

Linacotide for treating patients with irritable bowel syndrome with predominant constipation: a multicentre study of real-world data in China

Lan Liu, Weihao Zhang, Wei Zhao, Shuang Guo, Yaojun Wang, Xiaojun Lv, Bing Li, Haiping Wang, Enbin Xu, Quan Li, Qin Zhu, Xiao bo Gou, Weidong Zhao and Jianqiang Guo 

Abstract

Introduction: Linacotide, a guanylate cyclase C agonist that improves the symptoms of irritable bowel syndrome with predominant constipation (IBS-C), has been recently approved for IBS-C treatment. This study aimed to report real-world data on linacotide treatment in China.

Methods: This was a prospective multicentre study of the effectiveness of linacotide treatment in patients with IBS-C from 10 primary medical institutions. Changes in defecation, abdominal symptoms, the IBS symptom severity scale (IBS-SSS), IBS quality of life questionnaire (IBS-QOL), Zung Self-Rating Anxiety Scale and Self-Rating Depression Scale in patients were evaluated to determine the drug's clinical efficacy and safety.

Results: We enrolled 97 patients (mean age: 52.39 ± 13.99 years), 55 of whom were women (56.7%). In terms of efficacy, the number of the patients' defecation per week and Bristol stool form scale scores significantly increased at week 4 and week 12 compared with the values at the baseline. The baseline average IBS-SSS score was 211.01 ± 81.23 . Of the patients, 24 had severe IBS-C, and their IBS-SSS scores at week 4 (51.81 ± 54.42) and week 12 (9.3 ± 30.39) significantly decreased and showed a pronounced improvement. The IBS-QOL total scores at week 4 and week 12 gradually decreased compared with that at the baseline and the QOL significantly improved. Treatment satisfaction rate was 79.3% in week 4 and 100% in week 12, showing a gradually increased satisfaction and significant differences. However, 11 cases (11.3%) had diarrhoea.

Conclusion: Linacotide has proved to be a safe and effective drug to improve IBS-C symptoms and severity.

Keywords: abdominal pain, adverse events, Bowel movements, IBS-C, linacotide

Received: 5 November 2021; revised manuscript accepted: 17 March 2022.

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that is mainly characterised by abdominal pain, abdominal distension and altered bowel habits. The Rome criteria classify IBS into the following four subtypes: IBS with predominant constipation (IBS-C), IBS with

predominant diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M) and IBS unclassified (IBS-U).^{1,2} A literature review from Rome committees has revealed that the prevalence of IBS was 9.6% in Asia and 8.1% in North America, Europe, Australia and New Zealand.³ The prevalence of IBS in China was 1–18% of Rome I/II and 5–16% of Rome III.⁴

Ther Adv Gastroenterol

2022, Vol. 15: 1–12

DOI: 10.1177/
17562848221092596

© The Author(s), 2022.
Article reuse guidelines:
[sagepub.com/journals-](https://sagepub.com/journals-permissions)
[permissions](https://sagepub.com/journals-permissions)

Correspondence to:

Jianqiang Guo
Department of
Gastroenterology, The
Second Hospital of
Shandong University, NO.
247 of Beiyuan Street,
Jinan 250033, Shandong,
People's Republic of China
guo_jianqiang@126.com

Lan Liu

Weihao Zhang

Wei Zhao

Shuang Guo

Department of
Gastroenterology, The
Second Hospital of
Shandong University,
Jinan, China

Yaojun Wang

Department of
Gastroenterology,
Sunshine Union Hospital,
Weifang, China

Xiaojun Lv

Department of
Gastroenterology, Fangzi
District People's Hospital,
Weifang, China

Bing Li

Department of
Gastroenterology,
Wendeng District People's
Hospital, Weihai, China

Haiping Wang

Department of
Gastroenterology,
Rongcheng Hospital
of Traditional Chinese
Medicine, Weihai, China

Enbin Xu

Department of
Gastroenterology,
Rongcheng People's
Hospital, Weihai, China

Quan Li

Department of
Gastroenterology,
Shouguang Hospital
of Traditional Chinese
Medicine, Weifang, China

Qin Zhu

Department of
Gastroenterology, Linqu
People's Hospital,
Weifang, China

Xiao bo Gou

Department of

Gastroenterology, Longkou
Hospital of Traditional
Chinese Medicine, Yantai,
China

Weidong Zhao
Department of
Gastroenterology, Zibo
Municipal Hospital, Zibo,
China

According to Rome IV, IBS-C is a subtype of IBS with $> 1/4$ of bowel movements with the Bristol stool form scale (BSFS) types 1 or 2 and $< 1/4$ of bowel movements with the Bristol stool types 6 or 7, mainly characterised by abdominal symptoms (e.g. abdominal pain and abdominal distension), reduced bowel movements, hard stools, laborious defecation and poor defecation. Approximately one-third of cases of IBS are IBS-C.¹ Reports have commonly recommended lifestyle changes or long-term medication to control symptoms in patients with IBS-C.⁵ However, these treatments are mainly aimed at alleviating a single symptom, often with multiple switches of treatments and drugs without satisfactory efficacy.⁶ A study of the burden of IBS disease conducted in China reported that the total annual expenditure per patient was estimated at RMB 18,262.⁷ Thus, IBS imposes a huge financial burden on patients and healthcare systems.⁸

Linaclotide is a 14-amino acid guanylate cyclase C agonist that is rarely absorbed into the blood. It was approved by the Food and Drug Administration (FDA) in 2012 for the treatment of adult chronic idiopathic constipation and IBS-C, and China also approved linaclotide for the treatment of adult IBS-C. Based on the results of multiple clinical trials in 2019, linaclotide treatment resulted in significantly improved abdominal pain and bowel movements compared with a placebo.⁹ However, data from clinical trials may not accurately reflect the clinical practice setting.^{10,11} Real-world studies on linaclotide for IBS-C are few, and no real-world studies on linaclotide use in China or even in Asia have been conducted.^{12,13} Therefore, in this multicentre patient cohort, we aimed to determine the efficacy and safety of linaclotide in clinical practice by assessing changes in defecation, abdominal symptoms, the IBS symptom severity scale (IBS-SSS), the IBS quality of life questionnaire (IBS-QOL), the Zung Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) in patients with IBS-C who underwent a 12-week treatment with linaclotide.

Methods

This study was a multicentre, prospective, single-arm, observational real-world study. Patients with IBS-C were recruited from 10 primary medical institutions in Shandong Province from 1 September 2020 to 31 March 2021.

The study was approved by the research ethics committee of the Second Hospital of Shandong University (LCLL-2021-004) and was registered at the Chinese Clinical Trial Registry (ChiCTR2100052551). Each patient signed an informed consent form, and all patient details were simultaneously de-identified. The inclusion criteria were as follows: voluntary participation in this study and ability to abide by the study regulations, understand and adhere to the follow-up plan, and correctly record medication, symptom assessment and adverse events; Chinese patients aged ≥ 18 years; with IBS-C meeting the Rome IV classification; underwent colonoscopy in the previous 3 months and suspension of other medications for constipation for 1 week. The exclusion criteria were as follows: with contraindications to linaclotide, such as allergy to linaclotide or any excipients and known or suspected mechanical gastrointestinal obstruction; not expected to adhere to linaclotide alone; pregnant and lactating patients; participating in other clinical trials and those who were considered unsuitable for other reasons. This study was reported according to the Strengthening The Reporting of OBServational Studies in Epidemiology (STROBE) guidelines¹⁴ (see checklist in Supplementary Material).

The study was conducted in the context of real clinical practice, and the enrolled patients took 290 μg linaclotide orally once a day, half an hour before breakfast and were followed-up for 12 weeks after the enrolment. Patient self-evaluation records were completed daily after group entry and were collected at each follow-up. The self-assessment records contained basic information on the patients, daily medication, defecation and abdominal symptoms (Table 1). Medications for diseases, except IBS-C, were permitted during the study and documented in Table 1; however, administration of enema or other laxatives was prohibited. The patients were followed-up once a week during 0–4 weeks and once at 8 and 12 weeks; both face-to-face and the information collection and symptom assessment scale were completed (Table 2). A final follow-up by telephone was conducted within 1 week from study withdrawal. A visit record was completed for each follow-up to assess changes in bowel movements, abdominal symptoms, treatment satisfaction, scores on the IBS-SSS, IBS-QOL, SAS and SDS 12 weeks after linaclotide treatment, and adverse events and withdrawal (Table 3).

Table 3. Visit record.

Hospital		Date	
Name	Telephone number	Sex	Age
Height	Body weight	Blood pressure	Pulse
Nation	Diagnosis and medical history	Abdominal symptoms	Other discomfort
Start and end dates	Drug use	Defecation	Abdominal pain
	Linaclootide	Defecation frequency	Abdominal distension
	Combined medication (Name, dosage)	BSFS	Abdominal discomfort
IBS-SSS (Visits 1, 5 and 7)	SAS (Visits 1, 5 and 7)	SDS (Visits 1, 5 and 7)	
IBS-QOL (visits 1, 5 and 7)	Total score	1-8	9-15
		16-19	20-22
		23-25	26-29
		30-31	32-34
Patient satisfaction (visits 2-7)	Very satisfied	Satisfied	Basic satisfied
			Partially dissatisfied
			Completely dissatisfied
Reasons for quitting the study (exit study by follow-up on telephone)			
Note (other issues requiring documentation)			
Recorder and recording time			
BSFS, Bristol stool form scale; IBS-QOL, irritable bowel syndrome quality of life questionnaire; IBS-SSS, irritable bowel syndrome symptom severity scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale. 1. This visit record was filled out by the assigned doctor for each visit. 2. Defecation frequency: number of defecations per week. 3. Scores of abdominal pain, abdominal distension and abdominal discomfort within 24 h. The range is 0-10 with higher scores indicating more severe symptoms.			

mild anxiety, 60–69 for moderate anxiety and > 70 for severe anxiety. The standard cut-off scores for the SDS are < 53 for normal, 53–62 for mild depression, 63–72 for moderate depression and > 72 for severe depression.

Adverse events, tolerances and study withdrawal were recorded at each follow-up. The severity of adverse events, the causal relationship with linaclotide, and the tolerance and safety of the treatment were assessed according to the occurrence of adverse events.

Statistical analysis of data was performed using standard statistical methods and the SPSS 20.0 software (IBM Corporation, Armonk, NY, USA). Descriptive data are expressed as mean \pm standard deviation (SD); a paired *t*-test was used to compare pre- and post-treatment follow-up results, and multiple group results comparisons were analysed using one-way analysis of variance (ANOVA) or Kruskal–Wallis methods. In addition, data on grade variables, such as patient satisfaction scores, were analysed using the Mann–Whitney *U* test. Significance was set at $p < 0.05$.

Results

Patient demographic and baseline characteristics

Overall, 120 patients with IBS-C, who all signed informed consent forms and met the Rome IV classification for IBS-C, were recruited from 10 centres. Some patients who did not provide complete visit records ($n = 11$) or were lost to follow-up ($n = 12$) were excluded from the study. The remaining 97 patients provided complete follow-up records, of whom 43 (44.3%) continued linaclotide administration at 12 weeks, 39 (40.2%) stopped linaclotide treatment before 4 weeks and 15 (15.5%) stopped linaclotide treatment at 4–12 weeks (Figure 1).

Of the 54 patients (55.7%) without 12 weeks of linaclotide treatment, 30 quit the study due to significantly improved symptoms, 5 due to lack of efficacy, 11 due to excessive diarrhoea and 8 other patients withdrew for other reasons, such as economic issues and timing (Figure 1).

Finally, the 97 patients who met the linaclotide administration criteria were assessed for drug

efficacy. The main baseline demographic and IBS-C related features were evaluated for patients who completed the study (Table 4). The mean age of the participants was 52.39 ± 13.99 years; 55 were female (56.7%), and 42 were male (43.3%). At the initial enrolment, the average number of defecations per week was 2.03 ± 1.25 and the BSFS was 2.18 ± 0.72 . The average score of bloating was 3.18 ± 1.70 ; the average score of abdominal pain was 2.67 ± 1.91 and the baseline average IBS-SSS score was 211.01 ± 81.23 ; in this study, 24 patients (24.7%) had severe IBS-C. The number of participants who had anxiety was 12 (12.4%), with an average SAS score of 41.29 ± 11.46 , while 15 patients had depression (15.5%) with an average SDS score of 42.37 ± 11.08 . The IBS-QOL score was 57 ± 13.72 .

Effect of linaclotide treatment on bowel movements and abdominal symptoms

After linaclotide treatment, the number of defecations was 8.59 ± 3.61 at week 4 and 7.72 ± 2.03 at week 12 compared with the baseline (2.03 ± 1.25). The number of defecations significantly increased ($p < 0.05$) (Figure 2(a)). BSFS scores were 3.71 ± 0.84 at week 4 and 3.67 ± 0.68 at week 12, with a significant improvement in faecal traits ($p < 0.05$). Abdominal pain, abdominal distension symptoms and abdominal discomfort significantly improved at 4 and 12 weeks ($p < 0.05$) (Figure 2).

Effect of linaclotide treatment on IBS-SSS scores

The patients' IBS-SSS score after linaclotide treatment was 51.81 ± 54.42 at week 4, which was significantly lower than that at the baseline (Figure 3(a)). The IBS-SSS score decreased to 166.72 ± 103.78 at week 4 in 58 patients, 38 of whom had mild and moderate IBS-C with an IBS-SSS score of 62.63 ± 57.21 , which decreased from 105.1 ± 70.5 . In 18 patients with severe IBS-C, the IBS-SSS score was 30.56 ± 45.01 , which decreased from 287.5 ± 47.2 . The improvement was more significant in patients with severe IBS-C (Figure 3(b) and (c)).

Similar changes were observed in the data analysis at week 12, with an average IBS-SSS score of 9.3 ± 30.39 ; the score was significantly reduced compared with that at the baseline (Figure 3(a)).

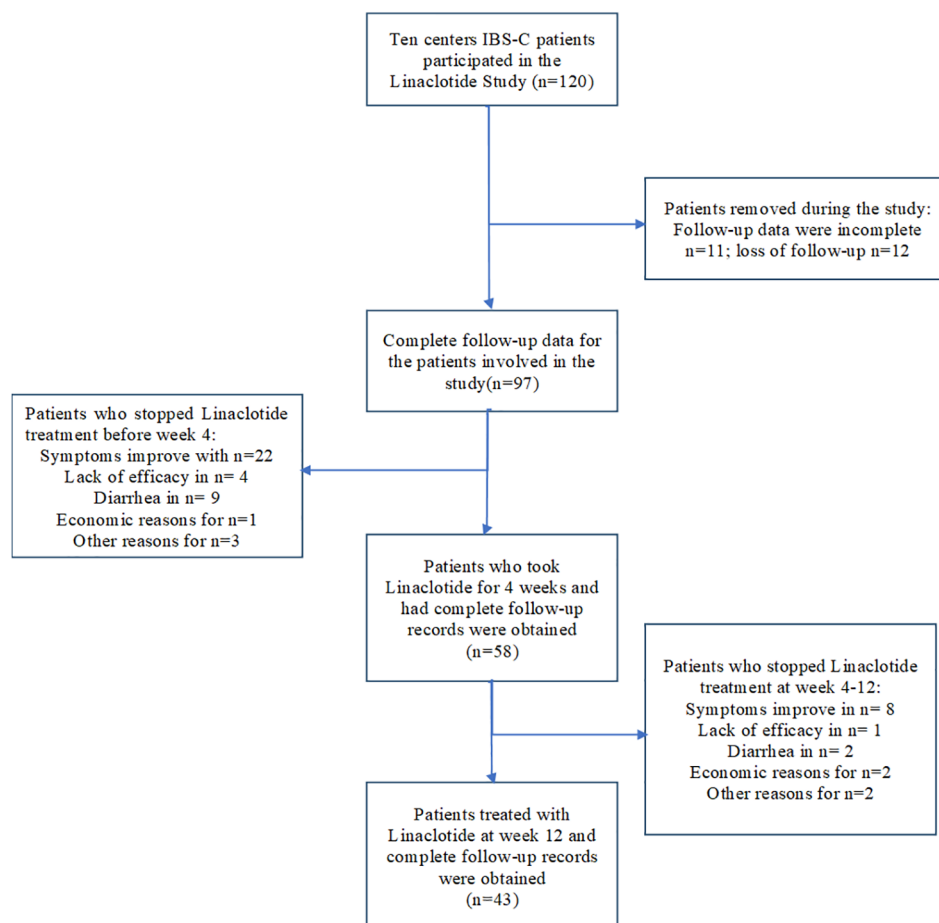


Figure 1. The participant selection process. Overall, 120 patients with IBS-C were recruited from 10 centres. Some patients who did not provide complete visit records ($n=11$) or were lost to follow-up ($n=12$) were excluded from the study. The remaining 97 patients provided complete follow-up records, of whom 43 (44.3%) continued linaclotide at 12 weeks, 39 (40.2%) stopped linaclotide treatment before 4 weeks and 15 (15.5%) stopped linaclotide treatment at 4–12 weeks.

The IBS-SSS score decreased from 225.1 ± 93.2 to 167.31 ± 72.72 at week 12 after treatment in 43 patients, 26 of whom had mild and moderate IBS-C with an IBS-SSS score of 14.42 ± 38.19 . In 17 cases with severe IBS-C, the IBS-SSS score decreased from 313.24 ± 29.47 to 1.47 ± 6.06 . The improvement was more significant in patients with severe IBS-C (Figure 3(b) and (c)).

At week 4, 58 patients' data were analysed. The IBS-SSS score decreased by more than 50 points in 51 patients; IBS-SSS decreased by less than 50 points in 4 patients; the score remained the same in 3 patients; no increase in IBS-SSS score was observed. At week 12, the data of 43 patients were analysed. The IBS-SSS score decreased by

more than 50 points in 42 patients, but the score was slightly (25 points) increased in 1 patient.

Effect of linaclotide treatment on IBS-QOL scores

The total IBS-QOL scores after linaclotide treatment were 45.6 ± 11.1 at week 4 and 39.77 ± 11.05 at week 12, showing a gradual decrease with significant improvements compared with the score at the baseline (Table 5).

After analysis, each dimension of the IBS-QOL score showed a gradual reduction and improvement (Table 5), and the dimension scale of emotional disorders, behavioural disorders, health

concerns and social function showed a significant reduction ($p < 0.05$), whereas the dimensionality measures of somatic thoughts, dietary restriction, sexual behaviour and interpersonal relationship did not improve at week 4 but subsequently improved at week 12.

Effect of linaclotide treatment on SAS and SDS scores

The SAS scores after linaclotide treatment were 34.74 ± 9.54 at week 4 and 31.91 ± 14.49 at week 12, showing a gradual decrease and significant improvement of the patients' anxiety levels ($p < 0.05$). Similarly, the SDS scores were 34.98 ± 10.39 at week 4 and 30.65 ± 13.74 at week 12, showing a gradual decrease and significant improvement in depressive symptoms ($p < 0.05$) (Figure 4).

Treatment satisfaction and adverse events

A satisfaction survey performed during linaclotide treatment revealed satisfaction rates of 29.79% at week 1, 48.19% at week 2, 79.31% at week 4 and 100% at week 12, which indicated progressive patient satisfaction and significant differences ($p < 0.05$). Partial or complete dissatisfaction with the treatment mainly occurred at weeks 1 and 2 (23 patients in week 1 and 15 patients in week 2) (Figure 5).

In the 12-week study period, 11 patients (11.3%) reported experiencing diarrhoea. By week 4, nine patients developed diarrhoea, four of whom experienced diarrhoea in the first week, two in the second week and three in the third week. By week 12, the number of patients suffering from diarrhoea increased to 11. Five patients withdrew from the study because of nonsignificant efficacy and three patients because of the cost.

Follow-up results of 30 patients who stopped treatment early because of improved symptoms

In total, 30 patients withdrew from the study prior to its completion because of significant efficacy. Five patients took linaclotide again after a period of drug withdrawal. Among these 30 patients, the number of defecations at week 12 was 6.93 ± 2.41 , which was significantly higher than that at baseline (2.23 ± 1.45) ($p = 0.039$). BSFS score at week 12 (3.53 ± 0.90) was significantly improved compared with that at baseline

Table 4. Patient demographic and baseline characteristics.

	Total
Age (years)	52.39 ± 13.994
Sex	Men, 42 (43.3%); Women, 55 (56.7%)
Height	166.21 ± 7.69
Weight	64 ± 13.38
Blood pressure	$130.24 \pm 12.66/82.34 \pm 12.87$
Heart rate	71.37 ± 7.13
Defecation frequency (times/week)	2.03 ± 1.25
BSFS	2.18 ± 0.72
Abdominal pain score	2.67 ± 1.91
Abdominal distension score	3.18 ± 1.70
Abdominal discomfort score	2.58 ± 1.76
IBS-SSS score	211.01 ± 81.23
IBS severity based on the IBS-SSS score, <i>n</i> (%)	
Normal (IBS-SSS score < 75)	2 (2.06%)
Mild (IBS-SSS score 75 to < 175)	32 (32.99%)
Moderate (IBS-SSS score of 175 to < 300)	39 (40.21%)
Severe (IBS-SSS score \geq 300)	24 (24.74%)
SAS	41.29 ± 11.46
No. of patients with anxiety	12 (12.37%)
SDS	42.37 ± 11.08
No. of patients with depression	15 (15.46%)
IBS-QOL score	57 ± 13.72
BSFS, Bristol stool form scale; IBS-QOL, irritable bowel syndrome quality of life questionnaire; IBS-SSS, irritable bowel syndrome symptom severity scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale. Data are expressed as mean \pm SD.	

(2.30 ± 0.65) ($p = 0.047$). Similarly, the abdominal pain score at week 12 (0.60 ± 0.77) was significantly improved compared with that at baseline (2.17 ± 2.11) ($p = 0.00$). Notably, the treatment satisfaction rate was 100%.

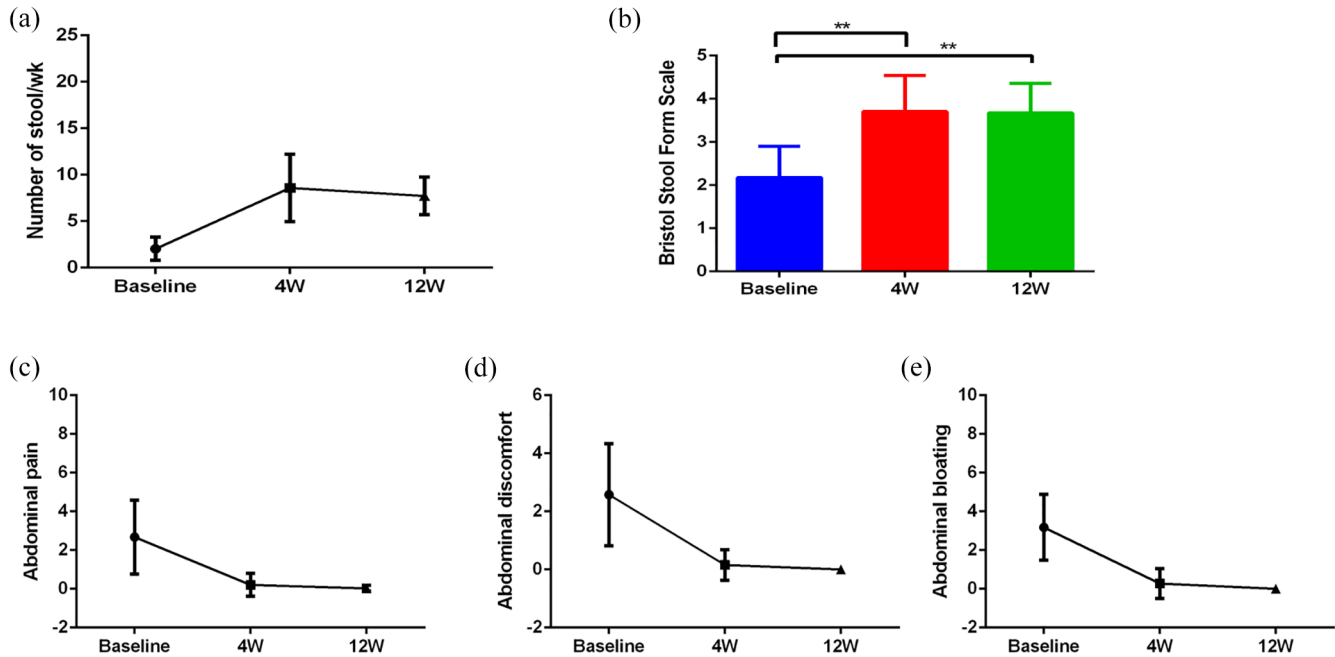


Figure 2. Effects of linaclotide treatment on bowel movements and abdominal symptoms. (a) After linaclotide treatment, the number of defecations significantly increased at weeks 4 and 12 ($p < 0.05$). (b) BSFS scores were significantly improved in faecal traits at weeks 4 and 12. (c)–(e) Abdominal pain, abdominal distension symptoms and abdominal discomfort significantly improved at 4 and 12 weeks ($p < 0.05$).

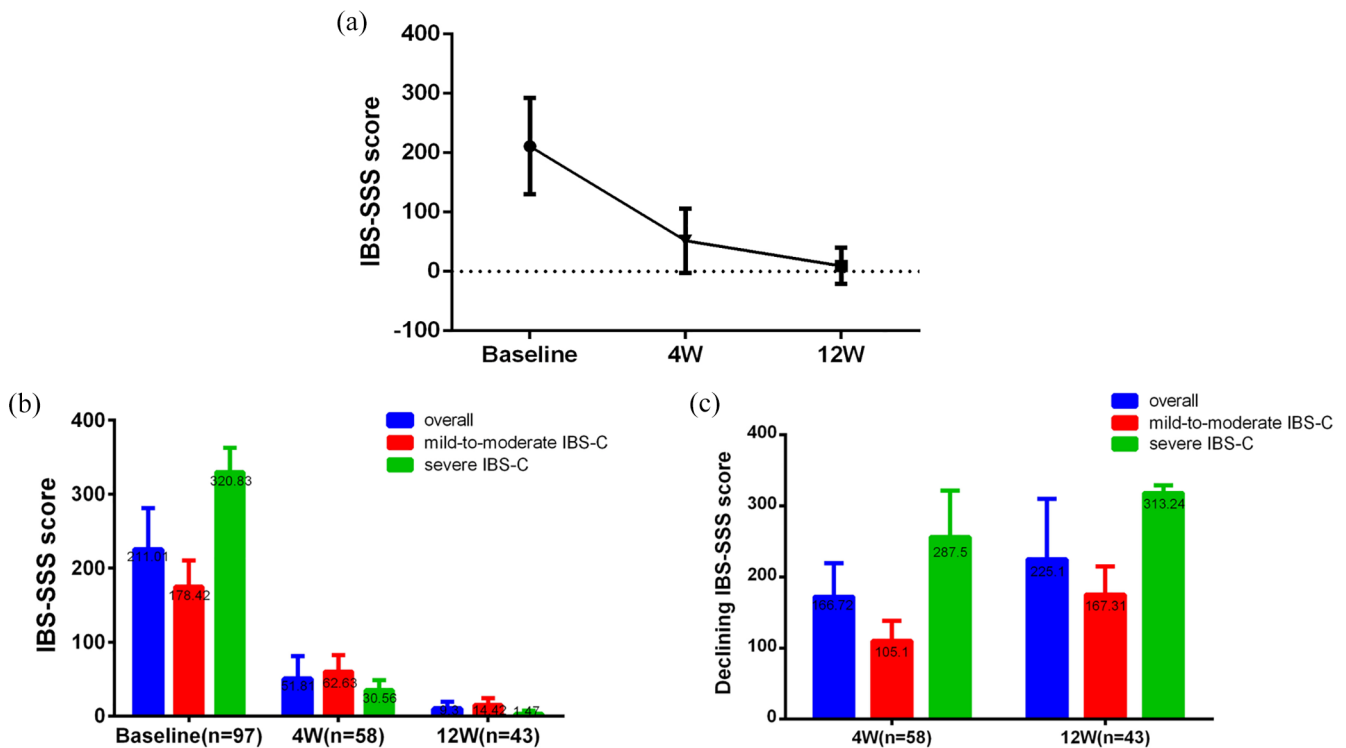


Figure 3. Effect of linaclotide treatment on the IBS-SSS scores. (a) The patients' IBS-SSS scores after linaclotide treatment were significantly lower at weeks 4 and 12 than that at the baseline. (b) and (c) For patients with mild and moderate IBS-C and severe IBS-C, IBS-SSS scores decreased significantly on weeks 4 and 12, and the improvement was more significant in patients with severe IBS-C.

Table 5. Effects of linaclotide treatment on IBS-QOL scores.

Dimension	Baseline (97 cases)	Week 4 (58 cases)	Week 12 (43 cases)
Total score	57 ± 13.72*	45.6 ± 11.1*	39.77 ± 11.05*
Emotional disorders	13.87 ± 5.17*	9.95 ± 2.31*	8.74 ± 2.06*
Behavioural disorder	13.06 ± 4.53*	9.66 ± 2.64*	8.14 ± 2.52*
The somatic mind	5.63 ± 2.14#	5.09 ± 2.68	4.37 ± 1.05#
Health concerns	7.41 ± 3.32*#	5.9 ± 3.64*	4.67 ± 3.54#
Diet restrictions	5.53 ± 2.55*	5.28 ± 3.12	4.37 ± 3.33*
Social function	5.21 ± 2.11*#	4.53 ± 1.45*	4.14 ± 0.68#
Sexual behaviour	2.34 ± 0.95*	2.17 ± 0.65	2.05 ± 0.31*
Human relationships	3.81 ± 1.39*	3.5 ± 0.94	3.33 ± 0.87*

Data are expressed as mean ± SD, the data were analysed using ANOVA and Significance was set at $p < 0.05$. *and # represent statistical differences between the tagged data.

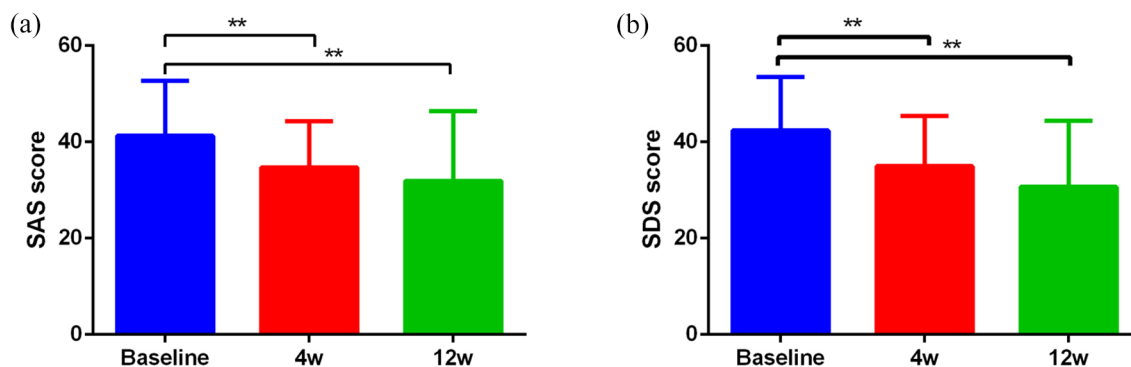


Figure 4. Effects of linaclotide treatment on the SAS and the SDS scores. (a) The SAS scores after linaclotide treatment showed a gradual decrease and significant improvement of the patients' anxiety levels at weeks 4 and 12 ($p < 0.05$). (b) The SDS scores also showed a gradual decrease and significant improvement in depressive symptoms at weeks 4 and 12 ($p < 0.05$).

Discussion

In this study, the symptom severity was significantly reduced based on the IBS-SSS score compared with that at the baseline, and linaclotide effectively and significantly improved abdominal distension and abdominal pain symptoms, with defecation frequency and BSFS at 4 and 12 weeks of treatment. This is consistent with the results of a linaclotide observational study in a clinical practice in Germany, which reported a significant reduction in abdominal pain and abdominal distension intensity and improvement in bowel

frequency compared with those at the baseline.¹⁵ The threshold for assessing the improvement in the total IBS-SSS score in this study was reduced by approximately 50 points, consistent with numerous studies using IBS-SSS for evaluation.^{16–18}

Linaclotide treatment also significantly improved the QOL. A previous phase 3 clinical trial demonstrated that linaclotide treatment significantly improved QOL compared with a placebo, with more than half of the patients demonstrating improved IBS-QOL scores after 12 weeks of

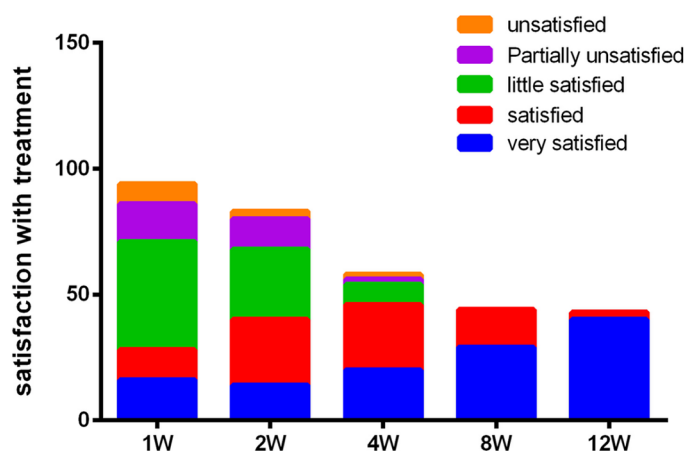


Figure 5. The satisfaction survey performed during the linaclotide treatment. The survey indicated progressive patient satisfaction and significant differences. Partial or complete dissatisfaction with the treatment mainly occurred at weeks 1 and 2.

linaclotide treatment.¹⁹ This study's results showed significant improvements in total IBS-QOL scores in all subscales, supporting the findings of previous studies. Individual analysis of the dimensions of the IBS-QOL score revealed that certain dimensions (mood disorders, behavioural disorders, health concerns and social function) showed a gradual reduction. Meanwhile, somatic thoughts, dietary restriction, sexual behaviour and relationships did not improve at week 4 but improved at week 12, indicating that their cognition required a long time to establish and change.

The most common adverse event associated with linaclotide treatment in this study was diarrhoea. The safety of linaclotide observed in this 12-week study was similar to that observed in phase 3 trials, and there was no indication of additional adverse events following long-term use. Diarrhoea was the most common adverse reaction associated with treatment,^{20,21} with 11.3% of patients reporting mild diarrhoea after linaclotide treatment and no patients developing severe diarrhoea. In clinical practice, diarrhoea is considered a marker of drug activity rather than an adverse event in many patients.⁹

In this study, approximately 79.3% and 100% of patients were very satisfied or satisfied with the ability of linaclotide to relieve IBS-C symptoms at weeks 4 and 12, respectively, similar to a previous

phase 3 IBS-C trial that showed that patients were relatively satisfied or very satisfied with the treatment effect at week 12.²² The patients' IBS-SSS scores after linaclotide treatment were 51.81 ± 54.42 at week 4 and 9.3 ± 30.39 at week 12. The satisfaction rate was basically consistent with the IBS-SSS score. There are two reasons for the gradual increase in the satisfaction rate to 100%: (1) the effect of linaclotide fully developed through the period of drug use and (2) patients with poor treatment response stopped taking the medication at an early stage.

At 12 weeks, linaclotide treatment was discontinued in 55.7% of the patients, while most patients stopped linaclotide in the first 4 weeks. The most common cause of withdrawal was symptom remission in approximately 30.9% of the patients, followed by adverse events in 11.3%. However, in two phase 3 clinical studies, linaclotide was stopped in 7.9% and 10.2% of the patients. This high withdrawal rate may be due to real-world studies reflecting the true wishes of patients, which may be higher than that in phase 3 clinical studies.^{20,21} Therefore, these results may represent a more actual result. Meanwhile, 30 patients stopped the treatment early because of improved symptoms. In the follow-up at week 12, the number of defecations, BSFS scores and abdominal pain scores were significantly improved. This indicates that linaclotide treatment perhaps elicits a long-lasting effect. Patients with IBS-C do not necessarily need to adhere to long-term medications; rather, the dosing frequency and interval of their medications can be adjusted according to their symptoms.

To reduce experimental bias, participants were required to stop taking laxatives for 1 week before enrolment and not take other laxatives during linaclotide treatment to accurately observe the therapeutic effect of linaclotide. Of course, we observed that some patients may have been lost to follow-up or dropped out of the study due to poor efficacy (five cases).

This study has some limitations. First, this study was observational in nature, with no control group but is reflective of the real-world data on linaclotide treatment. Second, the findings may have been influenced by confounding factors, such as diet and concomitant medications. Third, the sample size needs to be further increased.

Overall, the results of this multicentre, prospective, single-arm, observational study represent the first real-world study of linaclotide in China and demonstrate that linaclotide treatment effectively improves the severity of IBS-C and has good safety.

Author contribution(s)

Lan Liu: Conceptualisation; Data curation; Funding acquisition; Writing – original draft.

Weihao Zhang: Data curation; Formal analysis; Software; Writing – original draft.

Wei Zhao: Data curation; Formal analysis; Software; Writing – original draft.

Shuang Guo: Data curation; Methodology; Software; Writing – review & editing.

Yaojun Wang: Data curation; Writing – review & editing.

Xiaojun Lv: Data curation; Writing – review & editing.

Bing Li: Data curation; Writing – review & editing.

Haiping Wang: Data curation; Writing – review & editing.

Enbin Xu: Data curation; Writing – review & editing.

Quan Li: Data curation; Writing – review & editing.

Qin Zhu: Data curation; Writing – review & editing.

Xiao bo Gou: Data curation; Writing – review & editing.

Weidong Zhao: Data curation; Writing – review & editing.

Jianqiang Guo: Conceptualisation; Data curation; Project administration; Resources; Validation.

ORCID iD

Jianqiang Guo  <https://orcid.org/0000-0003-4164-2774>

Acknowledgements

The author (Lan Liu) had received the Jinan Clinical Medical Science and Technology Innovation Program (202019101). The author thanks Dr Edward C Mignot, Shandong University, for linguistic advice.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Jinan Clinical Medical Science and Technology Innovation Programme (202019101).

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data sets used and analysed during the current study are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. Mearin F, Lacy BE, Chang L, *et al.* Bowel disorders. *Gastroenterology* 2016; 150: 1393–1407. E5.
2. Chey WD, Kurlander J and Eswaran S. Irritable bowel syndrome: a clinical review. *Jama* 2015; 313: 949–958.
3. Sperber AD, Dumitrascu D, Fukudo S, *et al.* The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut* 2017; 66: 1075–1082.
4. Chang FY, Lu CL and Chen TS. The current prevalence of irritable bowel syndrome in Asia. *J Neurogastroenterol Motil* 2010; 16: 389–400.
5. Drossman DA, Camilleri M, Mayer EA, *et al.* AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; 123: 2108–2131.
6. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. *J Manag Care Pharm* 2004; 10: 299–309.
7. Moayyedi P, Mearin F, Azpiroz F, *et al.* Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. *United European Gastroenterol J* 2017; 5: 773–788.
8. Zhang F, Xiang W, Li CY, *et al.* Economic burden of irritable bowel syndrome in China. *World J Gastroenterol* 2016; 22: 10450–10460.

9. Rey E, Mearin F, Alcedo J, *et al.* Optimizing the use of linaclotide in patients with constipation-predominant irritable Bowel syndrome: an expert consensus report. *Adv Ther* 2017; 34: 587–598.
10. Yang Y, Fang J, Guo X, *et al.* Linaclotide in irritable bowel syndrome with constipation: a phase 3 randomized trial in China and other regions. *J Gastroenterol Hepatol* 2018; 33: 980–989.
11. Fukudo S, Nakajima A, Fujiyama Y, *et al.* Determining an optimal dose of linaclotide for use in Japanese patients with irritable bowel syndrome with constipation: a phase II randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil* 2018; 30: e13275.
12. Mascarenhas-Saraiva MJ and Mascarenhas-Saraiva M. Effectiveness and tolerability of linaclotide in the treatment of IBS-C in a ‘real-life’ setting: results from a Portuguese single-center study. *Neurogastroenterol Motil* 2019; 31: e13508.
13. Yiannakou Y, Agrawal A, Allen PB, *et al.* UK clinical experience up to 52 weeks with linaclotide for irritable bowel syndrome with constipation. *Therap Adv Gastroenterol* 2018; 11: 1–14.
14. Erik VE, Douglas GA, Matthias E, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.
15. Andresen V, Miehle S, Beck E, *et al.* Efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in a realworld setting – results from a German noninterventional study. *Z Gastroenterol* 2018; 56: 738–744.
16. Harvie RM, Chisholm AW, Bisanz JE, *et al.* Long-term irritable bowel syndrome symptom control with reintroduction of selected FODMAPs. *World J Gastroenterol* 2017; 23: 4632–4643.
17. Garsed K, Chernova J, Hastings M, *et al.* A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut* 2014; 63: 1617–1625.
18. Lackner J, Jaccard J, Baum C, *et al.* Patient-reported outcomes for irritable bowel syndrome are associated with patients’ severity ratings of gastrointestinal symptoms and psychological factors. *Clin Gastroenterol Hepatol* 2011; 9: 957–964.
19. Rao SS, Quigley EM, Shiff SJ, *et al.* Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. *Clin Gastroenterol Hepatol* 2014; 12: 616–623.
20. Rao S, Lembo AJ, Shiff SJ, *et al.* A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable Bowel syndrome with constipation. *Am J Gastroenterol* 2012; 107: 1714–1724.
21. Chey WD, Lembo AJ, Lavins BJ, *et al.* Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012; 107: 1702–1712.
22. Lacy BE, Lembo AJ, Macdougall JE, *et al.* Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. *Neurogastroenterol Motil* 2014; 26: 326–333.