Original Article

Factors associated with long-term efficacy of lubiprostone for chronic constipation

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The prevalence of chronic constipation in Japan is increasing, and is presently almost 1 in 5 people. Because constipation is common, especially in older patients, to avoid adverse events and polypharmacy, simple treatments at low doses are generally desired. Although the chloride channel activator lubiprostone is candidate drug that may solve these problems, factors associated with the long-term efficacy of lubiprostone monotherapy for chronic constipation in treatment-naive patients remain unclear. We here retrospectively investigated the clinical characteristics and factors of patients who achieved long-term constipation improvement with lubiprostone monotherapy. Seventy-four patients with chronic constipation treated with lubiprostone monotherapy (24 or 48 μg/day) from January 2017 to August 2018 were reviewed. Patient characteristics and clinical time-courses were compared between those who sustained improvement for 6 months, and those who became refractory to treatment. In 54 patients (76.1%), constipation improved by lubiprostone administration for 6 months. On multivariate analysis, a significant clinical factor associated with sustained improvement was a starting lubiprostone dose of 24 μg/day (odds ratio: 5.791; 95% confidence interval: 1.032–32.498; $p = 0.046$). A starting lubiprostone dose of 24 μg/day has efficacy to improve chronic constipation and to prevent adverse events of nausea and diarrhea in Japanese patients.

***Key Words*: constipation, lubiprostone, chronic disease, drug therapy, starting dose**

The prevalence rate of chronic constipation is increasing in Japan, as its population continues to age. A comprehensive survey of living conditions in Japan conducted by the Ministry of Health, Labour and Welfare in 2019 revealed that 2.54% of adult men and 4.37% of women had chronic constipation, and that the rates were even higher in the older population aged 65 years or older (6.41% in men and 7.23% in women).[1] Because treatment of chronic constipation imposes a large health economic burden on society,[2,3] constipation is a crucial problem that needs to be addressed. Treatment for chronic constipation is often required long-term, resulting in the use of multiple medications, with increases in the dose of osmotic laxatives and the addition of stimulant laxatives, particularly in older patients.[4] Although stimulant laxatives, such as magnesium oxide and sennosides have long been used in Japan, more options are now available for the conservative treatment of constipation, because new medications with different mechanisms of action have started to be covered by national health insurance. With this background, the *Clinical Practice Guidelines for Chronic Constipation 2017* was published by a research group affiliated with the Japanese Society of Gastroenterology.[5] However, despite this increase in medication options, guidelines as to which drugs should be used in which patients have not been established to date. It is therefore necessary to determine the characteristics of the new constipation drugs that are covered by national health insurance, to facilitate the appropriate selection of drugs and treatment strategies. In addition, to avoid adverse events and polypharmacy, simple treatments for chronic constipation that are effective at low doses are desired in clinical practice. Among the new therapeutic agents for chronic constipation, lubiprostone, which acts on intestinal mucosal epithelial function, promotes the osmotic secretion of intestinal fluids, thereby softening the stool and reducing the intestinal stool transit time, thus facilitating bowel movement.[6,7] A phase III randomized controlled trial (RCT) showed the efficacy of lubiprostone compared with placebo.[8] In a meta-analysis using RCTs, compared with the placebo group, the lubiprostone group showed significantly improved in 24 h spontaneous bowel movement (SBM) frequency [relative risk (RR): 1.55; 95% confidence interval (95% CI): 1.32–1.83], and weekly frequency of more than 3 SBMs (RR: 1.63; 95% CI: 1.39–1.91).[9] However, evidence for the long-term efficacy of lubiprostone in constipation-drug-naive Japanese patients with chronic constipation is not available, and factors associated with the long-term efficacy of lubiprostone monotherapy for chronic constipation have not been investigated to date.

Therefore, this study was aimed to identify approaches to further rationalize the treatment of chronic constipation for constipation-drug-naive Japanese patients, with the appropriate starting dose of lubiprostone. In addition, we retrospectively investigated the clinical characteristics of patients who achieved long-term improvement of constipation with lubiprostone monotherapy as an initial treatment, as well as the factors associated with this improvement.

Patients and Methods

A total of 74 constipation-drug-naive patients (27 men and 47 women; mean age, 68.1 ± 16.1 years) with chronic constipation, who were treated with lubiprostone monotherapy (24 or 48 μg/day) as an initial treatment at Tokyo Medical University hospital over a 20-month period (from January 1, 2017 to August 31, 2018) were retrospectively reviewed. In this study, chronic constipation was defined according to the *Clinical Practice Guidelines for Chronic Constipation 2017*, which were published by a research group affiliated with the Japanese Society of Gastroenterology in 2017 to guide the treatment of chronic constipation patients in Japan.[5] Patients with insufficient data in

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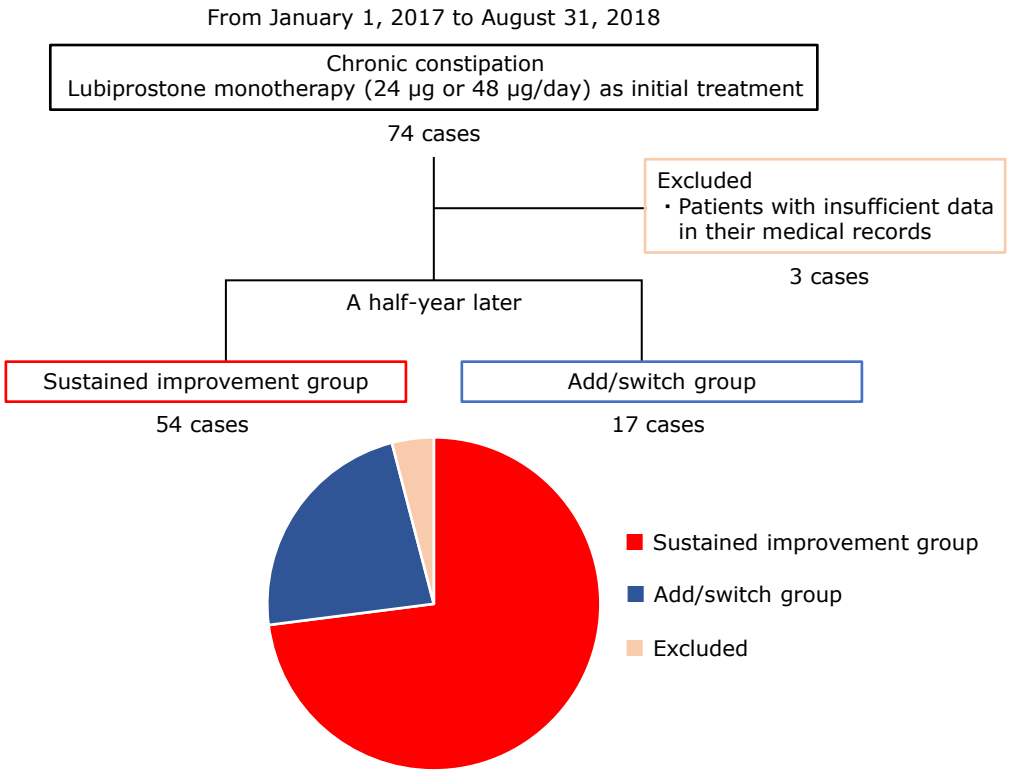

Fig. 1. Study design. Sustained improvement group: patients who showed sustained improvement of constipation with lubiprostone monotherapy. Add/switch group: patients who received additional or different drugs due to lubiprostone becoming ineffective during the follow-up period.

their medical records, those who were not followed up for more than 6 months, and those taking laxatives at the time of consultation were excluded (Fig. 1). The primary outcomes of this study were to clarify the long-term efficacy of lubiprostone for constipation-drug-naive Japanese patients with chronic constipation, and to identify clinical factors associated with the long-term improvement of constipation.

At 6 months after the initiation of lubiprostone therapy, patients were divided according to whether they showed sustained improvement of constipation with lubiprostone monotherapy (sustained improvement group), or whether their treatment was changed to a higher dose of lubiprostone or to a different medication due to low-dose lubiprostone becoming ineffective during the follow-up period, or due to adverse events (add/switch group). Although the Japanese regulatory approval documents and the package insert for lubiprostone state that the recommended dose of lubiprostone for adults is 24 μg twice a day, the daily dose of lubiprostone was determined at the discretion of the outpatient clinician (24 or 48 μg/day).

Ethics approval. As this study was a retrospective study, no clinical trial was registered. All procedures involving human participants were in accordance with the ethics standards of our institutional research committee and with the principles of the Declaration of Helsinki, and were approved by the Institutional Review Board of Tokyo Medical University (study approval number: T2020-0082). The need for written informed consent was waived because of the retrospective design of the study. The authors have no ethical conflicts of interest to disclose in association with this study.

Statistical analysis. The characteristics (age, sex, comorbidities, medication history, and history of abdominal surgery), starting dose of lubiprostone, and clinically significant adverse events associated with the treatment were investigated in both groups. The presence of comorbidities, including diabetes, hypothyroidism, chronic kidney disease, dementia, neurological disease, mental disorders, functional dyspepsia, irritable bowel syndrome (IBS) with predominant constipation, collagen disease, amyloidosis, and anal disease, as well as medication history, including the use of probiotics, anticholinergic drugs, antipsychotics, opioids, chemotherapeutic drugs, cardiovascular agonists, diuretics, aluminum hydroxide preparations, and oral iron preparations were also investigated. Age was expressed as the mean ± SD. Categorical variables for sex, comorbidities, initial dose of lubiprostone, history of oral medication, and number of abdominal symptoms excluding constipation are summarized as n, and compared using χ^2 tests and the t test between the sustained the improvement group and the add/switch group. Logistic regression analysis including possible factors was performed to determine the factors associated with the was improvement of constipation by lubiprostone treatment. A p value of less than 0.05 was considered to indicate a statistically significant difference between groups. Odds ratios (ORs) and 95% CIs were estimated for associations with the sustained improvement group. Statistical analysis was performed using IBM SPSS software (ver. 28.0, IBM Corp., Armonk).

Results

Patient characteristics. A total of 74 constipation-drug-naive Japanese patients with chronic constipation, who were initially treated with lubiprostone monotherapy (24 or 48 μg/day) were enrolled in this study (Fig. 1). Three patients (4.0%) with insufficient data in their medical records were excluded from the analysis, and a total of 71 patients were analyzed. Of the 71 patients, 54 (76.1%) were in the sustained improvement group, and 17 (23.9%) were in the add/switch group (Table 1). Many of

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Table 1. Patient characteristics

Total number	74
Sex (men/women)	27/47
Mean age ± SD (years)	68.1 ± 16.1

Comorbidities	
Diabetes	15
Hypothyroidism	5
Chronic kidney disease	21
Dementia	6
Neurological disorders	26
Mental disorders	14
Functional dyspepsia	10
Irritable bowel syndrome with predominant constipation	51
Collagen diseases	0
Amyloidosis	1
Anal disease	2
History of abdominal surgery	5

Initial dose (μg/day)	
24	32
48	42

Medical history	
Probiotics	3
Anticholinergic drugs (including anti-Parkinson's disease drugs)	15
Antipsychotics	13
Opioids	1
Chemotherapeutic drugs	5
Cardiovascular agonists	11
Diuretics	8
Aluminum hydroxide preparations	1
Oral iron preparations	2

Number of abdominal symptoms excluding constipation	
0	54
1	15
2	4
3	1

Table 2. Adverse events in patients treated with lubiprostone

	Sustained improvement group (n = 54)	Add/switch group (n = 17)
Nausea	0	0
Diarrhea	2	0
Abdominal pain	0	0
Vomiting	0	0
Abdominal distension	0	0
Dizziness	0	0
Fatigue	0	1

the patients were of advanced age, and the mean age was 68.1 ± 16.1 years. The male-to-female ratio was 1:1.7, with 27 men and 47 women. The most common comorbidity was IBS with predominant constipation (51 patients), followed by neurological disorders (26 patients) and chronic kidney disease (21 patients). Anticholinergic drugs, including anti-Parkinson's disease drugs, were the most commonly prescribed medication (15 patients), followed by antipsychotics (13 patients). The starting dose of lubiprostone was 24 μg/day in 32 patients and 48 μg/day in 42 patients. There was no statistically significant association between the starting doses and the severity of symptoms (p = 0.852).

Adverse events of lubiprostone. None of the patients in either group developed nausea, upon lubiprostone administration, and there was no significant difference in the rate of adverse events between the sustained improvement group and the add/switch group (Table 2).

Different characteristics between the sustained improvement group and the add/switch group. When patient characteristics of sex, age, comorbidities, initial dose of lubiprostone, history of oral medication, and number of abdominal symptoms excluding constipation were compared between the 2 groups, the prevalence of 2 factors, namely, the starting dose of lubiprostone and the use of anticholinergic drugs, significantly differed between the 2 groups (p = 0.004 and 0.009, respectively) (Table 3). The sustained improvement group had a higher rate of treatment with 24 μg/day of lubiprostone and anticholinergic drug use than those in the add/switch group.

Multivariate analysis of factors associated with the long-term efficacy of lubiprostone. On multivariate logistic regression analysis using the 6 variables (p<0.1) identified as possible predictors of constipation improvement in constipation-drug-naive patients, namely, hyperthyroidism, neurological disorders, history of abdominal surgery, initial dose of lubiprostone of 24 μg/day, and taking anticholinergic drugs and diuretics, the only initial dose of lubiprostone of 24 μg/day was identified as a statistically significant risk factor (OR: 5.791; 95% CI: 1.032–32.498; p = 0.046) (Table 4). The goodness of fit of the multivariate logistic regression model was confirmed to be valid by the Hosmer–Lemeshow test (p = 0.926).

Discussion

In the initial treatment of chronic constipation, it is important to minimize the occurrence of adverse events, and thereby maintain good adherence to medications. If the treatment is inappropriate or excessive doses of medications are used, frequent diarrhea and nausea are observed, leading to poor adherence medication. This may lead to a vicious cycle, namely, the deterioration of symptoms, decreases in patient satisfaction, and self-discontinuation of constipation treatment. In this study, we aimed to identify approaches to rationalize the treatment of chronic constipation using lubiprostone for constipation-drug-naive Japanese patients and to investigate the clinical characteristics of patients who achieved long-term improvement of constipation with lubiprostone monotherapy. We demonstrated that 76.1% of constipation-drug-naive Japanese patients showed improvement in their constipation by lubiprostone monotherapy for 6 months,

Table 3. Different patient characteristics between the sustained improvement group and the add/switch group

	Sustained improvement group	Add/switch group	*p* value
Total number	54	17	
Sex (men/women)	19/35	6/11	0.993
Mean age ± SD (years)	69 ± 15.6	62.6 ± 16.3	0.153
Comorbidities			
Diabetes	12	3	0.490
Hypothyroidism	2	3	0.085
Chronic kidney disease	14	7	0.230
Dementia	6	0	0.180
Neurological disorders	23	3	0.063
Mental disorders	11	3	0.056
Functional dyspepsia	6	1	0.463
Irritable bowel syndrome with predominant constipation	39	11	0.554
Collagen diseases	0	0	—
Amyloidosis	1	0	0.761
Anal disease	2	0	0.576
History of abdominal surgery	2	3	0.085
Initial dose of lubiprostone (μg/day)			
24/48	28/26	2/15	0.004
History of oral medication			
Probiotics	3	0	0.434
Anticholinergic drugs	15	0	0.009
Antipsychotics	10	3	0.624
Opioids	1	0	0.761
Chemotherapeutic drugs	3	2	0.344
Cardiovascular agonists	7	4	0.245
Diuretics	4	4	0.087
Aluminum hydroxide preparations	1	0	0.761
Oral iron preparations	1	1	0.424
Number of abdominal symptoms excluding constipation			
0/1/2/3	40/11/2/1	13/3/1/0	0.852

Table 4. Univariate and Multivariate analysis investigating factors associated with long-term efficacy of lubiprostone

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Hypothyroidism	0.179 (0.27–1.181)	0.085		0.157
Neurological disorders	3.462 (0.890–13.471)	0.063		0.143
History of abdominal surgery	0.179 (0.27–1.181)	0.085		0.215
Initial dose of lubiprostone, 24 μg/day	8.077 (1.682–38.784)	0.004	5.791 (1.032–32.498)	0.046
Anticholinergic drugs	1.385 (1.174–1.634)	0.009		0.998
Diuretics	0.260 (0.057–1.182)	0.067		0.156

Multivariate logistic regression analysis used the 6 variables ($p<0.1$ by the Univariate analysis) identified as possible predictors of constipation improvement in constipation-drug-naive patients.

and that on multivariate analysis, a significant clinical factor associated with the sustained improvement of constipation was a starting lubiprostone dose of 24 μg/day (OR: 5.791; 95% CI: 1.032–32.498; $p = 0.046$). Although dose adjustment depending on the characteristics of each patient is considered to be necessary, we think a lubiprostone dose of 24 μg/day (half-dose of the recommended dose in Japan), rather than a dose of 48 μg/day (standard-dose in Japan), is effective to maintain medication adherence in constipation-drug-naive Japanese patients with chronic constipation.

In recent years, adverse events due to polypharmacy in older patients has become a serious problem, and several chronic diseases, including constipation, are considered to be one of the major causes.[10] In Japan, for a long time, the main drugs used in clinical practice for chronic constipation were osmotic laxatives (e.g., MgO) and stimulant laxatives (e.g., senna, sennosides, and sodium picosulfate), and multiple medications were often required to control bowel habits.[11] The facts that the long-term use of magnesium-containing saline laxatives causes hypermagnesemia, particularly in patients with chronic renal diseases,[12]

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and stimulant laxatives causes intestinal dilation and elongation,[13–16] were serious problems in the Japanese medical community. To overcome these problems, the Japanese clinical guidelines for constipation recommends the use of lubiprostone or MgO as the first-line drug for constipation patients.[5] These guidelines recommends the use of lubiprostone or MgO as the first-line drug for constipation patients. Of several secretagogues, lubiprostone is an orally active prostone that locally and selectively activates chloride channel type 2 on the apical surface of the intestinal epithelium, and enhances intestinal fluid secretion without altering serum electrolyte levels. Lubiprostone treatment increases the frequency of SBMs, decreases colonic transit time, and improves quality of life (QOL) of patients with chronic constipation compared with placebo.[9] Many clinical trials have shown that lubiprostone improves abnormal bowel habits in patients with either idiopathic or opioid-induced constipation.[17–19] However, whether lubiprostone monotherapy can achieve long-term efficacy in constipation-drug-naive patients, and details of the clinical characteristics of patients who achieved long-term improvement of their constipation with lubiprostone monotherapy remained unclear. Most studies investigating the efficacy of lubiprostone analyzed patients who were receiving concomitant therapy of lubiprostone with other drugs, or patients that had previously been treated with constipation drugs. The strong point of our present study was that we demonstrated that 76.1% of constipation-drug-naive Japanese patients with chronic constipation showed improvement by lubiprostone monotherapy for 6 months. In addition, lubiprostone dose of 24 μg/day (half the dose recommended in Japan) was required to receive efficacy for maintenance of constipation in such patients. It would hence be useful to conduct a prospective RCT in the future to investigate the association between the effects of different lubiprostone doses (24 or 48 μg/day) and the severity of constipation, and factors that contribute to the therapeutic effects of constipation-drug-naive patients.

In phase II and III studies using lubiprostone in Japan, as adverse reactions, diarrhea, nausea and abdominal pain developed in 30.2%, 23.2%, and 5.7% of the patients respectively.[18,20] A late phase II dose-response study in Japan showed an increase in nausea and diarrhea in a dose-dependent manner (nausea: 16 μg/day, 0.0%; 32 μg/day, 7.0%; and 48 μg/day, 15.9%; and diarrhea: 0.0%, 9.3%, and 18.2%, respectively).[18] On meta-analysis, the incidence rate of treatment-associated adverse events by lubiprostone was 24.2% to 50.8% for idiopathic constipation, which was higher than that of the control group, and the incidence rate of nausea as a major adverse event in patients with idiopathic constipation (22.9%) was higher than that in patients with opioid-induced constipation (12.9%). Regarding avoiding the development of nausea and diarrhea, Sanomura *et al.*[21] reported that lubiprostone 12 μg/day titration therapy enables the optimal dosage to be reached while avoiding adverse events. In addition, on multivariate analysis in the present study, a significant clinical factor associated with the sustained improvement was a starting lubiprostone dose of 24 μg/day, rather than 48 μg/day. Accordingly, although dose adjustment depending on the characteristics of each patient is necessary, starting with a low dose of lubiprostone may be useful also for avoiding adverse events. To set the initial treatment dose, the severity of constipation of the patient should be accurately evaluated, and drug selection and dose setting should be performed with care before the drug is prescribed.

The second reason why the start of medication at the lower dose (24 μg/day) had efficacy for constipation was more effective than the higher dose was that it enabled good medication adherence. Maintaining good medication adherence is crucial for the treatment of chronic constipation, and the number of drugs to be taken has been reported as a factor that lowers medication adherence.[22] The use of a lower starting dose of lubiprostone reduces the number of pills the patient needs to take, as well as the frequency, thereby contributing to good medication adherence, and consequently, to the alleviation of symptoms. However, this study is a retrospective study, and we did not investigate medication adherence, so it is unknown whether adherence was really improved by the lower starting dose of lubiprostone.

With respect to the health economic aspects of chronic constipation, in the US that the frequency of constipation-related emergency outpatient visits increased by 41.5% from 2006 (497,034) to 2011 (703,391), and the total cost of constipation-related emergency outpatient visits increased by 121.4% from 2006 (732,886,977 USD) to 2011 (1,622,624,341 USD).[23] Given such significant increases in the frequency of emergency outpatient visits and the associated costs, and because pharmacotherapy for constipation is usually required long term, lubiprostone therapy at a low dose for a long period may lead to reduced medical costs owing to reductions in the costs of medications and the effective management of constipation.

Limitations of this study include that it was a retrospective, open-label, uncontrolled study on a small number of Japanese patients. Nevertheless, because the number of Japanese patients treated with lubiprostone remains limited, it will be useful in the future to clarify the clinical characteristics of new constipation drugs for Asians, particularly for the aging Japanese population, to make comparisons among races in the future. Secondly, the severity of chronic constipation symptoms, measured by the Bristol Stool Form Scale and the colon transit time of stool were not assessed in each patient before the administration of lubiprostone.[24] Therefore, a prospective study should be conducted to compare changes in the frequency of complete spontaneous bowel movement, the form of stool according to the Bristol Stool Form Scale, and QOL as measured by the Patient Assessment of Constipation Quality of Life questionnaire between before and after treatment with lubiprostone.

Conclusions

This retrospective study investigated the clinical characteristics of patients treated with lubiprostone and factors associated with sustained treatment effects in a small and selected group of Japanese patients. We demonstrated that three fourths of older constipation-drug-naive Japanese patients showed symptom improvement by lubiprostone monotherapy for long periods, and that a starting lubiprostone dose of 24 μg/day is recommended for the sustained control of constipation, owing to the lower incidence of adverse events.

Author Contributions

TMorise, MF, TK, and TI, study design, data analysis, and script preparation; TMorise, NN, SK, YY, AS, KU, YKoyama, AM, HY, TMatsumoto, and YKagawa, acquisition of data; MF, MS, TK, and TI, supervision of manuscript preparation. All authors have read and approved the submitted version of the manuscript.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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