week).[12] In addition, a high percentage of patients achieved spontaneous defecation within 24 hours (85.4%) and 48 hours (90.2%) and the changes in mean BSFS from the start to 1 week of treatment were also observed. The notable finding that bile acid is physiologically secreted not only after breakfast but also after lunch and dinner[16] may support the present findings. In addition, the time to onset of spontaneous defecation was 4 to 5 hours after pre-dinner administration, which was consistent with previous findings (about 5 hours after pre-breakfast administration).[12] There has been no report on the results of defecation onset over time after the first administration. However, the onset of defecation is much faster than that of conventional constipation drugs taken for a long time.[17] The time until the onset of spontaneous defecation after administration was varied among patients. Such difference may be dependent on the severity of constipation or comorbidities. However, the time to defecation after administration of elobixibat was almost fixed in each individual throughout the observation period. Furthermore, there were no patients who complained of sleep disorder or who could not continue taking pre-dinner elobixibat due to sleep disorder throughout the entire period, although a small number of patients awakened from sleep due to spontaneous defecation. If elobixibat can control fixed-time defecation, the timing of administration of elobixibat is critical for scheduled defecation according to a patient's lifestyle. All these findings indicate that selection of pre-dinner administration of elobixibat would be equivalent and possible for constipation treatment as well as pre-breakfast administration of elobixibat.

Bile acids increase mucosal permeability and may induce visceral hypersensitivity-associated abdominal pain.[18] Indeed, relatively high incidence of abdominal pain as an adverse event was

reported in previous clinical reports using elobixibat.[12] Therefore, increase in bile acid in the colon may trigger aggravation of some abdominal symptoms, particularly abdominal pain. However, pre-dinner elobixibat administration improved abdominal pain and bloating concomitant with constipation in the present study. In addition, the improvements were maintained by continuing intake of this medicine. This finding is clinically important because the effects on abdominal symptoms concomitant with constipation have not yet been evaluated. Because the present study showed the improvement of subjective symptoms such as abdominal pain and bloating in patients with chronic constipation, it may be interesting to address a possibility that elobixibat is also effective in patients with irritable bowel syndrome with constipation (IBS-C). However, IBS-C patients were excluded from this study. So, it is necessary to conduct a separate clinical study using elobixibat for patients with IBS-C.

Pre-dinner administration of elobixibat was associated with improved total score and subscales of JPAC-QOL until 8 weeks in this study. Its efficacy was also consistent with the previous findings, although the examined duration is shorter than that of the Japanese long-term treatment studies that lasted up to 52 weeks.[12,19] Elobixibat increased the frequency of completely SBM; in other words, patients with constipation may defecate without a feeling of residual stool. In addition, elobixibat affects the threshold for intracolonic pressure or chemical stimulation for colonic mucosa.[20] There may also be differences in the mucosal threshold for visceral sensation by increased concentration of bile acid in the colon between the evening and the morning. All these physiological phenomena may contribute to relief of symptoms and better QOL. However, detailed mechanism(s) of elobixibat for improving abdominal symptoms and QOL remain to be elucidated.

In this study, the number of patients at 4 weeks was quite different from the number at 8 weeks. We confirmed via clinical chart that patients, excluding those who discontinued, continued to take elobixibat and their symptoms improved. Unfortunately, the data of 17 patients at 8 weeks were incomplete. So, we could evaluate the data of only 19 patients at 8 weeks. This is a limitation of this retrospective chart review. There were no patients with soiling. However, we might have missed the opportunity to find out because we had no method to identify it. Additionally, there was no action for the 2 patients who did not come to the hospital. Thus, we did not know the details for these 2 patients. This study is a retrospective study of patients with chronic constipation who visited our clinic and took elobixibat before dinner. We explained to patients that elobixibat should be taken before dinner and confirmed it by interview at every visit. However, we did not check about the exact time when each patient actually took elobixibat. Therefore, this is another limitation of this study.

This is the first report showing that pre-dinner administration as well as pre-breakfast administration of elobixibat is effective for chronic constipation in actual clinical settings. In addition to defecation frequency and BSFS, sufficient improvement in abdominal pain and bloating would give patients satisfaction over time. Thus, a preferable management of defecation would also provide a better QOL to patients with chronic constipation.

Conclusions

Pre-dinner administration of elobixibat for patients with chronic constipation improved the frequency of SBM and BSFS, and reduced subjective symptoms such as abdominal pain and bloating. Present results also suggest that continuation of elobixibat could further improve both symptoms and QOL. Although there were differences in the spontaneous defecation onset time among individuals, it tended to be fast and fixed for each individual taking elobixibat. Therefore, a study of planned defecation along with the patients' lifestyle is expected to be conducted.

Declaration of Competing Interest

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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