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Original Research Article

Efficacy and Safety of Elobixibat in Elderly Patients with Chronic Constipation: A Single-center, Observational Study

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Abstract

Objectives: A retrospective, observational study was conducted to examine the efficacy and safety of elobixibat, a novel therapeutic agent for chronic constipation, in Japanese elderly patients aged ≥ 65 years with chronic constipation.

Methods: The study was conducted at Kunimoto Hospital. Patients who visited the hospital from April 2018 to March 2019 due to symptoms of chronic constipation and who took elobixibat were enrolled. The outcome measures were changes in the Constipation Scoring System (CSS) score and the Bristol stool form scale (BSFS) before and after elobixibat administration.

Results: The study included 150 patients. The total CSS score significantly improved from 11.7±4.5 at baseline to 9.3±5.2 two weeks after drug administration. The improvement was confirmed in six out of eight CSS items. The BSFS at baseline of 2.5±1.8 was improved to 3.4±1.7 two weeks after treatment, nearly close to the normal stool consistency of 4. Adverse reactions were observed in 18 of 150 patients (12.0%) with 21 events, most commonly diarrhea in nine patients (6.0%) and abdominal pain in eight patients (5.3%).

Conclusions: Elobixibat improved not only the frequency of bowel movements but also alleviated various symptoms of constipation, such as difficulty with evacuation and sensations of incomplete evacuation in elderly patients with chronic constipation. All adverse drug reactions were mild in severity with no safety concerns.

Keywords

chronic constipation, elderlies, elobixibat, laxatives, evacuation difficulty

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Introduction

According to the summary report of the "Prevalence of Constipation" from the 2016 Comprehensive Survey of Living Conditions in Japan, the prevalence of constipation has increased with age, with a rate of 65.0 (per 1000 population) in men and 80.5 in women over the age of 65 years, and 96.2 in men and 104.6 in women over the age of 75 years[1].

Chronic constipation is commonly treated with osmotic or stimulant laxatives in Japan with a rate of 81% and 51%, respectively, for elderly people aged ≥ 65 years[2]. The most commonly prescribed osmotic laxative in Japan is magnesium oxide. However, due to the possible adverse effects of hypermagnesemia in elderly patients, magnesium oxide has to be administered carefully, with a recommendation to measure magnesium levels periodically[3]. As for stimulant laxatives, concerns of drug resistance, dependence, and

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pseudomelanosis due to their long-term, continuous usage has led to their proposed use on as-needed or short-term use basis[3].

Elobixibat hydrate (hereinafter referred to as elobixibat), a novel therapeutic agent for the treatment of chronic constipation, was launched in April 2018 in Japan, ahead of the rest of the world. It inhibits the ileal bile acid transporter (IBAT) (also known as apical sodium-dependent bile acid transporter), which is expressed in the epithelial cells of the terminal ileum and reduces the reabsorption of bile acids, thereby increasing water secretion into the large intestinal lumen and inducing high amplitude propagating pressure waves. In other words, elobixibat has dual action, i.e., water secretion in the large intestine and promotion of bowel movement[4-7]. It improves constipation by action mechanisms that are different from conventional drugs for constipation, suggesting a plausible new therapeutic option for patients with constipation.

Elobixibat was found to improve the frequency of spontaneous defecation and stool consistency significantly, with favorable tolerability as compared to placebo in a randomized, placebo-controlled, double-blind study in patients with functional chronic constipation[8]. Likewise, an open-label, long-term study confirmed the efficacy and safety of elobixibat for 52 weeks of treatment[8]. On the other hand, the mean age of the subjects in these studies was 43.0 and 43.9, respectively, indicating insufficient clinical experience with elobixibat in elderly patients aged ≥ 65 years. Here, we examined the efficacy and safety of elobixibat in elderly patients with chronic constipation.

Methods

1. Study design

This was a retrospective, observational study to analyze the effects of elobixibat on chronic constipation based on the medical records of patients who visited our hospital. This study was performed in accordance with the Declaration of Helsinki, and it complied with the study protocol and "ethical guidelines for medical and health research involving human subjects". This study was approved by the Institutional Review Board of the Yamauchi Clinic (approval code: 2019-06-00065), and the study was registered with the Japanese University Hospital Medical Information Network (UMIN000037286).

Since this is a retrospective, observational study using existing data collected by the hospital, written consent was not obtained from the patients in advance. Therefore, the study contents were posted in the hospital to inform the subjects, providing them with the opportunity to refuse the use of their data in the study.

2. Study participants

The study included patients aged ≥ 65 years with chronic constipation who were confirmed to have started treatment with elobixibat between April 2018 and March 2019 at Kunimoto Hospital. Based on the Rome IV criteria for the diagnosis of chronic constipation, patients with chronic constipation who met at least two of the following six items were selected:

a. Straining during more than one-fourth of defecation episodes,

b. Lumpy or hard stools (Bristol stool form scale (BSFS)[9]: 1 or 2) during more than one-fourth of defecation episodes,

c. A sensation of incomplete evacuation during more than one-fourth of the defecation episodes,

d. A sensation of anorectal obstruction/blockage or difficulty with evacuation during more than one-fourth of the defecation episodes,

e. Manual maneuvers or enemas/suppositories to facilitate evacuation during more than one-fourth of defecation episodes, and

f. Fewer than three spontaneous bowel movements per week.

Patients with symptoms a, c, d, and e were classified as having evacuation difficulty type, those with symptoms f as having infrequent bowel motions type, and those with both symptoms as having mixed type.

Patients were excluded if they met with any of the following criteria:

1. History of hypersensitivity to elobixibat,
2. Confirmed or suspected intestinal obstruction due to tumor or hernia,
3. Constipation due to possible organic disease, and
4. If the attending physician determined that the administration of elobixibat was inappropriate.

3. Method of drug administration

Elobixibat was orally administered at a dose of 10 mg (5 mg × 2 tablets) once daily before meals. The dosage was adjusted between 5 and 15 mg per dose based on the symptoms. The combination use of drugs already used to treat constipation was allowed.

4. Evaluation of parameters

The following variables, recorded in the medical record in our routine practice that could be extracted from the medical record, were collected: background characteristics of the patients; the scores of Constipation Scoring System (CSS)[10]; and the BSFS values.

The outcome measures were comparison of the CSS total score and the CSS sub-scores between baseline and two weeks after drug administration. We also compared the

Table 1. Patients' Baseline Demographics (n=149).

Parameter	Classification	Number of patients (%)
Sex	Men	59 (39.6)
	Women	90 (60.4)
Age	65-74 yrs.	52 (34.9)
	≥75 yrs.	97 (65.1)
BMI	<25	113 (75.8)
	≥25	31 (20.8)
Pretreatment for chronic constipation within the past 2 weeks	None	43 (28.9)
	Yes	106 (71.1)
Concomitant medications for constipation	None	98 (65.8)
	Yes	51 (34.2)
BSFS	BSFS 1-2	88 (59.1)
	BSFS 3-5	41 (27.5)
	BSFS 6-7	17 (11.4)
Type of constipation	Evacuation difficulty type	87 (58.4)
	Mixed type	62 (41.6)
Dosage (mg/day)	5 mg/day	15 (10.1)
	10 mg/day	115 (77.2)
	10 mg ⇒ 5 mg/day	19 (12.8)

BMI: body mass index; BSFS: Bristol stool form scale.

BSFS values between baseline and two weeks after drug administration. The safety endpoints were adverse reactions, including their incidence, and the discontinuation rate.

5. Statistical analyses

For the CSS and the BSFS, we used the Wilcoxon signed-rank test for the comparative analysis. The results are represented as the mean±SD. The two-sided significance level was set at 5%. All statistical analyses were performed using R software version 3.4.0 (The R Development Core Team) or later.

Results

The study enrolled 150 patients who fulfilled the appropriate criteria within the study period. The safety evaluation included all 150 patients who received elobixibat at least once, while the efficacy analysis included 149 patients who had CSS scores. Discontinuation from the study was noted in 8 patients (5.3%) due to adverse reactions (diarrhea) in 3, adverse reactions (abdominal pain) in 1, self-determination in 2, and ineffective response in 2. Dose interruption was observed in 3 patients (2.0%), all of which were for personal reasons.

1. Patient demographics

The study included 90 women (60.0%) and 60 men (40.0%) aged 65-95 years (77.7±7.2 years). The mean height was 155.8±8.6 cm, the body weight was 55.3±9.7 kg, and the BMI was 22.78±3.60 kg/m^2. Complications, including hypertension and dyslipidemia, were observed in 137 patients (91.3%).

Table 1 shows demographics of the patient population (n=149). Constipation was classified into evacuation difficulty type (n=87) and mixed type (n=62). In the survey of "prior pharmacotherapy for constipation", conducted within two weeks before initiating elobixibat, 106 patients (71.1%) had a pretreatment history. Switching to elobixibat was noted in 55 patients, including BSFS 6-7 patients, while 51 patients used the same pretreatment concomitantly. The breakdown of concomitant drugs was 30 cases of suppositories, 24 cases of stimulant laxatives, 5 cases of osmotic laxatives, and others.

2. Efficacy to improve constipation

The total CSS score of 11.7±4.5 at baseline was significantly improved to 9.3±5.2 two weeks after drug administration (Table 2). After each item, an improvement was observed in the stool frequency, difficulty with evacuation, sensation of incomplete evacuation, time to evacuation, evacuation support, and the number of times/24 hours without bowel movement despite going to the bathroom; however, there was no improvement for abdominal pain. As for the duration of disturbed defecation, no test was conducted since the treatment period was two weeks. The BSFS at baseline of 2.5±1.8 was improved to 3.4±1.7 two weeks after treatment, nearly close to the normal stool consistency of 4 (Table 3).

Table 2. Changes in the CSS before and after Treatment (n=149).

	Baseline	Week 2 post-administration	*p*-value
Total CSS score	11.7 (4.5)	9.3 (5.2)	<0.001
Stool frequency	0.7 (1.0)	0.5 (0.8)	<0.001
Difficulty in evacuation	2.8 (1.3)	2.1 (1.6)	<0.001
A sensation of incomplete evacuation	2.2 (1.6)	1.7 (1.6)	<0.001
Abdominal pain	0.7 (1.3)	0.8 (1.3)	0.237
Time to evacuation	1.2 (1.1)	0.9 (0.9)	<0.001
Assisted bowel movements (laxatives, enemas, or manual maneuvers)	1.5 (0.6)	1.1 (0.8)	<0.001
Number of times/24 hours without bowel movement despite going to the bathroom	0.9 (0.8)	0.7 (0.7)	0.001
Duration (years) of suffering from disturbed defecation	1.6 (1.5)	1.6 (1.4)	—

Data are shown mean (SD).

CSS: constipation scoring system.

Table 3. Changes in the BSFS before and after Treatment.

	Baseline	Week 2 post-administration	*p*-value
BSFS value	2.5 (1.8)	3.4 (1.7)	<0.001

Data are shown mean (SD). The BSFS score was measured in 139 patients at baseline and at Week 2 after administration.

BSFS: Bristol stool form scale

3. Efficacy by the immediate pretreatment and the concomitant medications

The total CSS scores improved significantly, regardless of the immediate pretreatment within two weeks or the concomitant medications (Table 4).

4. Adverse drug reactions

Adverse drug reactions were observed as 21 events in 18 patients (12.0%) [6 (4.0%) in men and 12 (8.0%) in women] (Table 5). The most common events were diarrhea (n=9, 6.0%) and abdominal pain (n=8, 5.3%). Of the 18 patients who had adverse reactions, three (with diarrhea) and one (with abdominal pain) discontinued elobixibat treatment, while seven reduced the dosage. All events were mild in severity, with no serious reactions.

Discussion

We described the results of a retrospective observational study with elobixibat in Japanese elderly patients aged ≥ 65 years with chronic constipation. Evaluation using the CSS showed that elobixibat improved not only stool frequency, but also the overall symptoms of constipation with no safety concerns.

Elobixibat is a low-molecular compound that has been structurally developed based on a compound found in the search for a hyperlipidemia agent. It is a therapeutic agent for chronic constipation, containing elobixibat as an active ingredient inhibiting IBAT[4]. Elobixibat inhibits the reabsorption of bile acids in the terminal ileum, thereby increasing the volume of bile acids flowing into the large intestinal lumen. The bile acids reaching the large intestine result in secretion of fluid into the lumen, promoting the peristaltic movement induced by the colonic mucosa. Therefore, some patients may experience abdominal pain; however, the amplitude of the peristaltic contraction wave induced by elobixibat is not different from a physiological contraction wave[7]. Hence, discontinuation of the therapy due to adverse reactions is rare[8].

Chronic constipation is often classified as slow transit constipation, normal transit constipation, or defecatory disorder in Europe and the United States[11]; however, these classifications have not been adopted in Japan because transit studies are not covered by insurance. Therefore, in the "Guideline for the Management of Chronic Constipation 2017" in Japan, constipation symptoms are classified into infrequent bowel motions type and evacuation difficulty type based on the symptoms[3]. In patients with evacuation difficulty type, oral laxatives are less effective, resulting in the frequent use of suppository or enema support[3,10]. In addition, the rate of evacuation difficulty type increases in the elderly due to a lowered rectoanal sensation or reduced abdominal muscle strength[3]. Thus, elderly patients may experience poor efficacy with conventional osmotic laxatives or prosecretory agents. Consequently, based on our results, it is very meaningful that the dual actions of elobixibat were effective for difficulty in evacuation in the elderly. Injecting bile acids into the rectums of healthy volunteers reportedly reduces the rectal sensation threshold, suggesting elobixibat is a more appropriate drug for the elderly patients with diffi-

Table 4. Changes in the CSS by Pretreatment and Concomitant Medications (n=149).

Parameter	Classification	Number of patients	Baseline	Week 2 after administration	*p*-value
Immediate pretreatment within 2 weeks	Yes	106	12.2 (4.6)	10.2 (5.1)	<0.001
	No	43	10.4 (7.0)	7.0 (4.6)	<0.001
Concomitant medication for constipation	Yes	51	11.5 (4.2)	8.1 (5.1)	<0.001
	No	98	11.7 (4.7)	9.9 (5.2)	<0.001

Data are shown mean (SD).

Statistical analysis was performed using the Wilcoxon signed rank test.

CSS: constipation scoring system.

Table 5. Breakdown of Adverse Drug Reactions (n=150).

Number of subjects with adverse reactions	18
Number of adverse reactions	21
Type of adverse drug reaction	Event (%)
Diarrhea	9 (6.0)
Abdominal pain	8 (5.3)
Nausea	2 (1.3)
Anal pain	1 (0.7)
Fecal incontinence	1 (0.7)

culty in evacuation since it can improve reduced rectal sensation[6].

In our study, the total CSS scores improved significantly regardless of immediate pretreatment or concomitant medications. These results may be explained by the fact that elobixibat has different mechanisms of action than those of conventional drugs to relieve constipation, so they may exert efficacy in patients who do not respond well to existing drugs. Furthermore, its stable symptomatic improvement was observed up to week 52 in a long-term study[8], so it is expected to play a role as a stimulant laxative which can be used on a long-term basis.

Because bile acids are secreted when stimulated by diet, elobixibat is most effective when taken 20-30 minutes before meals. The rate of inhibition of bile acid absorption by elobixibat is 70% at 30 minutes after administration in mice[12]. As for the risk of colorectal cancer associated with the increase in bile acids, an increase in the influx of bile acids into the large intestine would not induce carcinogenesis according to the findings of a long-term, randomized controlled trial examining the preventive effects of inhibiting the absorption of the lipid system by ileectomy on arteriosclerosis that reported no significant difference in cancer mortality compared to the control group[13].

In a placebo-controlled, randomized, double-blind study conducted in patients with a mean age of 43 years, the safety analysis reported the incidence of adverse events of 8% in the placebo group and 30% in the 10 mg elobixibat group[8]. The detailed analysis revealed abdominal pain in 19%, diarrhea in 13%, lower abdominal pain in 4%, and nausea in 3% of the patients[8]. In our study, the incidence of adverse reactions in the elderly aged ≥ 65 years was as low as 12.0%, with an infrequent incidence of each reaction, demonstrating no safety concerns. Besides, the discontinuation due to adverse reactions was observed in only 4 patients (2.7%) which were due to diarrhea and abdominal pain.

The limitations of this study include its open observational design, absence of a control group, short observation period, and the inclusion of only Japanese patients. Thus, the results should be reconfirmed by conducting further randomized controlled trials. However, we believe that a case study closer to clinical practice was conducted successfully.

In conclusion, our results indicate that elobixibat increases the stool frequency and improves symptoms associated with constipation, such as difficulty with evacuation and a sensation of incomplete evacuation in general clinical practice. In addition, there was no particular concern with regard to the safety of elobixibat in elderly patients, suggesting a promising drug therapy which can be continued.

Conflicts of Interest

This work was supported by funding from Mochida Pharmaceutical Co., Ltd., and EA Pharma Co., Ltd. Tatsuya Abe received a lecture fee from Mochida Pharmaceutical Co., Ltd.

Author Contributions

T. Abe: Substantially contributed to the conception and design, acquisition, analysis, database maintenance, and data interpretation; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

M. Kunimoto: Substantially contributed to the conception and design, supplying patients, analysis, and data interpretation; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

Y. Hachiro: Substantially contributed to the conception and design, acquisition, obtaining follow-up data and analy-

sis; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

K. Ohara: Substantially contributed to data acquisition; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

M. Inagaki: Substantially contributed to data acquisition; critically drafted and revised the article for important intellectual content; and gave final approval of the version to be published.

M. Murakami: Substantially contributed to data acquisition; critically drafted and revised the article for important intellectual content; provided criticism of the article; and gave final approval of the version to be published.

Approval by Institutional Review Board (IRB)

Institutional Review Board of Yamauchi Clinic (Approval Code: 2019-06-00065)

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