

Long-term results of linaclotide in the treatment of constipation-type irritable bowel syndrome

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ABSTRACT

Background: constipation-predominant irritable bowel syndrome (C-IBS) is a prevalent, complex and multifactorial disorder that represents a challenge in terms of diagnosis and therapeutic management.

Objective: to evaluate the effectiveness, safety and treatment satisfaction of linaclotide in C-IBS patients.

Methods: prospective, single-center and observational study conducted in patients diagnosed with C-IBS. The patients were treated with linaclotide (Constella®, Allergan Inc., Irvine, CA), once-daily via an oral capsule of 290- μ g, 30 minutes before breakfast. The primary effectiveness endpoint was the number of bowel movements per week. The secondary endpoints included treatment satisfaction and changes from baseline in frequency and severity of symptoms (abdominal pain and bloating). This was assessed via an 11-point visual analog scale (VAS) reported by the patients in a daily register.

Results: thirty female patients were consecutively included. The median follow-up time was 18 months. The mean (standard deviation [SD]) number of weekly bowel movements significantly increased from 0.9 (0.6) at baseline to 4.7 (3.9) at the end of follow-up, $p < 0.0001$. Abdominal pain significantly decreased from 5.7 (2.3) at baseline to 3.1 (2.8) at the end of the follow-up period, $p < 0.0001$. Similarly, bloating significantly decreased from 6.8 (1.6) to 2.9 (2.5) at the beginning and end of the treatment period, respectively, $p < 0.0001$. The mean (SD) degree of satisfaction at the end of the study was 6.7 (3.0).

Conclusions: long-term linaclotide treatment in patients with C-IBS is effective and safe in the clinical setting.

Key words: Irritable bowel syndrome. Constipation. Linaclotide. Abdominal pain. Bloating.

INTRODUCTION

Irritable bowel syndrome (IBS) is a gastrointestinal (GI) disorder that affects up to 15% of the European and North American population (1-3). The disease is characterized by chronic or recurrent abdominal pain, constipation and/or diarrhea and a feeling of bloating/distention (4). The prevalence in Spain is 8.3% according to the former Rome III criteria (5,6).

IBS has been classified into different subtypes based on predominant bowel habits. This includes IBS with predominant constipation (C-IBS), IBS with predominant diarrhea (D-IBS), IBS with mixed bowel habits (M-IBS) and unclassified IBS (U-IBS) (6,7). The pathophysiology of IBS is complex and multifactorial and includes altered gastrointestinal motility, visceral hypersensitivity, mucosal immune system activation, gut microbiota alterations, malabsorption and intestinal microinflammation (8).

In clinical practice, C-IBS represents a challenge in terms of diagnosis and therapeutic management (9). Therefore, specific clinical guidelines must be established (10). Currently, disease management is based on a combination of lifestyle changes and the use of non-specific symptomatic treatment (11).

Linaclotide is a selective agonist of guanylate cyclase C (GC-C). The GC-C receptor is expressed on the luminal surface of intestinal epithelial cells and its activation leads to a significant increase in the intra- and extracellular concentrations of cyclic guanosine monophosphate (cGMP). cGMP is involved in a wide range of physiological processes.

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es including the regulation of intestinal fluid homeostasis (12,13) and the modulation of afferent gut nerve activity, which may be related to its analgesic effects (14,15). The efficacy and safety of linaclotide in patients with C-IBS have been demonstrated in two randomized, double-blind, placebo-controlled phase III multicenter clinical trials (16,17), as well as in additional analysis (18,19). Recently, a survey conducted in Canada concluded that linaclotide is the most satisfactory treatment for C-IBS and the authors recommended that it is considered as a first line of pharmacological treatment (20).

Linaclotide is the first of its kind and, currently, the only drug specifically indicated for the treatment of C-IBS in Europe. To the best of our knowledge, there have been no published studies in the clinical practice since the drug was approved in 2012. This study aimed to evaluate the efficacy, safety, and satisfaction of linaclotide treatment in C-IBS patients in a clinical setting.

METHODS

A prospective, open-label, observational and single-center study was performed on consecutive patients with C-IBS (according to the Rome III criteria [5]) between August 2014 and February 2017. The patients were treated with linaclotide (Constella®, Allergan Inc., Irvine, CA) via a once-daily oral capsule of 290- μ g, 30 minutes before breakfast.

The study protocol was approved by the ethical research committee of the Hospital Universitario de Salamanca. All patients were fully informed about the details of the study and provided their written informed consent prior to inclusion into the study. The ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice were followed.

Patients included in the study were male or female, aged 18 years or older, with a diagnosis of moderate to severe C-IBS with less than three bowel movements per week, which was refractory to previous treatment with laxatives. Patients with structural or functional GI alterations that could affect GI mobility, active peptic ulcer disease, or a history of diverticulitis or any chronic condition that could be associated with abdominal pain or discomfort were excluded. Patients who received the study medication and did not attend to the first follow-up visit performed one month after starting the treatment were excluded from the efficacy and safety analysis.

Patients were instructed to discontinue treatment with laxatives once linaclotide treatment was started in order to interfere as little as possible with the number of bowel movements and also due to the associated risk of diarrhea. Rescue medication with laxatives (the same that they had previously taken) was allowed in those patients whose treatment effectiveness was considered as insufficient. In addition to the baseline visit, follow-up visits were scheduled at months 1, 3, and 6 and every six months thereafter.

Study variables

The different study variables included the number of bowel movements per week, intensity of pain and bloating. These

data were collected by the patients in a daily register. The primary efficacy variable was the mean change in the frequency of bowel movements per week as compared to the mean number of bowel movements during the two weeks prior to the start of treatment. The secondary endpoints included the change in frequency and severity of symptoms (abdominal pain and bloating) from baseline assessed via an 11-point (0-10) visual analog scale (VAS).

Patients subjectively evaluated the degree of improvement and satisfaction with the treatment and three possible scenarios were established: a) complete improvement, if the patient experienced an improvement in the three evaluated clinical parameters (number of bowel movements/week, intensity of abdominal pain and abdominal bloating); b) partial improvement, if the patient experienced improvement in two of the three evaluated clinical parameters; and c) no-improvement if the patient had experienced an improvement in less than two parameters. Patients' satisfaction was measured via an 11-point (0-10) VAS. In addition, the frequency, intensity and severity of the adverse events (AE) were recorded in order to assess the safety and tolerability of the treatment.

Statistical analysis

A standard statistical analysis was performed using the MedCalc 17.6 (MedCalc Software bvba, Ostend, Belgium). A sample of at least 30 patients was required to detect a difference greater or equal than 2.5 units in the number of weekly bowel movements, assuming a standard deviation of 4 at a significance level of 0.05, with a power of 0.90. A follow-up loss rate of 10% was estimated.

Data are expressed as number (percentage), mean (standard deviation [SD], mean 95% confidence interval [95% CI]) or median (95% CI), as appropriate.

The last-observation-carried-forward method was used to evaluate the effectiveness of linaclotide treatment. Data were tested for a normal distribution using a D'Agostino-Pearson test. Comparisons between the pre- and post-treatment values were performed with the following variables: number of bowel movements per week, intensity of pain and bloating. If data were normally distributed, a two-tailed paired-samples Student's test was used to compare the means between quantitative variables. The Wilcoxon test or the Mann-Whitney U test were used as appropriate when the data was not normally distributed. Categorical variables were compared using the Chi-squared test and Fisher's exact test, as appropriate. A linear regression analysis was performed to evaluate the relationship between satisfaction with the treatment, as a dependent variable, and the changes in clinical variables (number of bowel movements per week, abdominal pain and abdominal bloating) as independent variables. The Pearson correlation coefficient (r) was used for linear regression analysis. A probability value of $p < 0.05$ was considered as statistically significant.

RESULTS

Of 110 patients screened (six males and 104 females), 30 met the inclusion criteria and were finally included in the

analysis. All the patients were female. Five (16.7%) of the 30 patients included in the study required concomitant medication with laxatives as a rescue therapy throughout the study. Linaclotide treatment was suspended in four patients due to an insufficient effectiveness. The mean age of the cases was 50.3 (11.3) years. The principal clinical and demographic characteristics are shown in table 1.

Thirteen (43.3%) patients discontinued the treatment during the study; seven patients due to a lack of effectiveness or an insufficient effectiveness despite the rescue therapy with laxatives. All left the study after the clinical visit at month 1; four due to a reduction of treatment effectiveness throughout the study (after three, four, 12 and 22 months of treatment, respectively) and two due to the suspension of the treatment and no disease relapse during the follow-up (at six and 12 months, respectively) (Table 2).

Table 1. Baseline demographic and clinical characteristics of the study population

	Characteristics
Number of patients	30
Age, years	
Mean (SD)	50.3 (11.3)
95% CI	46.1 to 54.5
Number of BM/week	
Mean (SD)	0.9 (0.6)
95% CI	0.7 to 1.1
Pain*	
Mean (SD)	5.7 (2.3)
95% CI	4.9 to 6.6
Bloating*	
Mean (SD)	6.8 (1.6)
95% CI	6.2 to 7.4

SD: standard deviation; CI: confidence interval; BM: bowel movements. *Measured via an 11-point (0-10) visual analog scale (VAS).

A complete improvement was observed at the end of the study in 63.3% (19/30) of the patients, with a median (95% CI) follow-up of 18.0 (8.4 to 25.7) months. Of the 30 patients evaluated at month 1, 23 (76.7%) improved with linaclotide treatment, 19 (63.3%) were classified as a complete improvement and four (13.3%), as partial improvement (pain and bloating). Of the 19 patients with a valid 12-month visit, 52.6% (10/19) were classified as a complete improvement. Of the 12 patients with a valid 24-month visit, five (41.7%) were classified as a complete improvement (Table 3).

The mean bowel movements per week significantly increased from 0.9 (0.6) at baseline to 4.7 (3.7) at the end of the study ($p < 0.0001$). Abdominal pain significantly decreased from 5.7 (2.3) at baseline to 3.1 (2.8) at the end of the follow-up period ($p < 0.0001$). Similarly, abdominal bloating significantly decreased from 6.8 (1.6) at the beginning to 2.9 (2.5) at the end of the treatment period ($p < 0.0001$). Table 4 shows the changes of the different study variables as compared to the baseline visit.

An increase of equal or greater than four bowel movements per week was observed in 56.7% (17/30) of patients. The complete improvement rate was significantly higher in patients that experienced an increase in the number of bowel movements of ≥ 4 at month 1 as compared to those with < 4 (94.1% versus 7.7%, $p < 0.0001$).

Table 3. Clinical improvement of the patients throughout follow-up

	Month 1 (n = 30)	Month 12 (n = 19)	Month 24 (n = 12)
Overall improvement, n (%)	23 (76.7)	12 (63.2)	7 (58.3)
Complete*, n (%)	19 (63.3)	10 (52.6)	5 (41.7)
Partial†, n (%)	4 (13.4)	2 (10.6)	2 (16.6)

n: number. *Increase in the number of bowel movements ≥ 1 and reduction of abdominal pain and abdominal bloating $\geq 30\%$. †Improvement in two of the three clinical parameters (increase in the number of bowel movements ≥ 1 , abdominal pain reduction $\geq 30\%$ and reduction in abdominal bloating $\geq 30\%$).

Table 2. Baseline clinical and demographic characteristics of the study patients with a lack of effectiveness or insufficient effectiveness despite rescue treatment with laxatives

Case	Age	Sex	Number of BM/week	Pain*	Bloating*	Time of treatment (months)	Cause of withdrawal
Case 1	53	F	0	2	6	1	Lack of effectiveness
Case 2	61	F	0	7	8	1	Lack of effectiveness
Case 3	46	F	1	8	8	1	Lack of effectiveness
Case 4	35	F	2	8	7	1	Lack of effectiveness
Case 5	50	F	1	6	6	1	Lack of effectiveness
Case 6	61	F	0	8	7	1	Lack of effectiveness
Case 7	60	F	0	7	8	1	Lack of effectiveness
Case 8	48	F	1	6	6	4	Loss of effectiveness
Case 9	55	F	1	8	4	3	Loss of effectiveness
Case 10	36	F	1	7	6	12	Loss of effectiveness
Case 11	67	F	1	5	8	22	Loss of effectiveness

F: female; BM: bowel movements. *Measured via an 11-points (0-10) visual analog scale (VAS).

Table 4. Overview of the changes of the number of bowel movements per week, abdominal pain and abdominal bloating as compared to baseline

Variable	Difference from baseline		
	Mean (SD)	95% CI	p [†]
Number of BM per week	3.8 (3.5)	2.5 to 5.1	< 0.0001
Pain*	-2.6 (2.2)	-3.4 to -1.8	< 0.0001
Bloating*	-3.9 (2.7)	-4.9 to -2.9	< 0.0001

SD: standard deviation; CI: confidence interval; BM: bowel movements. *Measured via an 11-point (0-10) visual analog scale (VAS). [†]Two-tailed paired-samples Student's t test.

A reduction of three units in abdominal pain or in abdominal bloating was reported by 53.5% (16/30) and 63.3% (19/30) of patients respectively. At month 1, more than 70% of patients indicated that they were satisfied with linaclotide treatment as compared to previous treatments. The level of patient satisfaction (Fig. 1) was maintained and there were no significant differences throughout the study; 6.9 (2.6) at month 1 *versus* 6.1 (2.5) at the end of the study ($p < 0.3865$).

The minimum percentage compliance of the patients with the daily register during the treatment period was 60%, with a mean of 70.0% (68.8% to 73.3%). Figure 2 shows the relationship between the changes in the clinical variables and the level of patient satisfaction. The level of satisfaction was 0.70 (standard error [SE] 0.10) units greater for each unit increase in the number of bowel movements per week. A reduction in pain of one unit resulted in an increased level of satisfaction of 0.84 (0.19) units. Similarly, a one unit reduction in bloating resulted in an increase in the level of satisfaction of 0.88 (0.13) units.

No serious adverse events (AE) were reported. Eleven (36.7%) patients reported at least one AE (diarrhea in eight [26.7%] patients and abdominal pain in three [10.0%] patients) throughout the study follow-up. Most of the reported AE were mild in severity (90.1%). One patient had an episode of diarrhea classified as moderate that was resolved without medication.

DISCUSSION

This study showed that the administration of a once-daily oral capsule of linaclotide that was administered 30 minutes

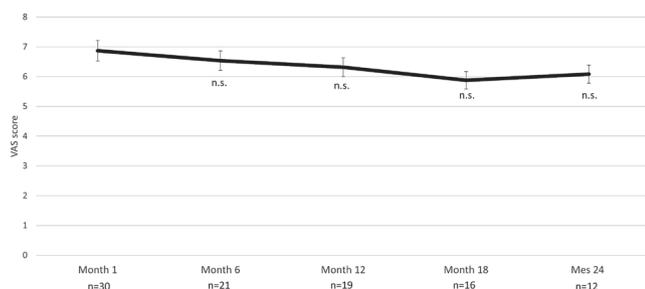


Fig. 1. Overview of the level of patient satisfaction throughout the study (n.s.: not significant).

before breakfast significantly improved the symptomatology (both abdominal and intestinal) of patients with C-IBS. The efficacy and safety of linaclotide in patients with C-IBS has been demonstrated in two randomized, double-blind, phase III multicenter clinical trials compared with a placebo (16,17). Other studies have also shown similar results (18,19).

The proportion of patients with an increased number of bowel movements per week that was equal or greater than four, or a reduction of three units in the abdominal pain scale or the sensation of bloating, is greater than that reported by phase III clinical trials (16,17). However, the comparison of the results is complex due to the different success criteria of study populations. The reported requirements of the responder definition in clinical trials with linaclotide are very strict and different from the definition of responder applied in the clinical practice (21).

In a *post-hoc* analysis of two randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 trial populations (16,17), the level of pain and the scale of abdominal discomfort during the previous 24-hours were recorded using an 11-point VAS (0: none; 10: very serious) (18). A responder was defined as a patient with an improvement of 30% or more from baseline in either the mean of the most severe abdominal pain score or the mean abdominal discomfort score (18). This had to be maintained for at least six weeks of the first 12 weeks of treatment.

With regard to patients treated with linaclotide, the improvement in abdominal pain/discomfort at week 12 was 54.8% and 54.1%, depending on the study. Furthermore, 39.4% and 37.0% of patients reported a considerably or complete improvement in the degree-of-relief of IBS symptoms during at least half of the follow-up time (18). In this study, eleven patients (36.7%) had a lack or loss of therapeutic efficacy throughout the study follow-up. The number of patients who abandoned the treatment due to an insufficient response was greater than that reported in other clinical trials, which was five (16) and 15 (17). However, it is difficult to establish a comparison with these studies as previously mentioned. Information with regard to the use of linaclotide in patients with C-IBS in clinical practice is limited.

The efficacy and safety of linaclotide in clinical practice was evaluated in a prospective and multicenter study, which included 375 patients with C-IBS and was conducted in 79 centers in Germany (22). The study had a median follow-up of five months and showed a change in the values at baseline and the last follow-up for bloating, pain and number of bowel movements of 4.9 *versus* 2.4, 5.3 *versus* 2.7 and 2.7 *versus* 4.4, respectively. The p value was < 0.0001 in all comparisons (22). Furthermore, the results of a multicenter study that included patients who were treated with linaclotide for four to 12 weeks reported a response to linaclotide rate (decrease > 75 points on the SII-SSS scale) of 45.4% and 36.1% at four and 12 weeks of follow-up, respectively (23).

A multicenter, open-label phase IIIb study that was conducted in Spain evaluated the effect of linaclotide in adults with moderate/severe IBS; 80% of patients in the per-protocol population showed some improvement at week 12 (24). Consistently with the results of our study, the response at

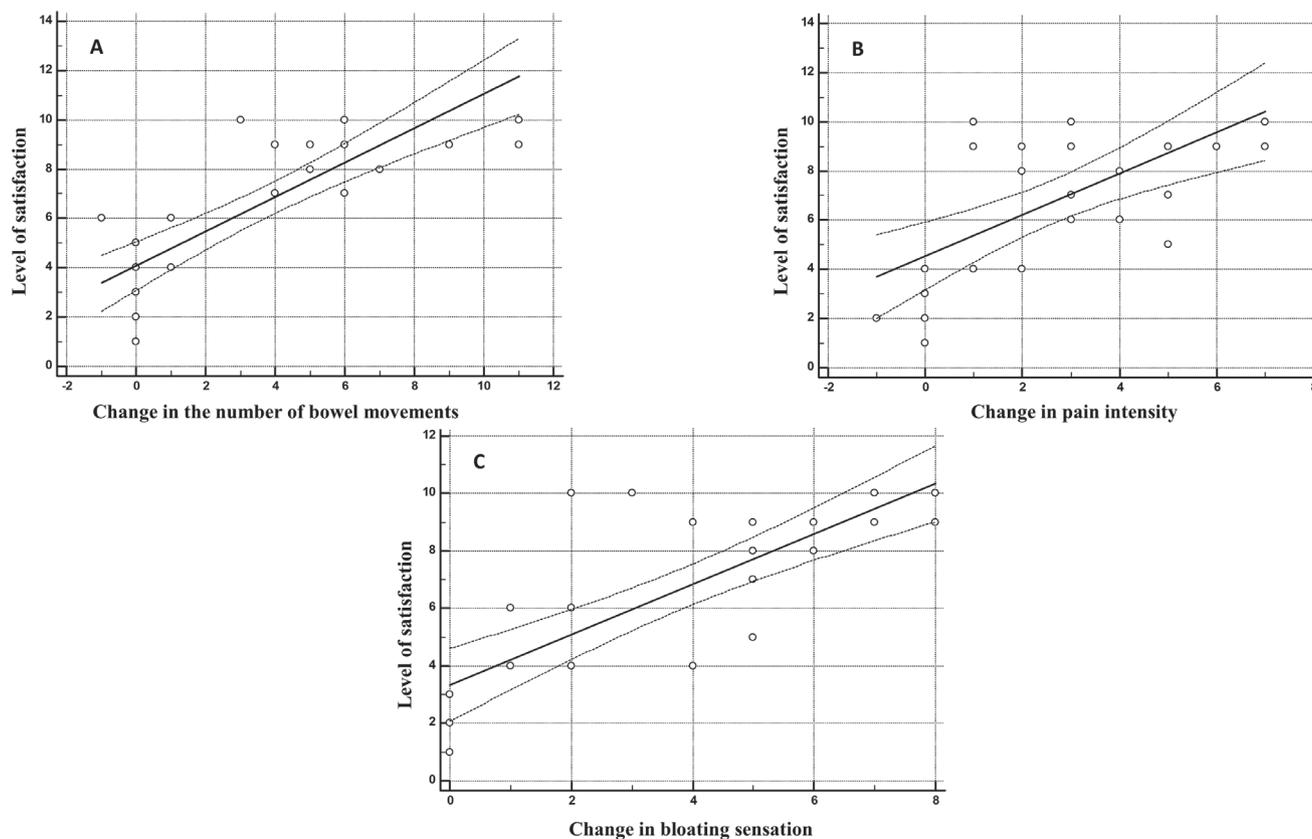


Fig. 2. Relationship between the changes in clinical variables and the level of patient satisfaction. A. Increase in the number of bowel movements ($r = 0.81$; 95% CI: 0.64-0.91; $p < 0.0001$). B. Reduction in pain intensity ($r = 0.63$; 95% CI: 0.34-0.11; $p = 0.0002$). C. Reduction in bloating sensation ($r = 0.78$; 95% CI: 0.58-0.89; $p < 0.0001$).

the end of follow-up was independently associated with that observed at week 4 (24).

The results of this study are in agreement with those observed in the German (22), English (23) and Spanish (24) studies. It should be noted that the median follow-up period of this study was 18 months, which is much longer than that of other studies published to date (22-24). A Spanish study of 22 patients that were followed up for 26 weeks reported a decrease in pain and an increase in the number of bowel movements (3-4 per week) as compared to baseline in 87% and 90% of patients, respectively (25). Furthermore, 85% of patients reported an overall improvement (25). The mean level of treatment satisfaction observed in this study did not decrease during follow-up and the score remained between 5.9 and 6.9 out of 10. These results are consistent with a survey performed in Canada, in which patients reported linaclotide as the most satisfactory treatment for C-IBS (20).

The improvement of the clinical parameters was significantly related with the level of treatment satisfaction and there were no significant differences between the two parameters; 36.7% of patients reported at least one AE, none were serious. This rate is similar to that observed in other studies (16-19,22-24), although slightly higher than that reported by Mínguez-Cortés (25).

This study has inherent limitations with regard to the interpretation of the results, mainly due to the fact that it is an open-label, non-randomized and non-controlled study

design. Nevertheless, the results are consistent with the findings of the randomized clinical trials that have evaluated linaclotide therapy (16-19).

In this study, the consistency of the stools was not evaluated; this may also be a limitation for the interpretation of the results. Furthermore, 36.7% of patients abandoned the treatment due to a lack or loss of efficacy during the study period. This could be a limitation when generalizing the results. Another limitation of the study is that the last observation obtained was carried-forward to perform the effectiveness analysis, which could result in a bias (26).

In summary, treating C-IBS patients with linaclotide is effective and safe in the long term in a clinical setting. This treatment significantly reduced the pain and bloating sensation and increased the number of spontaneous bowel movements per week. It would be interesting to perform multicenter studies that evaluate the possible factors related to the lack or loss of therapeutic efficacy over time.

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