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Elobixibat improves rectal sensation in patients with chronic constipation aged ≥60 years: a randomised placebo-controlled study

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ABSTRACT

Objective High rectal sensory thresholds (RSTs) are associated with chronic constipation (CC), especially in older patients. Bile acids (BAs) affect the RSTs of healthy individuals. Here, we aimed to investigate the effects of the BA transporter inhibitor elobixibat in patients with CC aged ≥60 years.

Design We prospectively compared the RSTs of 17 patients with CC aged ≥60 years with those of 9 healthy individuals of the same age range. We next performed a prospective, randomised, parallel-group, double-blind, placebo-controlled clinical trial of 17 patients with CC who administered elobixibat or placebo daily for 1 week. Using barostat methodology, their first constant sensation volume (FCSV), defaecatory desire volume (DDV), and maximum tolerable volume (MTV) thresholds; their rectal compliance; and their faecal BA concentrations were measured before and after treatment.

Results There were no significant differences in the RSTs of healthy individuals and patients with CC, but all of these tended to be higher in the latter group. Elobixibat increased the desire to defaecate, significantly reduced the threshold for FCSV (p=0.0018), and tended to reduce the threshold for DDV (p=0.0899) versus placebo. However, there were no differences in the MTV or rectal compliance of the two groups. The total faecal BA concentration increased, and particularly that of secondary BAs in the elobixibat group. Elobixibat was most efficacious in participants with a longer duration of CC and a history of treatment for CC.

Conclusion Elobixibat reduces the RSTs of patients with CC aged ≥60 years, which may be important for its therapeutic effects.

Trial registration number jRCTs061200030.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rectal sensory thresholds (RSTs) are high in chronic constipation (CC), especially in older patients.
⇒ In recent years, a few attempts to improve RSTs have been reported, but there have been no reports of pharmacologically induced improvements in RSTs.
⇒ The effects of high faecal bile acid concentrations on RSTs in CC are unknown.

WHAT THIS STUDY ADDS

⇒ Elobixibat significantly reduces the volume associated with the desire to defaecate; and is most efficacious in patients with a long duration of CC and a history of treatment of CC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The improvements in RSTs may be at least in part responsible for the beneficial effects of elobixibat on constipation.

INTRODUCTION

Chronic constipation (CC) is more common in older people,[1] and it is often clinically significant because it is associated with cardiovascular disease, stroke,[2] chronic kidney disease,[3] and prefrailty.[4] Although the pathophysiology of CC varies, slow colonic transit and high rectal sensory thresholds (RSTs) are important in older patients[5] ; and the RSTs of older patients are higher than those of younger ones.[6]

When the rectal wall is stretched, the pelvic nerves within are stimulated in response to an increase in intrarectal pressure. Typically, 50 mL of faeces is required to activate mucosal receptors, and 200 mL activates stretch receptors, producing an intense sensation.[7] This stimulus is transmitted to the hypothalamus via the defaecation centre in the sacral medulla, and then to the sensory area of the cerebral cortex, resulting in a desire to defaecate. To evacuate faeces comfortably and fully, it is essential that the faecal mass is perceived appropriately in the distal colon and rectum and that defaecation is prompt.[8] Thus, the RSTs must be normal, and high RSTs (rectal hyposensitivity (RH)) are associated with CC.[8] When the RSTs are high, there is no appropriate desire to defaecate and faeces

remain in the rectum. In a recent large survey, patients with CC were shown to have a significantly weaker desire to defaecate than healthy individuals, and the recovery of this desire to defaecate was associated with patient satisfaction.[9] A previous study showed that RH is present in 23% of adults with CC,[10] and another recent large study of intractable functional constipation identified RH in 25%, suggesting that high RSTs are important in severe CC.[8] However, there are no approved medications for the treatment of RH.

Bile acids (BAs) regulate cholesterol homeostasis and the digestion and absorption of lipids in the small intestine. When unabsorbed BAs enter the colon, they bind to transmembrane G protein-coupled receptor 5 (TGR5) on epithelial cells, activating cystic fibrosis transmembrane conductance regulator, and promoting chloride secretion and the release of 5-hydroxytryptamine, which acts on sensory nerves in the submucosa, triggering peristalsis.[11] BAs, as detergents, also alter intestinal permeability through the autophosphorylation of epidermal growth factor receptors, the dephosphorylation of occludin, and the rearrangement of tight junctions,[12] and are also involved in secretion and colonic motility.[13] Thus, an increase in the colonic concentrations of BAs following treatment with the ileal BA transport inhibitor elobixibat results in an increase in the number of bowel movements and improves faecal consistency, but also improves the quality of life (QOL) of patients with CC.[14 15] Recently, BAs were shown to affect the RSTs of healthy people,[13] but it is unknown whether elobixibat affects the RSTs of patients with CC.

In the present study, in Experiment 1, we performed a prospective study to identify differences in the RSTs of healthy individuals and patients with CC, all of whom were ≥60 years old. The reasons we chose a cut-off of ≥60 years are that there is likely to be less contamination with cases of irritable bowel syndrome and to create a sample of patients with similar characteristics to evaluate the pathophysiology of CC. In Experiment 2, we compared the effects of elobixibat and placebo on the faecal volume associated with a desire to defaecate (DDV, the primary outcome) and on the RSTs and bowel movements of patients with CC (the secondary outcomes), and identified the clinical characteristics of patients that are associated with the beneficial effects of elobixibat on rectal sensation.

MATERIALS AND METHODS

Ethics

The study conformed with the principles of the Declaration of Helsinki and the Ethics Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare, Japan. The study was approved by our Clinical Research Review Committee (approval no: CRB6200004), and written informed consent was obtained from all the participants. All authors had access to the study data (JRCT ID: jRCTs061200030, Japan Registry of Clinical Trials, https://rctportal.niph.go.jp/en/detail?trial_id=jRCTs061200030) and reviewed and approved the final version of the manuscript.

Experiment 1

Study design

We prospectively compared the RSTs of patients with CC who met the Rome IV criteria[16] and healthy individuals without CC, all of whom were ≥60 years old.

Recruitment method and inclusion/exclusion criteria

The participants were recruited online and the principal investigator explained the study to individuals who met the eligibility criteria at visit #1. Each participant received an identification code and completed an eligibility form and a defaecation diary.

The inclusion criteria for patients with CC were as follows: (1) fulfilment of the Rome IV criteria for functional constipation[16]; (2) age ≥60 years; and (3) the provision of written consent. The exclusion criteria were as follows: (1) patients with or suspected of having constipation owing to any organic disease or outlet obstructive constipation; (2) suspected biliary obstruction or a low level of bile secretion; (3) inability to take bisacodyl suppository; (4) malignancy; (5) a history of hypersensitivity to elobixibat; and (6) severe renal disease (creatinine >2.00 mg/dL), severe hepatic disease (total bilirubin >3.0 mg/dL, or aspartate aminotransferase or alanine aminotransferase activity >100 U/L), or severe cardiac disease.

The inclusion criteria for the healthy individuals were as follows: (1) bowel movements almost daily for ≥6 months, (2) age ≥60 years, (3) provision of written consent, and (4) absence of comorbidities.

Experimental protocol

The daily defaecation habits of the participants were recorded at visit #1, when they were temporarily registered. After a 1-week observation period, they were officially enrolled and underwent a physical examination, blood testing to determine eligibility and RST testing, as in Experiment 1 (figure 1A). During the observation period, the participants were asked to stay at home as usual; on the day before the examination, they were asked to stay at a designated hotel and eat a designated meal (a standardised dinner (623 kcal, protein 17.4 g, and fat 22.8 g) and breakfast (682 kcal, protein 27.4 g, and fat 22.7 g) on the day before and the day of testing); and on the day of the examination, they were asked to come to the hospital.

Experiment 2

Study design

We performed a prospective, randomised, parallel-group, double-blind, placebo-controlled clinical trial of ≥60-year-old patients with CC who met the Rome IV criteria[16] for functional constipation at our institution between October 2020 and May 2022. The patients with

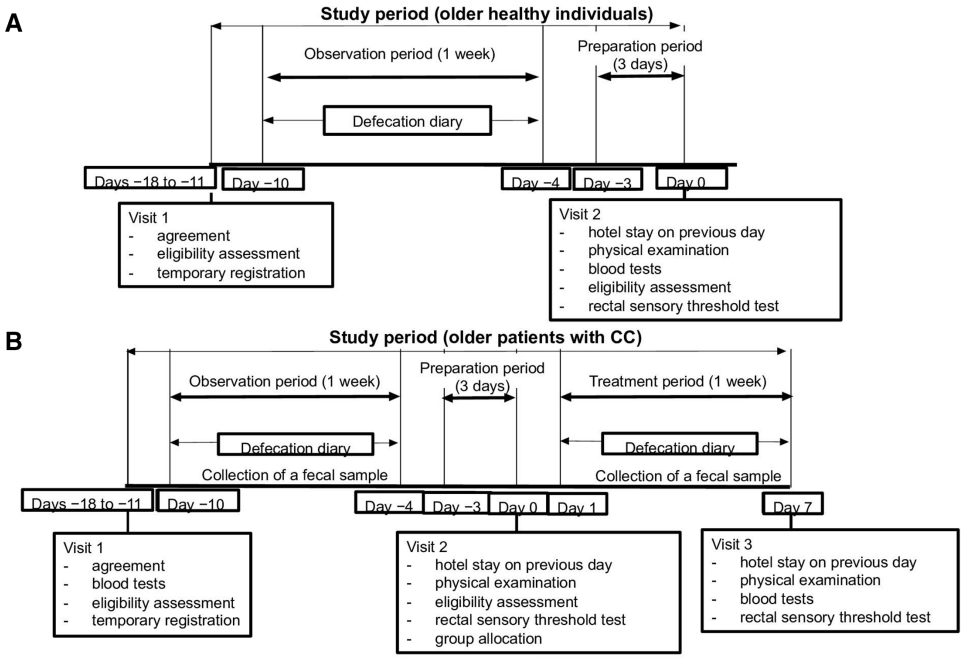

Figure 1 Experimental protocols. (A) Protocol for Experiment 1. (B) Protocol for Experiment 2.

CC aged ≥60 years who were enrolled in Experiment 2 had previously participated in Experiment 1.

Recruitment method and inclusion/exclusion criteria

The participants were recruited online and the principal investigator explained the study to individuals who met the eligibility criteria at visit #1. Each participant received an identification code and completed an eligibility form and a defaecation diary.

Experimental protocol

The participants' defaecation habits were recorded, blood testing was performed, and the participants were temporarily registered at visit #1 (figure 1B). After a 1-week observation period, they were officially enrolled and their symptoms were recorded at visit #2 (baseline). They underwent a physical examination and RST testing, then were randomly assigned to take 10 mg placebo or elobixibat daily for 1 week. Allocation was performed by the Satt Co.,Ltd (Tokyo, Japan), which was not directly involved in the study, using a stratified substitution block method, with sex as the allocation factor. The participants were subsequently blinded to the identity of the intervention. A placebo that could not be distinguished from the study drug was used.

The RSTs were measured again after treatment for 1 week. The BA concentrations of random stool samples were measured twice, at any time during the observation period and within 4–6 days of the commencement of drug administration. If required, bisacodyl could be taken once or twice during this period.

During the 7-day trial, the participants were asked to stay at home (days 1–5) as usual, stay at a hotel the day before the examination, eat a designated meal (day 6) and come to the hospital on the day of the examination (day 7).

Sample size

We estimated the detectable effect size with 80% power based on two-sample t-testing with a two-tailed α level of 0.05. The number of cases required was determined using the difference in the mean values previously obtained before and after the administration of chenodeoxycholic acid (CDCA),[13] because there have been no placebo-controlled studies of rectal sensation using elobixibat. This was calculated as ≥4 for one group and ≥8 for both groups, and therefore a target of n=10/group was adopted. We anticipated that a simple two-sample t-test would provide ≥80% power to detect similar pairwise differences using a pooled estimate of variation across two groups.

RST testing

RST testing was performed at visits #2 and #3. The test at visit #3 was performed ~5 hours after the administration of the study medication. The RSTs were measured using a validated rapid barostat bag before and after treatment.[17] A 10 cm thin-walled bag (S7-BR-1018, Mui Scientific, Mississauga, ON, Canada) with a maximum volume of 700 mL was used, with a silicone barostat catheter. The participants were pretreated as previously described.[18] They consumed a standardised dinner (623 kcal, protein 17.4 g, and fat 22.8 g) and breakfast (682 kcal, protein 27.4 g, and fat 22.7 g) on the day before and day of testing, respectively, did not eat for the preceding ≥4 hours, drank only water, and underwent a glycerine enema ~1 hour beforehand. As recommended,[19] the participants were positioned in the left lateral 20° Trendelenburg position and the bag was inserted so that the proximal end was

5 cm from the anus. An RBB Pump (P1-RBB-1, Mui Scientific) was used to inflate the bag at 120 mL/min, and the participants identified three well-established sensory thresholds: first constant sensation volume (FCSV), defaecatory desire volume (DDV), and maximum tolerable volume (MTV). Three measurements were made at 5-minute intervals, with one or two additional measurements if the measured values were highly variable, and median values were calculated. In addition, the pressure and volume data collected during these sensation studies were used to assess rectal compliance.

Measurement of faecal BA concentration

BA measurements were performed on faecal samples that were anonymously mailed to a laboratory (TechnoSuruga Laboratory Co., Ltd, Shizuoka, Japan). The total faecal BA concentration was defined as the sum of the individual BA concentrations, measured by liquid chromatography-quadrupole time-of-flight mass spectrometry. The faecal primary BAs were defined as cholic acid (CA)+CDCA, and the faecal secondary BAs as deoxycholic acid (DCA)+lithocholic acid (LCA). Faecal BA concentrations below the lower limit of quantification were imputed as missing values. The results are expressed as the amounts of total BAs, conjugated moieties, and primary and secondary BAs per gram faeces.

Statistical analysis

Normally distributed continuous variables are reported as mean±SD, and those with a skewed distribution are reported as median (IQR). Analysis of covariance (ANCOVA) models with baseline values as a covariate were created, and the differences between the groups and the associated 95% CIs were calculated. The paired Student's t-test was used for before/after data, and the two-sample t-test was used for comparisons with healthy adults, other than for the score on the Bristol Stool Scale, differences in which were identified using the Wilcoxon rank-sum test. We used the full analysis set (FAS), consisting of all the registered participants (n=17), except for those lacking efficacy data, to analyse efficacy. To test the robustness of the findings, a per-protocol set (PPS) was also analysed (n=16). A safety analysis was performed using data from participants who administered the drug at least once. SAS (V.9.4+; Cary, North Carolina, USA) and R (V.4.0.2+; R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis. P<0.05 was regarded as indicating statistical significance.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Experiment 1

Participants

Ten healthy individuals were assessed for eligibility, and one was excluded because he was taking medication for hypertension. Twenty patients were assessed for eligibility and three were excluded, two because of a score on the Bristol Stool Scale ≥6 and one because she took medication that was not permitted. Thus, 17 participants were enrolled. Consequently, 9 healthy individuals and 17 patients were enrolled (table 1). The patients enrolled were treatment naïve with respect to CC.

Differences in the RSTs of the two groups

All of the RST thresholds (DDV, FCSV, and MTV) tended to be higher in the patients with CC than in the healthy individuals, but there were no significant differences between the groups (table 2).

Table 1 Baseline characteristics of the participants in each group

	CC		Healthy individuals (n=9)
	Elobixibat (n=9)	Placebo (n=8)	
Sex (M/F)	5/4	4/4	7/2
Mean age (median, IQR)	69.0 (66.0–73.0)	67.0 (64.0–69.0)	66.0 (63.0–71.0)
Height (cm) (median, IQR)	165.9 (159.7–168.3)	158.7 (151.6–166.4)	167.3 (159.3–168.0)
Body mass (kg) (median, IQR)	65.1 (54.9–67.9)	49.9 (46.6–66.3)	60.4 (54.9–64.6)
Pre-existing condition	4 (44.4%)	4 (50.0%)	5 (55.6%)
Concomitant illness	4 (44.4%)	2 (25.0%)	0 (0%)
Duration of CC (years) (median, IQR)	30.0 (5.5–45.0)	8.0 (3.5–23.0)	–
History of treatment for CC	3 (33.3%)	2 (25.0%)	0 (0%)
Number of spontaneous bowel movements per week (median, IQR)	2.80 (2.00–4.20)	3.50 (1.70–4.43)	–
Number of complete spontaneous bowel movements per week (median, IQR)	0 (0.00–0.00)	0.58 (0.00–1.40)	–
Bristol Stool Scale (1/2/3/4/5/6/7)	3/0/3/1/2/0/0	1/4/1/2/0/0/0	–

CC, chronic constipation.

Table 2 Rectal sensory thresholds in healthy individuals and patients with CC aged ≥60 years

		N	Median	IQR	Difference	95% CI	P value
FCSV (mL)	Healthy	9	59.0	50.0–68.0	20.0	−13.16 to 53.15	0.2253
	CC	17	74.0	58.0–95.0			
DDV (mL)	Healthy	9	98.0	84.0–117.0	8.1	−26.32 to 42.52	0.6317
	CC	17	103.0	93.0–153.0			
MTV (mL)	Healthy	9	145.0	130.0–156.0	4.2	−35.72 to 44.13	0.8298
	CC	17	167.0	125.0–189.0			

Difference = value for the CC group − value for the healthy group.
CC, chronic constipation; DDV, defaecatory desire volume; FCSV, first constant sensation volume; MTV, maximum tolerable volume.

Experiment 2

Participants

Seventeen participants were enrolled and assigned to groups (table 1): nine were administered elobixibat and eight were administered placebo, and all completed the study. One participant used bisacodyl on the morning of RST testing; therefore, they were excluded from the PPS analysis (figure 2). Side effects were not recorded for either group.

Effect of elobixibat on the threshold volume for the desire to defaecate (DDV)

The FAS analysis showed that elobixibat significantly reduced the threshold for DDV (p=0.0433), but placebo did not (p=0.9131), and there tended to be a difference in the changes between the groups (p=0.0899) (figure 3A; online supplemental table 1). In the PPS analysis, elobixibat tended to reduce the threshold for DDV (−9.0 (−29.5, −2.0) mL, p=0.0924), but placebo did not (3.0 (−6.0, 13.5) mL, p=0.9131); the changes in the DDV thresholds in the two groups did not significantly differ (−14.2 (−33.55, 4.92) mL, p=0.1455).

Effects of elobixibat on the thresholds for FCSV and MTV

Elobixibat significantly reduced the threshold for FCSV (p=0.0017), whereas placebo did not (p=0.4385), and the difference in the changes between the two groups was significant (p=0.0018) (figure 3B). It also tended to reduce the threshold for MTV (p=0.0767), whereas placebo did not (p=0.2209); there was no difference in the changes between the two treatment groups (p=0.4819) (figure 3C; online supplemental table 1).

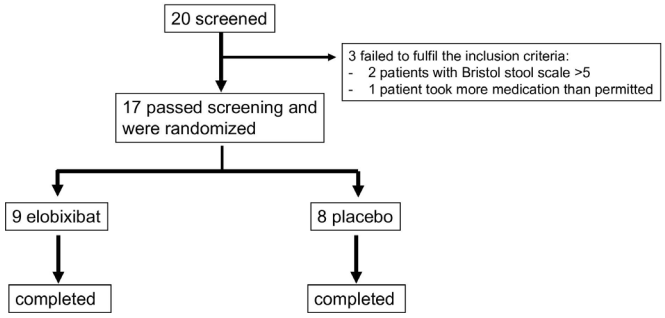

Figure 2 Enrolment and randomisation of the participants.

Effects of elobixibat on rectal compliance

There was no significant difference in the rectal compliance before and after drug administration in either group (table 3). There was also no difference in the changes between the two groups (p=0.2573).

Effects on spontaneous and complete spontaneous bowel movements (SBM and CSBM)

Elobixibat significantly increased the number of SBMs (change from baseline, 5.00 (1.67, 6.60), p=0.048), as did placebo (1.80 (0.47, 2.60), p=0.0141), and there tended to be a difference in the changes between the two groups (2.46 (−0.052, 4.972), p=0.0549) (table 1). It also tended to increase the number of CSBMs (1.00 (0.00, 3.60), p=0.0519), whereas placebo did not (0.80 (−0.08, 2.50), p=0.1228), and there was no difference in the changes between the two groups (0.89 (−1.369, 3.152), p=0.4395).

Effects on faecal BA concentration

The total faecal BA concentration significantly increased from baseline (mean change from baseline, 7.904±7.901 µmol/g, p=0.0120), as did that of secondary BAs (5.594±5.530 µmol/g), after the administration of elobixibat; and these effects were more marked than following placebo administration (p=0.0158) (online supplemental table 2). With respect to specific BAs, the increase in DCA was highly statistically significant (5.563±4.565 µmol/g, p=0.0039).

Clinical characteristics associated with the efficacy of elobixibat

Participants with CC who had a preserved desire to defaecate showed significant reductions in DDV following elobixibat administration (p=0.0433) (online supplemental table 3). Analysis of the between-treatment differences in the baseline-adjusted 7-day change in DDV in the older participants showed that a duration of CC ≥5 years (p=0.0200) and having a history of treatment for CC (p<0.0001) were associated with greater efficacy of elobixibat with respect to the RST for the desire to defaecate. Participants ≥65 years (p=0.0664) and women (p=0.0615) also tended to show more marked effects of elobixibat (table 4).

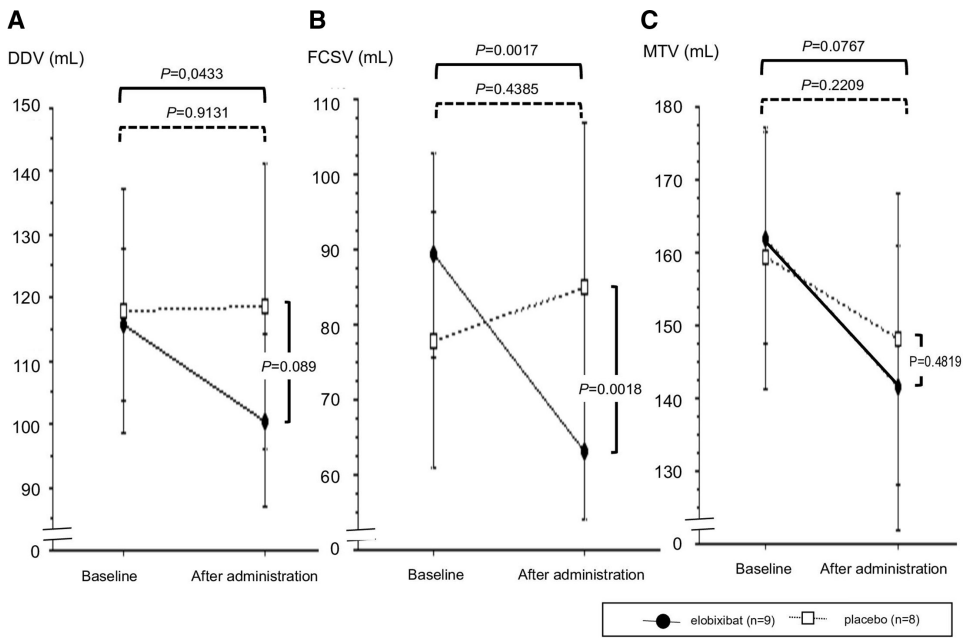

Figure 3 Changes in the rectal sensory thresholds of the two groups. (A) DDV before and after medication. (B) FCSV before and after medication. (C) MTV before and after medication. FCSV, first constant sensation volume; DDV, defaecatory desire volume; MTV, maximum tolerable volume. The Wilcoxon rank-sum test was used for statistical analysis.

DISCUSSION

We have shown for the first time that the BA transport inhibitor elobixibat improves the RSTs of patients with CC aged ≥60 years. Furthermore, these effects were found to be more marked in patients with a longer duration of CC and those with a history of treatment for CC.

The current approach to the treatment of CC aims to increase the number of bowel movements, facilitate defaecation, and ameliorate abdominal symptoms. Therefore, previous randomised controlled trials (RCTs) of laxatives have generally used endpoints of the number of bowel movements and QOL.[15 20] However, constipation in patients who experience stroke is associated with high RSTs, bowel thresholds, and thresholds of urgency, which also correlate with Patient Assessment of Constipation-QOL Scores.[21] A recent survey showed that patients with a persistent loss of desire to defaecate who do not show improvement have poor satisfaction with treatment.[9] In addition, a recent cross-sectional study of patients with refractory functional constipation showed that increases in RST are associated with more severe constipation, with symptoms including less frequent bowel movements, more pain during defaecation, prolongation of defaecation, greater need for digital disimpaction or enemas, and hard faeces.[8] Therefore, improving the desire to defaecate is essential for the satisfaction of patients with their treatment.

A recent study showed improvements in the desire to defaecate of patients with CC following electrostimulation therapy,[22] but its effects may not be consistent in every facility. Another study showed a drug-related improvement: Daikenchuto reduced the RST of children with severe constipation.[23] However, an RCT of Daikenchuto in adult women with functional constipation showed no significant effect on RST,[24] and a placebo-controlled, double-blind, randomised crossover trial of lubiprostone also showed no effect.[18] Therefore, it is important to identify new drugs that improve RSTs for the treatment of CC.

The intestinal microbiota has previously been shown to affect visceral sensory thresholds.[25] However, 2 weeks of elobixibat treatment was found not to cause significant changes in the intestinal microbiota,[26] and given the 1-week treatment period used in the present study,

Table 3 Rectal compliance

			N	Mean	SD	Median	IQR	P value
Rectal compliance (mL/mmHg)	Elobixibat	Observation period	9	6.06	3.10	5.67	4.37–6.74	
		Treatment period	9	6.70	3.51	5.45	4.73–8.61	
		Difference	9	0.64	2.05	1.16	0.21–1.40	0.3756
	Placebo	Observation period	8	6.66	2.27	7.01	5.51–7.98	
		Treatment period	8	5.89	2.90	5.43	3.74–8.01	
		Difference	8	−0.77	2.36	0.06	−2.44–0.61	0.3891

Table 4 Estimated between-treatment differences in the baseline-adjusted changes in DDV in participants with CC aged ≥60 years

Subgroup		Estimate	95% CI	SE	P value
Presence or absence of complications	Presence	−21.2	−45.56 to 3.15	12.43	0.0879
	Absence	−16.0	−43.17 to 11.15	13.86	0.2480
Age classification	<65 years	−30.3	−96.3 to 35.76	33.69	0.3689
	≥65 years	−16.5	−34.21 to 1.12	9.01	0.0664
Presence or absence of defaecation desire	Presence	−12.9	−31.62 to 5.82	9.55	0.1768
	Absence	–	–	–	–
Sex	Men	−7.5	−40.75 to 25.69	16.95	0.6570
	Women	−21.9	−44.87 to 1.06	11.72	0.0615
Duration of CC	<5 years	15.4	5.56 to 25.31	5.04	0.0022
	≥5 years	−25.5	−46.98 to 4.01	10.96	0.0200
History of treatment for CC	Positive	−17.6	−25.69 to 9.54	4.12	<0.0001
	Negative	−17.6	−41.70 to 6.44	12.28	0.1511

Change in DDV = DDV after 7 days of treatment − DDV before the treatment. Between-treatment difference = value in the elobixibat group − value in the placebo group.
CC, chronic constipation; DDV, defaecatory desire volume.

we hypothesised that BAs would improve RSTs directly via TGR5 receptors, rather than through changes in the microbiota. Recent studies have also shown that the administration of TGR5 agonists into the colon activates colonic sensory neurons, inducing afferent mechanical hypersensitivity via a TRPA1-dependent mechanism.[27] However, we cannot rule out an effect of elobixibat on RSTs via the gut microbiota.

We found significantly higher faecal concentrations of total and secondary BAs after elobixibat treatment. This did not change the ratio of primary to secondary BAs but significantly increased the faecal excretion of DCA. The shift towards secondary BAs during elobixibat treatment suggests that there was sufficient time for the 7α-hydroxylation of BAs during colonic transit. Because the participants were individuals with CC aged ≥60 years, many of them had prolonged colonic transit times, and it is possible that the 1-week treatment did not shorten their colonic transit times sufficiently to reduce this 7α-hydroxylation. This is partly corroborated by the lack of a significant difference in CSBM between the placebo and elobixibat groups. Thus, a longer duration of treatment may increase the percentage of primary BAs generated. These findings are consistent with the results of a previous study.[26] CDCA and DCA, which are secreted BAs, bind to colonic TGR5 receptors and promote motility.[28] Recent studies have also shown that the administration of TGR5 agonists into the colon activates colonic sensory neurons, inducing afferent mechanical hypersensitivity via a TRPA1-dependent mechanism.[27] Therefore, elobixibat may also have lowered the visceral perception threshold and sensitised the rectums of the participants. Thus, a BA-mediated improvement in RSTs represents a novel mechanism of action for the treatment of CC, especially in older patients.

Although the patients who showed improvements in RSTs had higher faecal concentrations of BAs, there were no correlations of the changes in RSTs with the changes in symptoms or in the faecal concentrations of BAs. This may be because of the small number of participants. Therefore, further, larger studies should be conducted to confirm or refute these findings.

The results of the present study, in which we found no differences in the MTV thresholds but significant differences in the FCSV and DDV thresholds before and after the administration of elobixibat, are likely to have been influenced by the severity of the CC. The patients enrolled in the study did not have severe or intractable CC, but rather a mild form of the type that is often encountered in daily practice. Therefore, if patients with severe or refractory CC were to be studied, significant differences may also be identified in the MTV thresholds. Thus, patients with severe or refractory CC should be included in future studies to evaluate this possibility.

The RSTs of patients with CC aged ≥60 years tended to be higher than those of healthy individuals in the same age range. A previous study[6] showed that the RSTs of older healthy people are higher than those of younger healthy people, and another showed that the RSTs of patients with slow-transit constipation are higher than those of healthy people, but that these do not differ between people with irritable bowel syndrome-related constipation and healthy individuals.[29] This lack of difference may be explained by the small sample size or the high RSTs of the participants. Therefore, it is possible that a significant difference may only be obtained in older patients with refractory CC who have prolonged colonic transit times. Furthermore, we cannot rule out the possibility that the sex distribution of the healthy control group (7 men and

2women) may have influenced the RSTs of and findings for this group.

There were several limitations to the present study. First, the sample size was small, although that the required sample size for the determination of the primary endpoint was calculated a priori. Second, colonic transit time was not assessed, but this has been evaluated previously.[30] Third, we measured the BA concentrations of random faecal samples, rather than total BA excretion. Fourth, we found that elobixibat significantly reduced the RST for DDV, and there was a non-significant trend towards a difference between elobixibat and placebo. In addition, FCSV was significantly reduced by elobixibat, and the effects of elobixibat and placebo differed significantly. However, further clinical studies of patients with a lack of desire to defaecate are warranted.

In conclusion, elobixibat improves the RSTs of patients with CC aged ≥60 years, and this effect is more marked in those with a long history of CC and in those who have already been treated for CC. The improvements in RSTs may be at least in part responsible for the beneficial effects of elobixibat on constipation. However, large multi-centre prospective studies should be performed to confirm these findings.

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