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Treatment of Chronic Constipation using Elobixibat in a Real-World Setting: A Retrospective Cohort Study using an Electronic Medical Records Database in Japan

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ABSTRACT

Background: Chronic constipation is a common condition affecting people of all ages; therefore, the socioeconomic burden of chronic constipation is nonnegligible. Elobixibat (ELO), an ileal bail acid transport inhibitor, was launched in Japan in 2018. However, evidence of its use in diverse populations is limited.
Objectives: This study aimed to evaluate the prescription of ELO, risk factors associated with ELO discontinuation, and the continuation of stimulants or saline laxatives during ELO treatment in a real-world setting using an extensive electronic medical records database that primarily includes data from acute-care hospitals.
Methods: Data of patients prescribed for ELO from April 1, 2018, to March 31, 2022, were extracted from the database. The discontinuation of ELO and stimulant or saline laxatives during ELO treatment was evaluated using the Kaplan-Meier method. The Cox proportional hazards model evaluated risk factors associated with laxative discontinuation.
Results: In total, 11,062 patients were evaluated. The rate of ELO discontinuation within 360 days of initiation was 78.7%. Hospitalized at the ELO initiation, stage 5 chronic kidney disease, and diagnosis of constipation by departments of obstetrics and gynecology or by departments of malignant neoplasm were identified as risk factors for discontinuation. Diagnosis of constipation, diabetes mellitus, Parkinson's disease, and previous laxative treatment was associated with a lower risk of ELO discontinuation. The prescription rate of stimulants and saline laxatives markedly decreased after ELO initiation; furthermore, nearly half of patients who were continuously prescribed ELO discontinued these laxatives within 360 days.
Conclusions: The discontinuation of ELO was associated with various factors and using ELO may be beneficial in the withdrawal of concurrent stimulants and saline laxatives. These findings may help effectively manage chronic constipation.

Introduction

Constipation is a condition that involves difficult or infrequent stool passage, hard stool, or a feeling of incomplete evacuation.[1] It occurs without any known cause but may be related to physical or mental abnormalities, comorbidities such as Parkinson's disease (PD) and diabetes mellitus, and medication such as anticholinergic agents. The diagnosis of constipation is generally based on the Rome IV criteria.[2] Chronic constipation (CC) is defined when the onset of the symptom is at least 6 months before the diagnosis and persists for at least 3 months before the diagnosis.[3]

The median prevalence of constipation is estimated to be 16% (range, 0.7%–79%) in adults and 12% (range, 0.7%–29.6%) in children, and it was suggested that sex, aging, socioeconomic status, and education are associated with the prevalence of constipation.[4] In Japan, the prevalence of constipation is 20.4% in males and 38.8% in females, and the prevalence in those aged 15 to 50 years is female-dominant, whereas this dominance is lost in those older

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than age 50 years.[5] The prevalence is also known to increase with age, and the influence of age on the increased prevalence is more remarkable in men than in women.[3]

Patients with CC have a low quality of life (QOL) and labor productivity and higher indirect costs than those without CC.[6] In addition, CC is associated with the onset of cardiovascular disease and chronic kidney disease (CKD).[7–10] Therefore, the socioeconomic burden of CC is nonnegligible.

In Japan, stimulant laxatives (43.8%) and osmotic laxatives (36.4%) are the most common drugs for constipation.[11] Their short-term or need-based prescription is recommended because long-term use of stimulant laxatives may cause drug resistance.[1,3] Magnesium-based saline laxatives (MgLx) can cause severe hypermagnesemia, especially in patients with renal impairment.[1] In Japan, careful prescription of MgLx is recommended in the elderly, despite normal kidney function, along with monitoring of serum magnesium levels.[12,13]

Recently, new laxatives with novel mechanisms of action, such as linaclotide,[14] lubiprostone,[15] and polyethylene glycol,[16] have been launched. Elobixibat (ELO) was approved for treating CC in Japan in 2018. ELO is a selective ileal bile acid (BA) transporter inhibitor, and its low systemic bioavailability during oral administration supports local action in the gut.[17,18] ELO increases the delivery of BAs to the proximal colon, increases colonic fluid secretion and motility, accelerates colonic transit, and improves bowel function.[19] BAs are metabolically active substances implicated in the pathogenesis of gastrointestinal diseases, such as CC.[20] BAs are secreted from hepatocytes into the bile and flow into the small bowel. More than 90% of conjugated BAs are absorbed from the terminal ileum via the ileal BA transporter. BAs are endogenous laxatives because they stimulate bowel motility, and excess BAs cause diarrhea, which is attributed to the secretion of water and electrolytes.[17] Under these mechanisms, ELO can improve frequency of spontaneous bowel movements and stool consistency, resulting in relieving constipation-related symptoms in idiopathic CC.[21]

The effects of ELO in usual care settings have been reported.[22–25] However, these reports targeted small and specific populations. Therefore, these results were not sufficient to estimate the effects on the general population, and it was impossible to evaluate the use of ELO among patients with different demographic characteristics. Although early discontinuation of laxatives has been reported, factors associated with discontinuation remain unknown.[26] This study aimed to evaluate the characteristics of patients who receive ELO, risk factors associated with ELO discontinuation, and management of CC in diverse populations in a real-world setting using a large electronic medical records (EMR) database.

Material and Methods

Data Source and Study Population

This study used the real-world data database (RWD-DB), which is maintained by the Health, Clinic, and Education Information Evaluation Institute (Kyoto, Japan) with support from the Real World Data Co, Ltd. (Kyoto, Japan). The database includes the medical records of approximately 23 million patients from more than 200 medical institutes nationwide in Japan as of 2021. The data included demographic information, diagnoses, prescriptions, procedures, and laboratory results from outpatient and inpatient settings. Data were anonymized and automatically extracted from the EMR of each medical institution. Each individual was assigned a unique identifier, valid within the same institution. Information on data collection was available at each medical institution, and opt-out was possible at a patient's request.

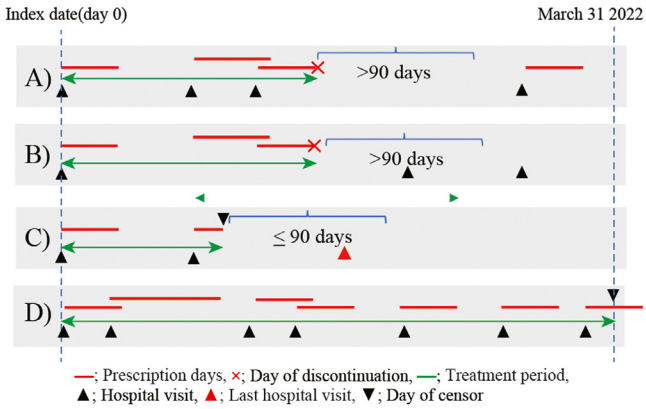


Figure 1. Algorithms for discontinuation of medication. Discontinuation of medication was defined as the absence of medication for more than 90 days after the theoretical end of the previous prescription (TEPP). The discontinuation day was defined as the TEPP of the last prescription before discontinuation. The follow-up was censored at the last follow-up date or March 31, 2022, whichever came first.

Patients with prescriptions for ELO were extracted from the RWD-DB. The index date (day 0) was defined as the first date of the ELO prescription. Patients whose index date were not from April 1, 2018, to March 31, 2022, or without a history of hospital visits from day −180 to day −1 (look-back period) were excluded. Patients were followed-up from the index date to the last visit or March 31, 2022, whichever came first.

Study variables and definitions

Medications, medical procedures, and diagnoses were identified using the Anatomical Therapeutic Chemical Classification code/receipt code/generic name, category code/receipt code, and the International Classification of Diseases 10th Revision code/receipt code (Supplemental Table 1).

Inpatient status based on the index date was evaluated using the EMR or the Format 1 file in the Diagnosis Procedure Combination data.[27] Departments that diagnosed patients with constipation on the index date were detected using department names (Supplemental Table 1) of the disease records in the EMR. If multiple departments were recorded, all departments were used.

Senna-, sennoside-, picosulfate-, and rhubarb-containing products were categorized as stimulant laxatives. Saline laxatives were defined as MgLx, and secretagogues included lubiprostone and linaclotide. Bisacodyl, carbon dioxide-producing drugs, glycerol, the medical procedure of enema, and disimpaction were categorized as laxative rescues.

Discontinuation of medication was defined as the absence of medication (eg, ELO or any laxative drug of interest) for more than 90 days after the theoretical end of the previous prescription. The discontinuation day was defined as the theoretical end of the previous prescription of the last prescription before discontinuation (Figure 1). The follow-up was censored at the last follow-up date or March 31, 2022, whichever came first. In the discontinuation of stimulant and saline laxatives analyses, the date of discontinuation of ELO was also used for censoring.

Daily doses of laxatives were calculated for each compound. The daily dose of saline laxatives was calculated based on the dose of magnesium salt, regardless of molecular weight.

On-label treatment of ELO was defined as age 20 years or older on the index date, a daily dose of ELO of 5 to 15 mg/d, and diagnosis of CC on the index date. Hypermagnesemia was defined as >1.23 mmol/L according to Common Terminology Criteria for Adverse Events version 5.0.[28]

Statistical Analysis

Drug survival was evaluated using the Kaplan-Meier method. The risk factors for drug discontinuation were evaluated using the Cox proportional hazard model, and the hazard ratio (HR) and 95% CI were calculated. First, the base model was constructed based on sex and age categories. Then, hospitalized at the index date, comorbidities, previous laxatives, previous other medications, and departments that diagnosed constipation were sequentially added to the model. Factors with HR <0.909 or >1.1 were selected in each step. Changes in the proportion of each laxative prescription between the day of the latest laxative prescription during the look-back period and the index date were evaluated using the McNemar exact test. The mean (SD) and HR (95% CI) were expressed as mean (SD) and HR (95% CI [lower limit–upper limit]), respectively.

Python version 3.9.7 (Python Software Foundation, Wilmington, Delaware) and R version 3.6.3 (R Foundation for Statistical Computing. Vienna, Austria) were used for all the statistical analyses.

Ethics

The protocol of this study was approved (No: RI20210227) by the ethics committee of the Research Institute of Healthcare Data Science (Tokyo, Japan), and the study was registered (ID: UMIN000048352) in the University Hospital Medical Information Network Clinical Trial Registry (Tokyo, Japan). This study was performed in accordance with the Declaration of Helsinki guidelines.

Results

Patient characteristics of the study population

A total of 11,780 patients with prescriptions for ELO were extracted from the RWD-DB. Subsequently, 718 patients were excluded due to the exclusion criteria (5 patients were excluded due to the index date was out of the study period, and 713 patients did not have a previous visit); finally, 11,062 patients were enrolled in this study (Figure 2).

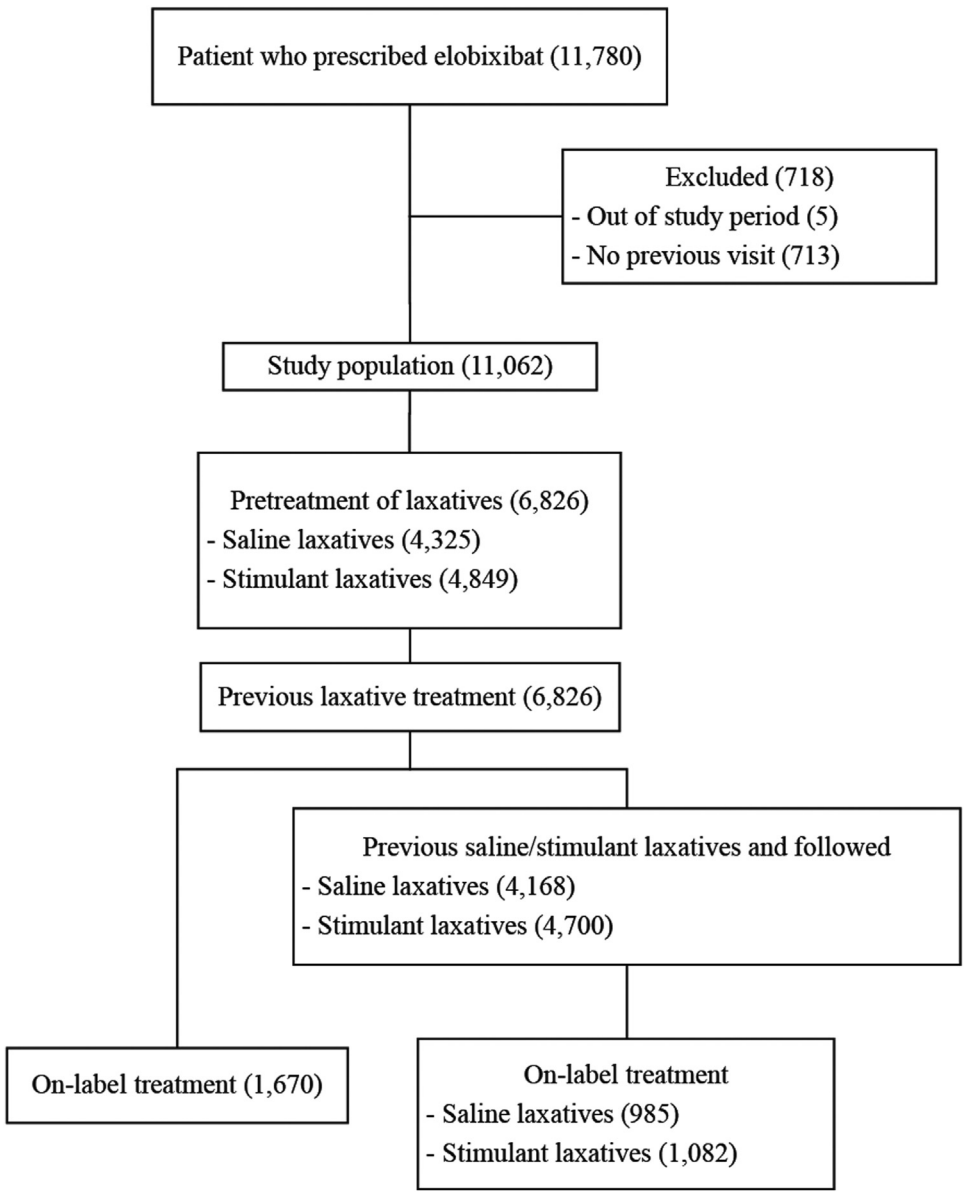


Figure 2. Patient flow chart.

Table 1
Patient characteristics in the study population.

	Total	Continuation	Discontinuation
n* (% in total)	11,062 (100)	3545 (32.0)	7517 (68.0)
Female†	5514 (49.8)	1787 (50.4)	3727 (49.6)
Age‡,§, y	73.0 (13.7)	74.0 (13.3)	72.5 (13.8)
In-patient†,§	5075 (45.9)	1609 (45.4)	3466 (46.1)
Diagnosis of constipation†,§	8819 (79.7)	2773 (78.2)	6046 (80.4)
Chronic constipation	2889 (26.1)	926 (26.1)	1963 (26.1)
Diagnosing department			
Internal medicine (excluding GI medicine)	3598 (32.5)	1101 (31.1)	2497 (33.2)
GI medicine	1466 (13.3)	460 (13.0)	1006 (13.4)
Surgery (excluding GI surgery)	1327 (12.0)	392 (11.1)	935 (12.4)
Comorbidity†,‖			
Diabetes mellitus	4476 (40.5)	1424 (40.2)	3052 (40.6)
Malignant neoplasm	4091 (37.0)	1208 (34.1)	2883 (38.4)
Heart failure	3129 (28.3)	1012 (28.5)	2117 (28.2)
Spinal disease	2922 (26.4)	872 (24.6)	2050 (27.3)
Chronic kideny disease	2520 (22.8)	784 (22.1)	1736 (23.1)
Hepatic disease	2287 (20.7)	707 (19.9)	1580 (21.0)
Parkinson's disease	722 (6.5)	277 (7.8)	445 (5.9)
Stage 5 chronic kidney disease	423 (3.8)	96 (2.7)	327 (4.4)
Scleroderma	32 (0.3)	14 (0.4)	18 (0.2)
Muscle wasting or atrophy	1799 (16.3)	653 (18.4)	1146 (15.2)
Prescription of laxatives†,¶	7075 (64.0)	2355 (66.4)	4720 (62.8)
Stimulant laxative	4849 (43.8)	1636 (46.1)	3213 (42.7)
Sennoside	3684 (33.3)	1200 (33.9)	2484 (33.0)
Senna	294 (2.7)	122 (3.4)	172 (2.3)
Picosulfate	1868 (16.9)	655 (18.5)	1213 (16.1)
Rhubarb	102 (0.9)	45 (1.3)	57 (0.8)
Saline laxatives	4325 (39.1)	1416 (39.9)	2909 (38.7)
Lactulose	207 (1.9)	67 (1.9)	140 (1.9)
M4000E	196 (1.8)	85 (2.4)	111 (1.5)
Secretagogues	1971 (17.8)	653 (18.4)	1318 (17.5)
Lubiprostone	1503 (13.6)	504 (14.2)	999 (13.3)
Linaclotide	651 (5.9)	208 (5.9)	443 (5.9)
Rescues†,¶	2084 (18.8)	714 (20.1)	1370 (18.2)
Bisacodyl	263 (2.4)	100 (2.8)	163 (2.2)
Carbon dioxide producing drugs	767 (6.9)	254 (7.2)	513 (6.8)
Enemas (glycerol)	1043 (9.4)	339 (9.6)	704 (9.4)
Enema procedure	66 (0.6)	24 (0.7)	42 (0.6)
Disimpaction procedure	549 (5.0)	188 (5.3)	361 (4.8)

GI = gastrointestinal; M4000E = macrogol 4000 plus electrolytes.
* Values are presented as n (% of the total).
† Values are presented as n (%).
‡ Values are presented as mean (SD).
§ At the index date (day 0).
‖ Day −180 to day 0.
¶ Day −180 to day −1.

The mean (SD) age was 73.0 (13.7) years, and 49.8% were women (Table 1). Approximately half of patients were admitted to the hospital on the index date. Diagnosis of constipation was established in 79.7% of patients; however, diagnoses for CC were less frequent (26.1%). Diagnoses of constipation were primarily made by the departments of internal medicine, gastrointestinal, and surgery (32.5%, 13.3%, and 12.0%, respectively).

The most common comorbidity was diabetes mellitus (40.5%), followed by malignant neoplasm (37.0%), heart failure (28.3%), spinal disease (26.4%), CKD (22.8%), and hepatic disease (20.7%).

The proportion of patients previously prescribed laxatives was 64.0%, and the most common laxatives were saline laxatives (39.1%) and sennoside (33.3%). Stimulant laxatives were prescribed to 43.8% of the study population. The details of the patient demographics are shown in Supplemental Table 2.

The prescription of ELO or other laxatives and serum magnesium measures on the index date

The mean daily dose of ELO was 12.9 mg/d, and 70.6% of the patients received 10 mg/d (Table 2). The median of the first prescription duration was 10 days, and 38.8% of patients were prescribed ELO for 2 to 7 days; however, 20.2% were prescribed the drug for ≥29 days. Saline, stimulant, and rescue laxatives were prescribed in 22.5%, 19.5%, and 6.7% of patients, respectively.

The prescription rate of saline laxatives did not differ between age groups. Serum magnesium was measured in 21.6% of the study population, and the proportion of measurement was higher in those aged 65 years or older than in aged 20 to 64 years (22.5% and 18.0%, respectively). Hypermagnesemia was observed in 4.3% of patients with test results of serum magnesium level.

Continuation of ELO after the index date

In total, 7517 patients discontinued ELO during the follow-up period (Table 1). The mean age was 74.0 years in patients who continued ELO and 72.5 years in patients who discontinued ELO. The proportions of women were 50.4% and 49.6%, respectively. Diagnoses of malignant neoplasm, spinal disease, and stage 5 CKD were more frequent in patients who discontinued ELO (38.4%, 27.3%, and 4.4%, respectively) than in those who continued ELO (34.1%, 24.6%, and 2.7%, respectively), and PD, scleroderma, muscle wasting, or atrophy were less frequent in patients who discontinued (5.9%, 0.2%, and 15.2%, respectively) than in those who continued (7.8%, 0.4%,

Table 2
Prescriptions of elobixibat, other laxatives, and serum magnesium on the index date.

Prescription details		Elobixibat			
		Total	Age group		
			0–19 y	20–64 y	65 y and older
No. of patients		11,062 (100)	40 (0.4)	2197 (19.9)	8825 (79.8)
In-patient		5075 (45.9)	6 (15.0)	842 (38.3)	4227 (47.9)
Diagnosis of constipation		8819 (79.7)	37 (92.5)	1796 (81.7)	6986 (79.2)
Chronic constipation		2889 (26.1)	7 (17.5)	618 (28.1)	2264 (25.7)
Daily dose, mg	mean (SD) [median]	12.9 (18.4) [10.0]	9.1 (7.1) [10.0]	12.1 (15.7) [10.0]	13.2 (19.0) [10.0]
	<5	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
	5	2266 (20.5)	15 (37.5)	366 (16.7)	1885 (21.4)
	10	7810 (70.6)	24 (60.0)	1657 (75.4)	6129 (69.5)
	15	288 (2.6)	0 (0.0)	63 (2.9)	225 (2.5)
	≥20	696 (6.3)	1 (2.5)	111 (5.1)	584 (6.6)
Prescription days	mean (SD) [median]	18.3 (21).6 [10.0]	23.8 (18.1) [19.5]	18.9 (21.6) [14.0]	18.1 (21.6) [8.0]
	−1	695 (6.3)	1 (2.5)	117 (5.3)	577 (6.5)
	2–7	4288 (38.8)	9 (22.5)	780 (35.5)	3499 (39.6)
	8–14	2337 (21.1)	9 (22.5)	517 (23.5)	1811 (20.5)
	15–21	749 (6.8)	1 (2.5)	177 (8.1)	571 (6.5)
	22–28	759 (6.9)	3 (7.5)	158 (7.2)	598 (6.8)
	29–56	1458 (13.2)	15 (37.5)	282 (12.8)	1161 (13.2)
	57–84	506 (4.6)	1 (2.5)	105 (4.8)	400 (4.5)
	≥85	270 (2.4)	1 (2.5)	61 (2.8)	208 (2.4)
Stimulant laxatives		2159 (19.5)	6 (15.0)	381 (17.3)	1772 (20.1)
	Sennoside	1398 (12.6)	2 (5.0)	243 (11.1)	1153 (13.1)
	Senna	175 (1.6)	0 (0.0)	31 (1.4)	144 (1.6)
	Picosulfate	737 (6.7)	5 (12.5)	147 (6.7)	585 (6.6)
	Rhubarb	44 (0.4)	0 (0.0)	9 (0.4)	35 (0.4)
Saline laxatives		2494 (22.5)	15 (37.5)	502 (22.8)	1977 (22.4)
Lactulose		120 (1.1)	0 (0.0)	24 (1.1)	96 (1.1)
Secretagogues		713 (6.4)	1 (2.5)	150 (6.8)	562 (6.4)
	Lubiprostone	529 (4.8)	1 (2.5)	111 (5.1)	417 (4.7)
	Linaclotide	226 (2.0)	0 (0.0)	53 (2.4)	173 (2.0)
Rescues		744 (6.7)	4 (10.0)	113 (5.1)	627 (7.1)
	Bisacodyl	96 (0.9)	0 (0.0)	12 (0.5)	84 (1.0)
	Carbon dioxide producing drugs	251 (2.3)	2 (5.0)	37 (1.7)	212 (2.4)
	Enemas (glycerol)	333 (3.0)	2 (5.0)	54 (2.5)	277 (3.1)
	Enema procedure	4 (0.0)	0 (0.0)	3 (0.1)	1 (0.0)
	Disimpaction procedure	128 (1.2)	0 (0.0)	15 (0.7)	113 (1.3)
Magnesium, mmol/L		2390 (21.6)	5 (12.5)	395 (18.0)	1990 (22.5)
	mean (SD) [median]*	0.9 (0.2) [0.9]	0.9 (0.1) [0.8]	0.9 (0.2) [0.9]	0.9 (0.2) [0.9]
	Hypermagnesemia*	103 (4.3)	0 (0.0)	18 (4.6)	85 (4.3)

M4000E = macrogol 4000 plus electrolytes.
* Values are presented as proportion (%) in the patients with laboratory test results.

Table 3
Discontinuation of elobixibat in the study population.

Day	0	30	60	90	180	360
At risk	11,062	6248	4438	3483	2129	1110
Cumulative incidence	0	3763	4963	5665	6557	7116
Continuation, %	100.0	63.2	50.2	41.9	30.3	21.3
95% CI	100.0–100.0	62.3–64.2	49.2–51.2	40.9–42.9	29.4–31.3	20.3–22.2

and 18.4%, respectively). Previous laxative use was less frequent in patients who discontinued (62.8%) than in those who continued (66.4%).

The discontinuation of ELO was observed immediately after the index date (Table 3). The ELO continuation rates at 30 and 60 days after the index date were 63.2% (day 0–30; 1.19%/d) and 50.2% (day 31–60; 0.43%/d), respectively. Subsequently, the increase in the discontinuation rate became moderate (days 61–90; 0.28%/d, 91–180; 0.13%, 181–360; 0.05%/d). The cumulative probability of drug survival was 21.3% on day 360.

Risk factors for the ELO discontinuation

The Cox proportional models for the discontinuation of ELO were exploratory, and the final model was evaluated (see Model 9 in Supplemental Table 3). The risk of discontinuation of ELO was higher in the 20 to 34 years age group than in the 50 to 64 years age group (HR = 1.22; 95% CI, 1.03–1.45) (Figure 3). Inpatients on the index date, stage 5 CKD, and diagnosis of constipation by a department of obstetrics and gynecology or by a department of malignant neoplasm were also associated with higher risks of ELO discontinuation (HR = 1.54; 95% CI, 1.46–1.63; HR = 1.38; 95% CI, 1.23–1.54; HR = 1.39; 95% CI, 1.18–1.63; and HR = 1.25; 95% CI, 1.02–1.54, respectively).

In patients with a constipation diagnosis (HR = 0.68; 95% CI, 0.63–0.73), diabetes mellitus (HR = 0.90; 95% CI, 0.86–0.94), PD (HR = 0.76; 95% CI, 0.6–0.84), and muscle wasting or atrophy (HR = 0.87; 95% CI, 0.82–0.93), previous treatment of laxatives (ranged from 0.69 to 0.86), prescription of H1-receptor antagonists (HR = 0.88; 95% CI, 0.81–0.96), and diagnosis for constipation by psychiatric departments (HR = 0.78; 95% CI, 0.71–0.86) were associated with lower risk of ELO discontinuation.

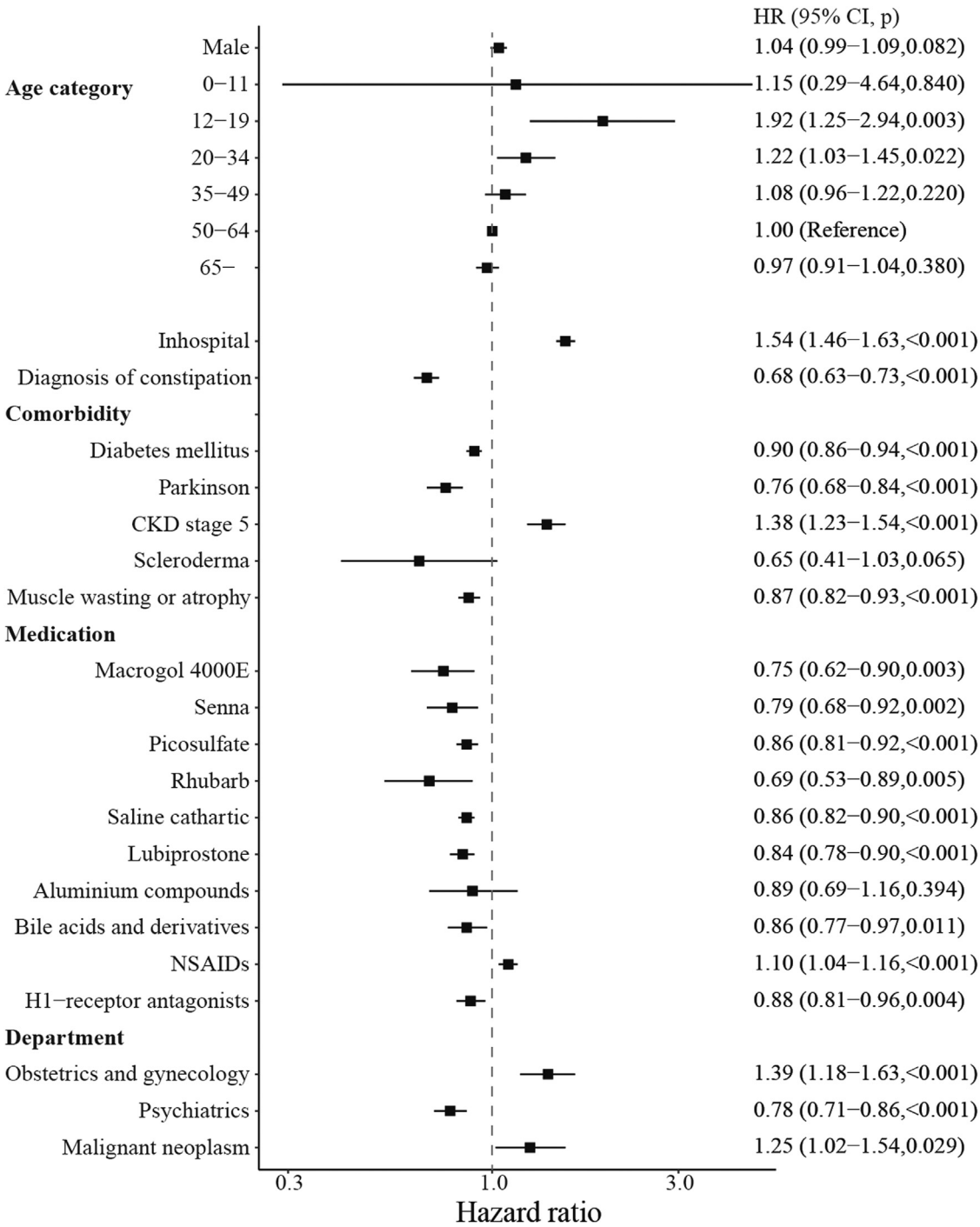


Figure 3. Factors associated with the discontinuation of elobixibat. CKD = chronic kidney disease; HR = hazard ratio; NSAIDs = nonsteroidal anti inflammatory drugs.

Prescription for laxatives in patients with pretreatment for laxatives

Changes in laxative prescription before and after ELO initiation were evaluated in patients with previous laxative treatment. A total of 6826 patients who received laxative treatment during the look-back period and have at least 1 visit after the index date were evaluated for changes in laxative treatment between the last laxative prescription date during the look-back period and the index date (Table 4). The prescription rates of stimulants (from 52.2% to 21.7%, especially sennoside [from 37.0% to 14.5%]), saline laxatives [from 48.7% to 26.0%], lubiprostone [from 15.6% to 6.0%], linaclotide [from 6.7% to 2.2%], and lactulose [from 2.1% to 1.2%]) decreased from the index date compared with the previous prescription date. However, macrogole 4000 plus electrolytes were the same in both prescriptions (from 1.4% to 1.6%).

Of the 6826 patients with laxative pretreatment, 5156 were off-label treatment (age <20 years: 27; out of daily dose: 835; without CC diagnosis: 4974), and 1670 patients were prescribed on-label treatment for ELO. Similarly, the proportion of other laxatives decreased on the index date compared with the previous prescription in this subpopulation (Table 4).

Table 4
Prescription of laxatives in patients with previous prescription of laxatives.

Prescription	Patients with a previous prescription of laxatives			
			Treated with on-label elobixibat	
	Previous	Index date	Previous	Index date
n*	6826 (61.7)	6826 (61.7)	1670 (15.1)	1670 (15.1)
Stimulant laxatives†	3566 (52.2)	1480 (21.7)‡	808 (48.4)	330 (19.8)‡
Sennoside	2526 (37.0)	990 (14.5)‡	603 (36.1)	223 (13.4)‡
Senna	174 (2.5)	108 (1.6)‡	39 (2.3)	22 (1.3)§
Picosulfate	1015 (14.9)	487 (7.1)‡	204 (12.2)	109 (6.5)‡
Rhubarb	62 (0.9)	29 (0.4)‡	9 (0.5)	3 (0.2)
Saline laxatives	3321 (48.7)	1774 (26.0)‡	803 (48.1)	416 (24.9)‡
M4000E	95 (1.4)	112 (1.6)	25 (1.5)	29 (1.7)
Lactulose	144 (2.1)	80 (1.2)‡	31 (1.9)	18 (1.1)‖
Secretagogues†				
Lubiprostone	1065 (15.6)	410 (6.0)‡	312 (18.7)	102 (6.1)‡
Linaclotide	457 (6.7)	153 (2.2)‡	145 (8.7)	38 (2.3)‡

M4000E = macrogol 4000 plus electrolytes.
* Values are presented as n (% of study population).
† Values are presented as n (% of the at risk).
‡ $P < 0.001$.
§ $P < 0.01$.
‖ $P < 0.05$.

Continuation of stimulant or saline laxatives in patients with ELO treatment

The continuation of stimulants or saline laxatives during ELO treatment was evaluated. The number of patients who received stimulants and saline laxatives pretreatments were 4849 and 4325, respectively. Of these, 4700 and 4168 patients had at least 1 visit during the follow-up period, respectively (Supplemental Table 4). Under the concomitant use of ELO, the cumulative incidences of withdrawal of the stimulant and saline laxatives were 20.7% and 16.0% at day 30, 29.7% and 22.8% at 60 days, and 55.4% and 46.3% at 360 days, respectively (Figure 4A). The withdrawal rate of stimulant laxatives was higher than that of saline laxatives.

Among the patients with pre-treatment with stimulant and saline laxatives, 1082 patients and 985 patients were maintained on-label treatment for ELO during the follow-up periods, and 3618 patients and 3183 patients were excluded due to off-label treatment (age <20 years: 15 and 14; out of daily dose: 633 and 494; and without CC diagnosis: 3483 and 3078) (Figure 4B). The withdrawal rates of saline laxatives were the same as those in the population without considering on-label treatment, and the withdrawal rate for stimulant laxatives was less frequent (48.5% on day 360) (Figure 4B).

Discussion

Our study was the first nationwide study in Japan to investigate the current status of laxative treatment in 11,780 patients with ELO prescriptions using routinely collected data from medical institutions. We used the RWD-DB for the following reasons: individuals from newborn infants to elderly patients were included, it contained laboratory findings, and it provided information on the department that diagnosed constipation from the EMR.

In the study population, 79.8% of the patients were aged 65 years or older (Table 2). ELO was approved for the treatment of CC in Japan in January 2018, based on the results of the Phase III study, which enrolled patients with a mean age of 43 years,[29] and adequate safety and efficacy information for elderly patients has not been made available; however, the efficacy and safety of ELO in patients aged 65 years and older were reported to be the same as in the Phase III study.[22,23] In 45.9% of the study population, ELO prescriptions were started in an inpatient setting. The data source of the RWD-DB is mainly based on acute care hospitals that use the Diagnosis Procedure Combination-based Per-Diem Payment System.[27] Therefore, it may bias the current study because acute illness or acute exacerbation of the chronic disease is common in patients from these hospitals and these patients may face complications such as constipation.

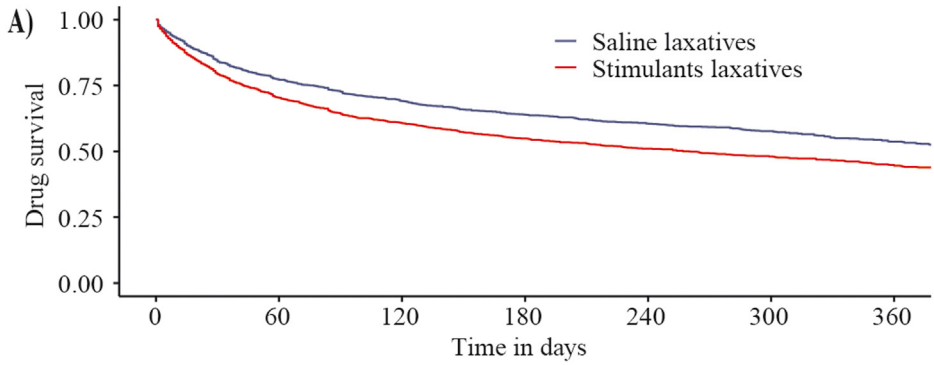
In the Comprehensive Survey of Living Conditions, the people who complained of constipation were predominantly women (43.7 out of 1000 women and 25.4 out of 1000 men). On the other hand, the difference was less in those aged 65 years and older (72.3 out of 1000 women and 64.1 out of 1000 men).[30] The proportion of women (49.8%) in this study may be influenced by the high proportion of elderly individuals, chronic comorbidity, and in-hospital setting of our study population.

The diagnosis rate of constipation was 79.7%; however, CC was less frequent (26.1%), despite the approval of ELO for CC in Japan. In the Diagnosis Procedure Combination data, some diseases (such as hemiplegia or paraplegia) were less correctly recorded.[31] This evidence suggested that CC is also less correctly recorded in the EMR, which explains our study's low diagnosis rate of CC. It was supported by the fact that 64.0% of the study population had been prescribed laxatives previously, and concomitant laxatives were prescribed at the initiation of ELO (19.5% for stimulant laxatives and 22.5% for saline laxatives). These results suggested that many patients in our study received ongoing management for constipation, namely, management for CC.

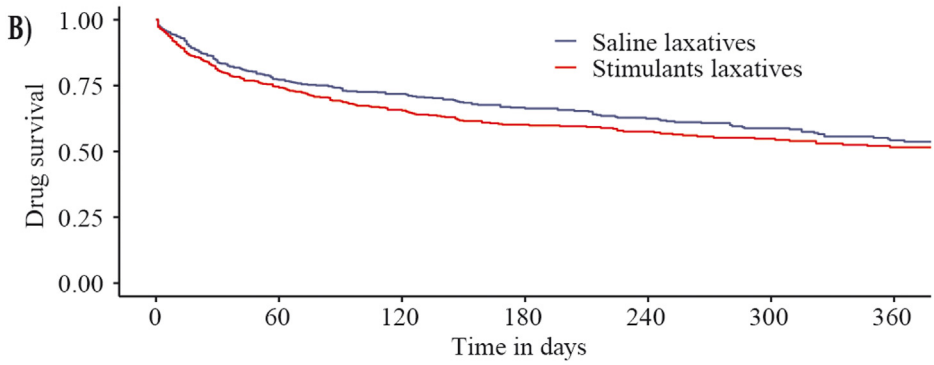
The initial dose was 10 mg/d (70.6%) (Table 2). This study did not calculate the percentage of patients who changed their ELO dose during treatment. Patients with more severe constipation may receive an ELO dose of 15 mg/d to relieve the symptoms. In the post hoc analysis of 2 pooled Phase III trials in which the doses of ELO were up- or downtitrated by patients themselves according to their symptoms, 66% of patients with very severe constipation were uptitrated to 15 mg/d at week 52.[21]

In this study, many patients discontinued ELO within 30 days, with a 30.3% continuation rate at 180 days (Table 3). This result was similar to that of a database study of other constipation medicines (linaclotide or lubiprostone) in the United States.[26]

After ELO prescription, the cumulative probability of ELO discontinuation was 78.7% at 360 days (Table 3). In addition, the risk of discontinuation was higher (HR = 1.54; 95% CI, 1.46–1.63) in inpatient settings (Figure 3). Inpatients undergoing surgery or chemotherapy may experience temporal but severe constipation.[32,33] There have been reports of a higher prevalence of con-



	Day	0	30	60	90	180	360
Stimulant laxatives	At risk	4700	2509	1725	1339	832	393
	Cumulative incidence	0	831	1078	1214	1380	1500
	Continuation (%)	100.0	79.3	70.3	64.3	54.9	44.6
	95% CI	100.0-100.0	78.0-80.6	68.8-71.9	62.6-66.0	52.9-56.9	42.3-47.0
Saline laxatives	At risk	4168	2494	1814	1456	905	467
	Cumulative incidence	0	576	755	853	1001	1114
	Continuation (%)	100.0	84.0	77.2	72.7	63.9	53.7
	95% CI	100.0-100.0	82.8-85.3	75.7-78.7	71.0-74.3	62.0-65.9	51.3-56.1



	Day	0	30	60	90	180	360
Stimulant laxatives	At risk	1082	633	455	360	212	100
	Cumulative incidence	0	184	229	258	297	319
	Continuation (%)	100.0	80.8	74.2	69.1	60.1	51.5
	95% CI	100.0-100.0	78.3-83.3	71.3-77.2	65.8-72.4	56.3-64.2	47.0-56.5
Saline laxatives	At risk	985	629	473	390	233	111
	Cumulative incidence	0	143	187	205	238	270
	Continuation (%)	100.0	83.7	77.1	74.0	66.3	54.2
	95% CI	100.0-100.0	81.3-86.2	74.3-80.1	70.9-77.2	62.6-70.2	49.5-59.4

Figure 4. Discontinuation of stimulant or saline laxatives in a patient after initiating elobixibat treatment. (A) Drug survival in patients with pretreatment of stimulant or saline laxatives and at least 1 visit during the follow-up period. (B) Drug survival in patients with pretreatment of stimulant or saline laxatives, at least 1 visit during the follow-up, and on-label use of elobixibat.

stipation in patients with cancer.[34] ELO may have been temporarily prescribed during the hospital stay of these patients. Twelve percent of patients were diagnosed with constipation by a surgery department (Table 1), and the diagnosis for CC by departments of malignant neoplasm was a risk factor for discontinuation (HR = 1.25; 95% CI, 1.02–1.54]) (Figure 3). Inpatients in departments of malignant neoplasm showed almost double the risk of ELO discontinuation (multiplied by both HRs: $1.51 \times 1.25 = 1.89$). Owing to the characteristics of this DB containing a large amount of inpatient data, the high discontinuation rate of ELO in this study may be overestimated compared with that in the general population.

Patients with end-stage CKD often have complications, such as constipation[35]; furthermore, magnesium or stimulant laxatives are not recommended because of the increased risk of hypermagnesemia or resistance, respectively.[1,12] ELO relieved symptoms of constipation in patients receiving dialysis.[24] However, there was a high risk of ELO discontinuation in patients with stage 5 CKD (HR = 1.38; 95% CI, 1.23–1.54), many of which required dialysis despite the minimal effect of CKD on ELO discontinuation (see Model 2 in Supplemental Table 3). We speculate that many patients with stage 5 CKD needing dialysis may receive prescriptions for constipation from another specialized medical institution after the initiation of ELO. It was reported that among 23 patients undergoing dialysis treated with ELO for 12 weeks at a dialysis clinic, only 2 patients discontinued ELO.[24] It suggested that the high risk of discontinuation in this study was influenced by the information bias of RWD-DB.

The risk of ELO discontinuation is lower in patients with diabetes mellitus, PD, or muscle wasting/atrophy. Diabetes mellitus, PD, and myopathies are well-known, common medical conditions complicated with CC[1,36,37]; therefore, patients with these comorbidities may need long-term treatment for CC. Recently, the improvement of spontaneous bowel movement and QOL under ELO treatment in patients with diabetes mellitus was reported,[38] and a double-blind clinical trial in patients with PD is ongoing.[39]

The risk of ELO discontinuation was lower in patients with previous laxative treatments (HR = 0.69 for rhubarb and HR = 0.86 for picosulfate/saline laxatives). Patients with severe constipation or dissatisfaction with previous treatment may be prone to discontinuing ELO.

Patients diagnosed with constipation in psychiatric departments also had a low risk of ELO discontinuation. Patients with psychiatric diseases may require long-term management at the same medical institute, and antipsychotic agents such as anticholinergics may cause CC as a side effect,[40] and therefore, these patients may require long-term laxative treatment. The efficacy of ELO in psychiatric departments, mainly in patients with depression, has been reported.[25]

The proportion of stimulant and saline laxative prescriptions in the look-back period was 43.8% and 39.1%, respectively (Table 1). Compared with the results of previous studies, the ratio of stimulants was almost equal (43.8% vs 42.6%), and the proportion of saline laxatives was lower in the present study (39.1% vs 54.6%).[23] Saline laxatives tend to be prescribed to patients with mild constipation. A higher proportion of saline laxative prescription in the previous study may reflect a higher proportion of mild constipation than this study.

The proportion of stimulants and saline laxatives decreased from before the index date to the index date (52.2% vs 21.7% and 48.7% vs 26.0%, respectively). In addition, approximately 50% of patients experienced the withdrawal of stimulant or saline laxatives (55.4% and 46.3%, respectively) 360 days after ELO initiation (Figure 4). These results suggest that ELO may be helpful for the withdrawal of stimulants or saline laxatives in the early phase of treatment and long-term treatment for CC. Due to induced resistance by the long-term use of stimulant laxatives, a short-term or need-based prescription was recommended.[1,3] Effects of stimulant laxatives for constipation act via stimulation of high-amplitude propagated contractions.[3] Administration of ELO rapidly induces a mild stimulation of high-amplitude propagated contractions by BA in an animal model[41]; therefore, ELO might partly act as an alternative to stimulant laxatives. In addition, MgLx may cause severe hypermagnesemia in patients with renal impairment and/or in elderly populations.[1,12,13] However, only 22.5% of the study patients aged 65 years and older were monitored for serum magnesium level at the index date, and 4.3% showed hypermagnesemia. ELO promotes water secretion in the colon same as the saline laxatives; therefore, it could be used as an alternative to saline laxatives like MgLx. Withdrawal of these agents under ELO treatment may be of clinical benefit to patients.

Limitations

Because the RWD-DB is anonymized at each medical institution, obtaining patient data after being referred to another hospital is impossible. In addition, the DB consists mainly of acute-care hospitals, and many patients may experience hospital referrals. Therefore, data from the RWD-DB may not fully reflect clinical practice in Japan. Because the discontinuation of ELO was defined based on prescription, actual adherence could not be evaluated. In addition, the reasons for discontinuation of ELO, such as relief of symptoms and adverse events, cannot be determined because symptoms of CC, stool consistency and QOL were not recorded in the database. Errors in data entry for diagnosis codes may occur during routine medical care, causing misclassification in this study.

Conclusions

The rate of discontinuation of ELO, 360 days after initiation, was 78.7%. The risk factors for discontinuation were defined as younger age, inpatient setting, stage 5 CKD, and a diagnosis of constipation by a department of malignant neoplasm. Various diagnoses and treatments such as constipation, diabetes mellitus, and PD and previous treatment with laxatives were associated with a lower risk of ELO discontinuation. The prescription rate of stimulants and saline laxatives was markedly decreased after ELO initiation, and about half of patients discontinued these laxatives within 360 days. Our findings may be helpful for the management of CC in real-world care settings.

Declaration of Competing Interest

EA Pharma Co, Ltd and Mochida Pharmaceutical Co, Ltd, funded this study. EA Pharma Co, Ltd has a license for elobixibat in Japan.

Hisanori Masaki and Sonoko Ishizaki are full-time employees of EA Pharma Co, Ltd. Koji Shimamoto and Shoichiro Inokuchi are full-time employees of Real World Data Co, Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

CRediT authorship contribution statement

Hisanori Masaki: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Koji Shimamoto:** Conceptualization, Methodology, Data curation, Formal analysis, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Shoichiro Inokuchi:** Conceptualization, Methodology, Data curation, Formal analysis, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sonoko Ishizaki:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2023.100724.

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