Treatment of Small Intestinal Disease in Systemic Sclerosis With Octreotide

A Prospective Study in Seven Patients

George C. Nikou, MD, PhD, Christos Toumpanakis, MD, PhD,† Christina Katsiari, MD, PhD,‡ Dionisios Charalambopoulos, MD, PhD,‡ and Petros P. Sfikakis, MD, PhD‡*

Background: Symptoms associated with small intestinal involvement in patients with systemic sclerosis (SSc) are usually severe and resistant to treatment.

Objectives: To assess the safety and efficacy of octreotide in refractory small intestinal disease complicating SSc.

Methods: Seven female patients (aged from 37 to 64 years old) with SSc were included in the study. All of them had symptoms compatible with small bowel pathology, nonresponding to several prokinetic agents. The patients received either subcutaneous octreotide, 0.1 mg twice daily, or intramuscular octreotide LAR (long-acting-release), 20 mg/mo. Symptom severity was assessed at baseline and at various follow-up points in a scale of 0–3, for each symptom. Significant gastrointestinal pathology was excluded by gastroscopy, colonoscopy, and small bowel enemas before octreotide administration.

Results: All patients responded to octreotide, and a significant reduction from symptom severity at baseline (mean ± SD: 2.9 ± 1.1) was noted even in the first following month (1.3 ± 0.5, $P = 0.0006$). A significant disturbance of defecation in 2 patients improved dramatically. Short relapses were noticed in patients who were initially treated with subcutaneous octreotide. These patients were subsequently treated with octreotide LAR, resulting in an overall symptom reduction at 6 months (0.7 ± 0.5, $P = 0.003$), which was sustained during follow-up (median follow-up: 14.4 months). No side effects were noted.

Conclusion: These results suggest that long-term treatment with octreotide LAR may be a safe and effective approach for treatment of small intestinal disease in patients with SSc.

Key Words: systemic sclerosis, small intestine, chronic intestinal pseudoobstruction, prokinetic agents, octreotide, octreotide LAR

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From the *Section of Gastroenterology, 1st Department of Propaedeutic Internal Medicine, Medical School, University of Athens, Greece; †Centre for Gastroenterology, Royal Free Hospital, London, UK; and ‡Section of Rheumatology, 1st Department of Propaedeutic Internal Medicine, Medical School, University of Athens, Greece.

Reprints: Christos Toumpanakis, MD, Centre for Gastroenterology, Royal Free Hospital, London, NW3 2QG. E-mail: toubanakis@yahoo.gr or c.toumpanakis@medsch.ucl.ac.uk

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Two forms of systemic sclerosis are generally recognized: the limited cutaneous (80% of patients) and the diffuse cutaneous (20% of patients) form.[1] The manifestations of these conditions are quite diverse and include abnormalities of the vasculature and involvement of multiple organ systems, including the musculoskeletal, renal, pulmonary, cardiac, and gastrointestinal (GI) system.

Many patients with systemic sclerosis (SSc) have some degree of GI involvement, with approximately one-half being symptomatic.[2] It has been demonstrated that any part of the GI tract from mouth to anus may be involved. Esophageal disease is the earliest visceral manifestation and remains, also, the most common cause of GI symptoms in these patients. It has been estimated that 90% of patients with SSc have esophageal dysfunction as detected by motility testing, although many of them remain asymptomatic.[3] Anorectal and colonic is the next most frequent involvement, occurring in 50%–70% of patients.[4] However, although they are less common, the manifestations of the small intestine have proved to be the most severe and resistant to treatment with malabsorption, dysmotility, and chronic intestinal pseudo-obstruction (CIPO).[5]

CIPO is a rare syndrome characterized by symptoms and signs of intestinal obstruction in the absence of any mechanical lesions to account for the findings. It is caused by a heterogenous group of systemic conditions and by disorders of the visceral smooth muscle or myenteric plexus.[6]

Many agents, including antibiotics and prokinetic medicines, have been used for the treatment of the small bowel disease among patients with SSc.[7,8] However, their efficacy is limited, possibly because of the irreversibility of nerve and muscle damage in some patients and the wide and often unknown extent of the effects in the gut.

Some authors suggest that octreotide, a long-acting somatostatin analog, could improve small bowel motility in these patients. However, the number of patients in these studies is rather low.[9]

In this article, we describe the efficacy of octreotide in 7 patients with SS and small intestine disease. Furthermore, in the majority of them finally, the long-acting preparation of octreotide, octreotide LAR (long-acting release) was administered. It should be pointed out that this is the first report for the therapeutic role of octreotide LAR in patients with SSc and GI involvement in the literature to date.

MATERIALS AND METHODS

We studied 7 female patients (37 to 64 years old) with systemic sclerosis. The duration of their disease ranged from 4 to 30 years. Four of them had the diffuse cutaneous, and 3 of them had the limited cutaneous form of SSc. Their disease was characterized as "diffuse cutaneous SSc" when a symmetric skin thickening proximal to the elbows and knees (upper arms, thighs, anterior chest, abdomen) was documented at any time during the illness. On the contrary, patients were defined to have "limited cutaneous SSc" if either no skin thickening or thickness limited to the distal extremities (never proximal to the elbows or knees) was found.[10] All of them suffered from: (1) intermittent abdominal pain, (2) nausea, (3) vomiting, (4) bloating, and (5) disturbed defecation (defined as >4 bowel movements per day or no bowel movements for 2 or more days) for at least the 2 previous years before the study. Moreover, 3 of them had been hospitalized time and again because of episodes of incomplete adynamic ileus during the last 2 years.

Inclusion criteria for the study were:

a. Diagnosis of SSc, according to the criteria developed by the Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee.[11]
b. Treatment with several prokinetics agents in the past with poor results.
c. Absence of vagotomy or any other major gastroduodenal surgery in the past.
d. Absence of significant GI pathology (including bacterial overgrowth). Every patient underwent a gastroscopy, colonoscopy, and small bowel enema before octreotide administration. Small intestinal mucosal pathology and bacterial overgrowth were excluded by intestinal mucosal biopsies and aspiration of fluid from the proximal jejunum (gold standard method), respectively.
e. Absence of any other disease (i.e., diabetes mellitus) that could affect intestinal motility.

Symptom's severity was arbitrarily assessed at baseline and at various follow-up points in a scale of 0–3, each for the 5 symptoms described above (0 indicating no symptoms, 1, mild symptoms, 2, moderate symptoms interfering but not preventing daily activities, and 3, severe symptoms preventing patients' daily activities, maximum score: 15) (Table 1). The daily symptom scores were summed before therapy, 1 month, and 6 months after the initiation of therapy. Furthermore, the number of bowel movements was counted in all patients during the same period.

The study was approved by the hospital ethics committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients were informed in terms of the purpose of the study and the rare adverse effects of octreotide and gave their informed, signed consent before their inclusion in the study.

The first 4 patients of the study received initially subcutaneous (Sc) octreotide, 0.1 mg twice daily, and 2 of them were switched over to the long-acting form of octreotide (octreotide LAR) when it became commercially available. The other 3 patients were treated with intramuscular (IM) octreotide LAR, 20 mg/mo, from the beginning. The administration route of octreotide, the duration of therapy, the follow-up, and the outcome in each patient are described in Table 2.

TABLE 1. Symptom Scoring

Symptom
Abdominal pain
Nausea
Vomiting
Bloating
Disturbed defecation
Symptom scale
0: No symptoms
1: Mild symptoms
2: Moderate symptoms, interfering with but not preventing daily activities
3: Severe symptoms preventing daily activities

Minimum score: 0; maximum score: 15.

RESULTS

All patients had used prokinetic agents (metoclopramide, cisapride, domperidome, and erythromycin) during the previous years with disappointing results.

All patients responded to octreotide treatment since a significant reduction of symptom severity from baseline (mean ± SD: 2.9 ± 1.1, range: 4–12) was observed the

TABLE 2. Treatment With Octreotide

Patient No.	Form of Disease	Form of Octreotide	Dosage of Octreotide	Follow-Up (mo)	Outcome
1	dcSSc	Sc	0.1 mg, bd	9	Temporary improvement
2	dcSSc	Sc	0.1 mg, bd	11	Temporary improvement
3	lcSSc	Sc	0.1 mg, bd/⌓ LAR, 20 mg/mo	16	Permanent improvement
4	lcSSc	Sc	0.1 mg, bd/⌓ LAR, 20 mg/mo	14	Permanent improvement
5	dcSSc	IM	LAR, 20 mg/mo	9	Permanent improvement
6	lcSSc	IM	LAR, 20 mg/mo	18	Permanent improvement
7	dcSSc	IM	LAR, 20 mg/mo	24	Permanent improvement

dcSSc indicates diffuse systemic sclerosis; lcSSc, limited systemic sclerosis; Sc, subcutaneously; IM, intramuscularly; bd, twice daily.
⌓: Patients 3 and 4 were switched over to octreotide LAR 3 month after the initiation of treatment.

following month (1.3 + 0.5, $P = 0.0006$). It should be pointed out that in the sixth patient of our study, who was treated with octreotide LAR, complete relief of her symptoms was noticed 1 month, as well as 6 months, after the initiation of therapy, while the same results were noticed in the fifth patient (with the highest symptom score before therapy) 6 months after the administration of octreotide LAR (Fig. 1) A significant disturbance of defecation, i.e., more than 25 bowel movements per week, in 2 patients improved dramatically; no treatment-induced changes in stool frequency were noted in the remaining 5 patients (Fig. 2).

Bloating seemed to be the symptom most resistant to therapy. Several relapses (regarding bloating and slight abdominal pain) of short duration were noticed within 12 months after the initiation of treatment in patients who were treated with Sc octreotide. These patients were subsequently treated with octreotide LAR 20 mg/mo, resulting in an overall reduction of symptoms at 6 months (0.7 ± 0.5, $P = 0.003$), which was sustained during follow-up (range: 9–24 months, median follow-up: 14.4 months).

No adverse effects were reported to us during therapy. Two of our patients (patients 1 and 2) stopped the treatment (1 patient died due to a myocardial infarction and the other had a rapid progression of her basic disease), while all the others continue the treatment with octreotide LAR until today. All of them have noticed a significant improvement of their quality of life in terms of the symptoms of the GI tract.

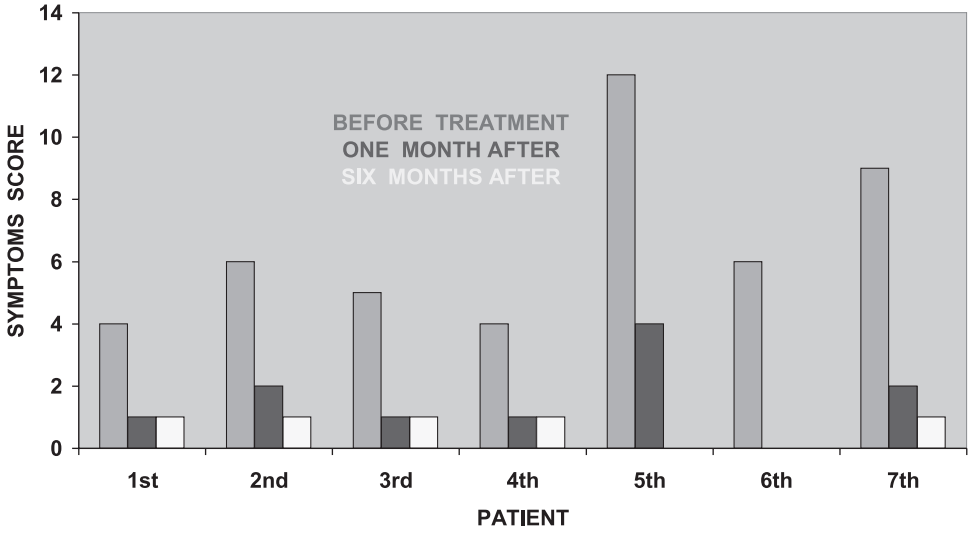

FIGURE 1. Results after administration of octreotide. Alteration of symptom scores of the patients, 1 and 6 months after the initiation of treatment with octreotide.

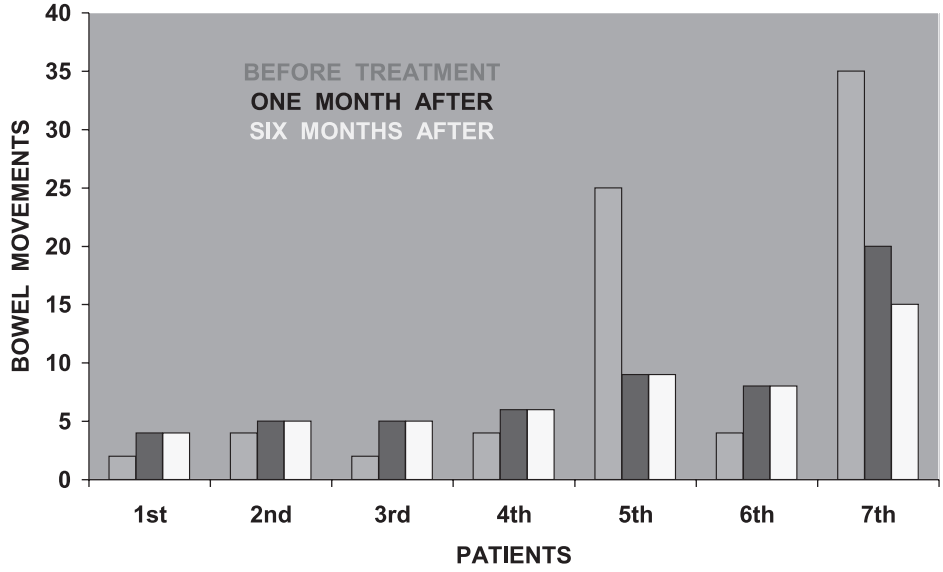

FIGURE 2. Number of bowel movements per week. Effect of octreotide on the patients' bowel movements, 1 and 6 months after the initiation of treatment.

DISCUSSION

Clinical, symptomatic, and significant GI involvement occurs in approximately 50% of all patients with SSc and tends to be late in the course of the disease.[12] However, in diffuse cutaneous SSc, early visceral manifestations have been described and gut involvement may actually precede skin lesions. All parts of the GI tract (from the mouth to anus) may be involved.

In 3 of our patients, GI involvement occurred early in the course of their disease and affected initially the esophagus, producing symptoms of gastroesophageal reflux. In contrast, in the remaining 4 patients, symptoms of the GI tract occurred many years after skin involvement.

The principal pathologic abnormalities of the GI tract consist of smooth-muscle atrophy and gut wall fibrosis. Such abnormalities are generally similar throughout the entire system.

Sjogren[13] advanced the theory that systemic sclerosis affects the GI tract by an orderly series of steps that results in progressive dysfunction. According to this hypothesis, the disease begins with an initial neural disorder, progresses to muscle dysfunction, and ends with fibrosis.

As for the small intestine, it has been reported that 20%–60% of patients with SSc have abnormal small bowel function, while more than one-half have a histologic abnormality at postmortem biopsies.

The pathologic changes in the small bowel of patients with SSc consist also of smooth-muscle atrophy and deposition of collagen around Brunner glands, leading to periglandular sclerosis. This feature is said to be pathognomonic of intestinal scleroderma and may occur in the absence of radiologic changes.[14] However, this finding is of limited clinical value, since small intestinal biopsies rarely include the submucosal layer.

Manometric studies[15,16] report that proximal small bowel postprandeal motility was usually reduced in symptomatic patients. The results of these studies support the hypothesis that both neuropathic and myopathic stages occur in the small bowel of patients with scleroderma.

The major manifestations of small intestinal involvement are due to reduced peristalsis, resulting in stasis and intestinal dilatation. The latter causes abdominal distention and pain arising from dilated bowel loops. Furthermore, intestinal stasis with possible bacterial overgrowth may lead to fat malabsorption and weight loss. A rare complication is CIPO that may result in recurrent obstructive symptoms and alteration in bowel habit. Except for connective tissue diseases, CIPO may be a complication of abnormalities of the nervous, endocrine and metabolic systems, intraabdominal inflammation, and drug-induced states.[17]

All the patients of our study described significant symptoms of the small bowel (abdominal pain, bloating, nausea, vomiting, disturbed defecation), while 3 of them had developed CIPO. The diagnosis of small bowel involvement in our patients relied on patients' history and the absence of other structural abnormalities. Small bowel manometry was not performed, as the experience in terms of precise evaluation of its results is still limited.

The treatment of small bowel disease among patients with SSc mainly consists of the management of malabsorption, dysmotility, and recurrent pseudo-obstruction.[18]

Malabsorption, which is primarily due to small bowel bacterial overgrowth, should be treated with oral antibiotics.[19] The antibiotics are usually rotated, since continuous therapy with 1 agent may result in the emergence of resistant organisms and an increased relapse rate. The choice of the special antibiotic is sometimes empiric, but it may be relied on the sensitivities of aspirated organisms. Ciprofloxacin, amoxycilin, tetracycline, and metronidazole are the most commonly used antibiotics.

As for dysmotility and pseudo-obstruction, prokinetic agents such as metoclopramide, cisapride, domperidone, and erythromycin had been widely used in the past.

Metoclopramide was the first truly efficacious prokinetic drug. It is both a dopaminergic antagonist and a cholinergic agonist. Metoclopramide has been shown to increase lower esophageal sphincter (LES) pressure, increase gastric emptying, and also antral and small bowel peristalsis and transit.[20] Also, it crosses the blood–brain barrier and has a central antiemetic effect. However, as it is a dopamine antagonist, it has important extrapyramidal side effects and may cause irreversible tardive dyskinesia.

Cisapride is chemically related to metoclopramide but is devoid of antidopaminergic effects and therefore does not cause extrapyramidal effects. In the esophagus, it increases the LES pressure and the amplitude of peristaltic contractions. In the stomach, it increases both liquid and solid emptying via increasing both fundic and antral contractions and improving the antroduodenal coordination, while in the small intestine it speeds the transit time.[21]

Domperidone is a specific dopamine-receptor antagonist that stimulates upper GI motility and has also antiemetic properties (that cisapride lacks). As it does not readily cross the blood–brain barrier, it has a lesser propensity for causing central nervous system adverse effects, compared with metoclopramide.[22]

Erythromycin, a macrolide antibiotic, can increase gastric emptying and increase the peristaltic response of the small bowel to eating.[7] These effects appear with lower doses than are required for the drug's antibiotic action.

Although the above-mentioned agents were a central element to therapy for small bowel disease in patients with SSc in the past, their prolonged use was often disappointing. All of our patients had been treated with these prokinetic agents with no improvement of their symptoms.

Octreotide, a long-acting somatostatin analogue, has been observed to both inhibit and stimulate GI peristalsis associated with the interdigestive motility of the gut. It inhibits gastric emptying and antral and colon motility, while it increases orocecal transit time.[23] Whether this effect is achieved by a direct action on the intestinal muscle layer or by suppression of the release of intestinal peptide-like motilin is still a matter of controversy. There are some published studies in the literature, which report success in treating small series of patients with SSc and small bowel dysfunction, with administration of Sc octreotide.[9,24–27] However, there have

been no sufficient data on the long-term efficacy of this treatment in larger series of patients. Furthermore, there were no published reports for the use of octreotide LAR in these patients to date.

In our study, 7 patients with SSc and small bowel disease were treated with octreotide. Four of them were treated initially with Sc octreotide 0.1 mg twice daily. The first dose was given early in the morning and the second at bedtime. The medicine was given in low doses and far from meals to prevent steatorrhea, which could be due to impaired pancreatic secretion and mucosal absorption. Three of our patients were treated with octreotide LAR, 20 mg IM/month, from the beginning. Octreotide LAR is a new pharmacologic form of octreotide, which is currently the treatment of choice in patients with acromegaly and in patients with gastroenteropancreatic (GEP) neuroendocrine tumors.[28] The efficacy of octreotide treatment was evaluated in our patients with a specific questionnaire before treatment, 1 month, and 6 months after treatment. The results were quite impressive, as there was a significant reduction in the symptom score especially after 6 months of treatment. Most of them reported a permanent remission of the symptoms of the small intestine, especially those with octreotide LAR, which provides steadily higher levels of the drug in serum. None of them reported any adverse reaction, which could be associated with the prolonged use of octreotide such as cholelithiasis.

In conclusion, we suggest that long-term treatment with octreotide, and especially with octreotide LAR, could be cost-effective in patients with SSc and small intestine disease who do not respond to prokinetic drugs, as it may control their symptoms sufficiently and permanently. Therefore, it may improve their quality of life. However, further multicentric studies with a large number of patients are needed so that octreotide could be established as a standard therapy in these patients.

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