

# Linacotide for The Treatment of Refractory Lower Bowel Manifestations of Systemic Sclerosis

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## Research article

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# Abstract

**Objective:** Lower gastrointestinal tract involvement can affect up to 50% of SSc patients, and may result in malabsorption, pseudo-obstruction, hospitalization, and death. We report our experience with linaclotide, a selective agonist of guanylate cyclase C, for SSc patients with refractory lower GI disease.

**Methods:** We performed a analysis of patients seen at the Johns Hopkins Scleroderma Center and identified patients prescribed linaclotide for refractory lower GI manifestations. Patients had clinical data prospectively collected in our longitudinal database. Linaclotide responders were on medication for at least 12 months with documented effectiveness by the treating physician.

**Results:** Thirty-one patients with SSc were treated with linaclotide. Twenty-three of these patients (74%) had severe GI disease on initiation of linaclotide (Medsger GI score  $\geq 3$ ), as defined by recurrent pseudo-obstruction, malabsorption, and/or need for artificial nutrition. The majority of patients (90.3%; 28/31) had a treatment response, while only three patients (9.7%) reported ineffectiveness or intolerable side effects. Low-dose linaclotide ( $\leq 145$  mcg daily) was used in 18 patients and was effective in 94%. High-dose therapy ( $>145$  mcg daily) was effective in 11 of 13 patients (85%). Common side effects were diarrhea, cramping, or bloating (11/31, 35%). Ineffectiveness, cost, and abdominal pain were complaints cited among those who discontinued therapy.

**Conclusion:** Linaclotide is a well-tolerated and efficacious pro-secretory and pro-motility agent that can be used to manage refractory lower GI manifestations in SSc. We found that low-dose linaclotide is an effective option and may be better tolerated, though a subset of patients may require high dose regimens.

## Key Points

- Lower GI dysmotility in SSc can result in significant morbidity and mortality
- The utilization of novel agents is needed to treat SSc patients with severe GI disease
- Linaclotide is a safe, effective treatment and may be tolerated in lower doses in SSc

## Introduction

Up to 90% of patients with systemic sclerosis (SSc) have gastrointestinal complications [1]. Lower gastrointestinal tract involvement can affect nearly 50% of SSc patients, and may result in malabsorption, recurrent pseudo-obstruction, hospitalization, and death [1–4]. A number of promotility and prosecretory agents exist for colonic dysmotility, but their usage is often limited by adverse effects or limited evidence in SSc [1, 5, 6].

Linaclotide is a selective agonist of guanylate cyclase C (GC-C) and has been demonstrated to be a safe, effective prosecretory and promotility option for refractory constipation in other conditions. The activation of cyclic guanosine monophosphate (cGMP) by GC-C on intestinal epithelial cells increases intestinal secretion and gut motility through nerve activity and fluid homeostasis [7, 8]. Linaclotide for

treatment of constipation demonstrated efficacy in multiple randomized, double-blind, placebo-controlled multicenter clinical trials, and across several different disease processes [9–12]. To date, however, no studies have evaluated linaclotide in patients with autoimmune disorders, including SSc.

In this study, we report our experience with linaclotide's tolerability and benefit in SSc patients with severe, refractory GI dysmotility, recurrent pseudo-obstruction and/or significant constipation who do not respond adequately to first line agents. We aim to provide rheumatologists, who do not routinely use this class of medications, with another therapeutic option for managing SSc-related lower bowel complications in patients with more severe disease.

## Methods

### Study Population

All patients were seen at the Johns Hopkins Scleroderma Center as part of routine clinical care between August 2012 and January 2019. Patients with SSc who were prescribed linaclotide during their time in our Center were identified in our clinical database. Inclusion criteria for the case series required age greater than or equal to 18 years old and a diagnosis of SSc based on 2013 ACR/EULAR criteria, 1980 American College of Rheumatology (ACR) criteria or satisfying at least three of five CREST criteria [13]. All patients were required to have constipation (i.e.  $\leq 3$  bowel movements per week), with continued symptoms despite at least one other medication (e.g. polyethylene glycol, senna). Symptom response was defined by a documented response to treatment without intolerable side effects in the medical record, and/or continuing treatment for at least 12 months. All included patients were required to have at least one follow-up visit or telephone note documenting compliance with the medication.

Written informed consent was obtained from all patients. The present study was approved by the Johns Hopkins Institutional Review Board. This research was performed without formal patient or public involvement.

### Clinical Phenotyping

All patients had data prospectively collected as part of the Johns Hopkins Scleroderma Center Cohort. Clinical data is collected at baseline and every six months on all patients within our cohort. The database includes demographic and clinical data, such as age at first clinical visit, sex, race, disease duration, SSc skin subtype, and autoantibody status. Specific organ involvement is defined by Medsger severity scores and objective measures [2]. For GI symptoms, we also use the University of California, Los Angeles Gastrointestinal Tract Instrument (UCLA GIT 2.0) questionnaire [14]. Autoantibody data was systematically obtained on all patients using the commercially available line immunoblot assay (Systemic Sclerosis Profile Euroline [IgG]; Euroimmun, Lubeck, Germany).

Once identified, the patients' charts were reviewed to collect details of medication history, including all promotility agents used as an outpatient prior to, during, or after linaclotide initiation. The date of first

linaclotide prescription was designated as the index visit. All subsequent outpatient notes and telephone calls were reviewed for documentation of medication adherence or discontinuation, dose modification, response to treatment, and reported adverse effects.

We designated patients as treatment responders if they were adherent to the medication for at least 12 months. Patients still receiving treatment or who stopped the medication due to cost concerns were included as responders regardless of length of treatment if they had documentation of symptom improvement. Patients were classified as non-responders if they stopped the medication within the first 12 months due to lack of response or intolerable side effects. High dose linaclotide was defined by a dose of greater than 145 mcg daily. Low dose linaclotide included patients with 145 mcg daily dosing or less, including as needed regimens.

## Statistical analysis

Chi square and Fishers exact tests were used to compare dichotomous variables. Student's t-tests were used to assess differences between parametric continuous variables in low and high-dose groups. Non-parametric continuous variables were evaluated with the Wilcoxon-Mann-Whitney test. All statistical analyses were performed using Stata, version 14.2 (StataCorp, College Station, TX). The present study was approved by the Johns Hopkins Institutional Review Board.

## Results

### Patient attributes

We identified 38 candidate study subjects within the Johns Hopkins Scleroderma Center database who were prescribed linaclotide. Seven patients were excluded from our analysis: 1 patient did not meet SSC criteria, 2 patients initiated therapy prior to their initial evaluation in our center, and 4 lacked appropriate follow-up after initiating linaclotide.

The 31 patients included in our study had a mean age of 52 years ( $\pm$  11 years). They were predominantly female (29/31 patients, 94%) and Caucasian (21/31, 70%). Median disease duration (from earliest symptom - Raynaud's or non-Raynaud's) was 9 years (IQR: 5–14 years). Commonly affected extra-intestinal organs included Sicca symptoms (26/31, 87%), lung involvement (Medgser score > 1) (22/31, 76%), and Raynaud's phenomenon (19/31, 61%). Antibodies present among these patients included anti-Scl-70 (7/31, 24%) and anti-CENP (7/31, 24%). Additional clinical features, including extra-intestinal manifestations, the presence of other autoantibodies, and medications used prior to linaclotide are show in Table 1. Of note, polyethylene glycol (22/31, 71%), docusate (13/31, 42%) and senna (10/31, 32%) were the most commonly used medications for constipation prior to linaclotide.

Table 1  
Patient Demographics

<i>Clinical variable</i>	<b>n = 31</b>
Age at first linaclotide dose, mean (SD)	52 (11)
Female sex, % (n)	94 (29)
White race, % (n)	70 (21)
SSc type: Diffuse cutaneous disease, % (n)	32 (10)
Disease duration in years, RP or non-RP, median (IQR)	9 (5–14)
Medsger GI score at initiation of linaclotide, % (n)	0 (0)
• 0 (Normal)	6 (2)
• 1 (Requiring medications for reflux or abnormal small bowel series)	19 (6)
• 2 (High-dose reflux medications or antibiotics for bacterial overgrowth)	65 (20)
• 3 (Malabsorption syndrome or episodes of pseudo-obstruction)	10 (3)
• 4 (Requiring total parental nutrition)	
Sicca symptoms, % (n)	87 (26)
Myopathy, % (n)	42 (13)
Cardiac involvement (Medsger $\geq 1$ ), % (n)	59 (17)
Lung involvement (Medsger $> 1$ ), % (n)	76 (22)
Raynaud's (Medsger $\geq 2$ ), % (n)	61 (19)

<i>Clinical variable</i>	<b>n = 31</b>
Antibody status	24 (7)
• Anti-Scl-70 antibodies, % (n)	24 (7)
• Anti-CENP antibodies, % (n)	10 (3)
• Anti-RNA pol-3 antibodies, % (n)	14 (4)
• Anti-U3RNP antibodies, % (n)	1.03 (0.55)
UCLA GIT 2.0 constipation score, mean (SD) n = 9	70
Whole gut scintigraphy data	(7/10)
• Abnormal large bowel transit at 72 hours, % (n)	9.5 (0–84)
• Percent large bowel emptying at 72 hrs, median (IQR)	71
Medications used prior to linaclotide	(22/31)
• Polyethylene glycol, % (n)	32 (10/31)
• Senna, % (n)	42 (13/31)
• Oral docusate, % (n)	13 (4/31)
• Docusate suppository, % (n)	10 (3/31)
• Tegaserod, % (n)	29 (9/31)
• Lubiprostone, % (n)	13 (4/31)
• Pyridostigmine, % (n)	3 (1/31)
• Prucalopride, % (n)	
<i>UCLA GIT (None-to-mild: 0.00-0.49); Whole gut scintigraphy (Normal % colonic emptying at 72 hours ≥ 67%)</i>	

The majority of patients in our study had severe lower GI disease. At the time of linaclotide initiation, 23 patients (74%) were classified as having severe GI disease by their treating physician [history of recurrent pseudo-obstruction, malabsorption, or need for artificial nutrition (Medsger GI severity score of  $\geq 3$ )] [2]. Ten patients also had whole gut scintigraphy studies, with 70% (7/10) of these patients having severely abnormal colonic transit [median percent colonic emptying of only 9.5% at 72 hours (normal  $\geq 67\%$ )]. Nine patients had UCLA GIT scores completed prior to linaclotide initiation, and had scores in the severe range (1.01-3.00), with a mean constipation domain score of 1.03 (SD: 0.55).

## Symptom response and dosing

Patients in our study were on therapy for a mean duration of 22.6 months (SD  $\pm$  18 months) and 90% (28/31) of patients responded to treatment with linaclotide. We then compared response and side effects

reported in patients who required low versus high-dose linaclotide (Table 2). In our cohort, 13 patients (42%, 13/31) were on a high dose prescription whereas 18 patients were on a low-dose regimen (58%, 18/31). Diarrhea, cramping and bloating were common side effects in both groups, with 50% (9/18) in low dose and 15% (2/13) in the low dose group. Six patients (1 low dose and 5 high dose) stopped the medication due to lack of efficacy with this treatment. This ranged from short term failures (3 months) to discontinuation after 51 months of usage

Table 2  
Linaclotide usage

<i>Clinical variable</i>	<b>High-dose Linaclotide (n = 13)</b>	<b>Low-dose Linaclotide (n = 18)</b>	<b>p-value</b>
Frequency, doses per week, median (IQR)	7 (7–7)	7 (1–7)	0.774
Average daily dose in mcg, mean (SD)	273 (32)	137 (24)	< 0.0001
Side effect:	15 (2/13)	11 (2/18)	n/a
• Abdominal pain, % (n)	15 (2/13)	50 (9/18)	
• Diarrhea, cramping, or bloating, % (n)	8 (1/13)	6 (1/18)	
• Nausea, % (n)	8 (1/13)	6 (1/18)	
• Unspecified/did not tolerate, % (n)			
Length of treatment in months (SD)	21 (12–50)	13.5 (7–27)	0.1382
Weight change on linaclotide, lb, median (IQR)	0.8 (-3.8-1.4)	-0.6 (-3.7-1.4)	0.5914
<i>High-dose: &gt;145 mcg daily linaclotide, low-dose: ≤145 mcg daily. IQR = intra-quartile range, SD = standard deviation</i>			

## Discussion

This is the first report examining the tolerability and clinical response of SSc patients with severe GI disease to linaclotide for the treatment of constipation. Our experience suggests that linaclotide is a safe and effective option in SSc patients with significant lower GI disease manifestations who have not responded adequately to other medications. Patients used linaclotide for a mean duration of 22.6 months for treatment. We found that 90% (28/31) of patients had a favorable response to linaclotide. While, diarrhea, bloating, and abdominal pain were common side effects, no major drug-related adverse events were reported in this cohort of SSc patients, which was likely related to the minimal systemic absorption of this medication.

The majority of patients in this study had severe lower GI disease, with 74% having a history of recurrent pseudo-obstruction or malabsorption (n = 20) and/or were dependent on total parenteral nutrition (n = 3). Though pseudo-obstruction in SSc has historically been attributed to small bowel dysmotility, in our Scleroderma Center, we have found that pseudo-obstruction in SSc is instead associated with severe colonic hypomotility (unpublished data). A recent study suggests that severe colonic involvement is under-reported in the SSc population, and that this complication is associated with a high mortality rate of 27% [4]. Table 1 illustrates that the patients in our cohort tried multiple medications without sufficient symptomatic relief prior to linaclotide initiation. Linaclotide now provides physicians another therapeutic option in the management of such patients in the outpatient setting. Prospective randomized-controlled studies will be important in determining whether the early initiation of linaclotide in patients with lower GI disease manifestations, such as colonic dysmotility, can reduce the risk of recurrent pseudo-obstruction, hospitalization, and death in the longer term.

The majority of patients in our study (90%) on linaclotide therapy reported an improvement in their symptoms. Two patients discontinued therapy due to a lack of efficacy of high-dose linaclotide, and these patients had also not responded to lubiprostone, pyridostigmine, and prucalopride. Importantly, one of these non-responders was also on opiate medications (124 morphine equivalent dosing/day), suggesting that rheumatologists should consider specifically targeting opioid-induced constipation when appropriate (i.e. methylnaltrexone).

We had objective GI transit data from thirteen patients in the cohort who underwent nuclear medicine-based whole gut scintigraphy, and 76.9% (10/13) of patients had significantly delayed colonic transit at 72 hours. Despite normal transit by scintigraphy in three patients, all had relief with linaclotide, suggesting that SSc patients may benefit from linaclotide whether or not they have dysmotility. This may be related to dual action of linaclotide, as both a pro-secretory and pro-kinetic agent. Though prior trials of linaclotide reported only high dose prescriptions (290 daily dosing) [9, 10], we identified positive results in patients on both high and low doses of medication.

It is interesting that 3 of the patients with significant lower bowel symptoms had normal colonic transit. None of these patients required high-dose linaclotide. This suggests that SSc patients may have other mechanisms for constipation (e.g. dysbiosis, anorectal dysfunction) outside of transit delays [4, 15]. Characterizing important GI subsets and targeting therapy within the SSc population may help optimize GI treatment responses.

Our study has many strengths. We report a large case series of patients with SSc who were treated with linaclotide for refractory constipation. All patients were seen in the Johns Hopkins Scleroderma Center with standardized data collection and medication reconciliation. The patients in our study have a long follow-up time and systematic screening of a spectrum of SSc-specific clinical features and autoantibodies. As a retrospective series, our data collection was limited by the intrinsic heterogeneity related to clinical documentation and the absence of a matched control group, which will be a focus of future work.

## Conclusions

Linaclotide may be a safe and effective treatment for SSc patients with significant lower GI disease who do not respond to standard treatments. We find that despite severe disease, many patients experienced relief with low dose linaclotide. Determining whether early initiation of linaclotide could reduce or prevent pseudo-obstruction or other severe complications in patients at risk will be an important question for future studies.

## Declarations

**Ethics approval and consent:** Written informed consent was obtained from all patients. The present study was approved by the Johns Hopkins Institutional Review Board

**Consent for publication:** No personal health information is included requiring consent for publication.

**Competing interest:** No financial or non-financial competing interests to declare.

**Availability of data and materials:** The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

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**Author Contributions:** ED was responsible for data collection and manuscript writing, FW was responsible for patient care and manuscript editing, ZM was responsible for patient care, data analysis, and manuscript editing.

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