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Hot Topics

Managing Gastrointestinal Complications in Patients With Systemic Sclerosis

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Abstract

Objective We sought to critically evaluate the literature published over the past 3 years on the management of gastrointestinal complications in systemic sclerosis (SSc). We emphasize interesting and important new findings to bring the reader up-to-date. We also discuss controversial discoveries and hypotheses currently of interest.
Methods We conducted a literature search on PubMed over the last 3 years using the keywords "systemic sclerosis," "gastrointestinal," "scleroderma," and "treatment." We also screened clinicaltrials.gov for ongoing trials relevant to the gastrointestinal complications of SSc. Reference lists from recent reviews on the management of gastrointestinal complications of SSc to identify articles that might have been missed in the initial search.
Results One hundred three publications and ongoing clinical trials were identified. We eliminated all case reports and review articles. Ultimately, we had 58 articles remaining and we prioritized what we found to be the strongest and/or novel findings to discuss in this review.
Conclusions Advances in the management of gastrointestinal disease in SSc continue to evolve. The application of novel therapies and the repurposing of existing therapies for the management of gastrointestinal involvement are shaping the therapeutic arsenal so that we can more effectively manage these complex patients.

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by fibrosis, progressive vasculopathy, and internal organ dysfunction [1]. Gastrointestinal (GI) complications of this disease are common, affecting over 90% of patients [2]. Manifestations range broadly in severity and in the regions of the gut involved. Some patients may only experience mild gastroesophageal reflux disease (GERD) throughout their disease course, while others may experience severe lower bowel complications (e.g., recurrent pseudo-obstruction and malabsorption syndrome) and may ultimately require total parenteral nutrition (TPN) to sustain life [2–4].

While the pathogenesis of SSc-related GI disease is still not fully understood, it is recognized that diet, microbiota dysbiosis, and abnormal GI transit all may contribute to patients' symptoms (Fig. 1) [2, 5, 6]. For example, it is reported that fructose intolerance is present in up to 40% of patients with SSc, and that it contributes significantly to patients' symptoms [6]. Recent studies have also demonstrated that patients with SSc have specific alterations in their GI microbial composition and that these changes are associated with GI symptoms [5, 7, 8••]. Finally, SSc patients may experience GI dysmotility anywhere from the esophagus to the colon, and this can lead to a variety of symptoms associated with GERD, gastroparesis, pseudo-obstruction, and other serious complications [2, 9]. In a subset of patients with rapidly progressive lower GI dysmotility, autoimmunity plays a role in pathogenesis, with pathogenic antibodies to muscarinic-3-receptors on GI smooth muscle cells disrupting normal neuromuscular communication and GI transit. These abnormalities are reversible with intravenous immunoglobulins [10••, 11]. Given the spectrum of factors that contribute to clinical GI manifestations in SSc, an accurate diagnostic evaluation and the targeted therapeutic strategy is important.

In this review, we sought to critically evaluate the literature published over the last 3 years in the management of SSc-related GI disease, emphasizing interesting and important new findings, to bring readers up-to-date on the key advances in this area. As therapies currently vary depending on the etiology of the symptoms and the anatomical region of the GI tract affected, we have organized this manuscript accordingly. We will begin by highlighting important updates from the past few years in treating specific manifestations of GI dysfunction in SSc, reference ongoing clinical trials, and provide a critique of existing literature, including major areas that need to be addressed in future studies.

Methods

We performed a literature search using PubMed with the search terms "gastrointestinal" and "scleroderma," and applied the following filters: Classical Article, Clinical Study, Clinical Trial, Clinical Trial Protocol, Clinical Trial, Phase I,

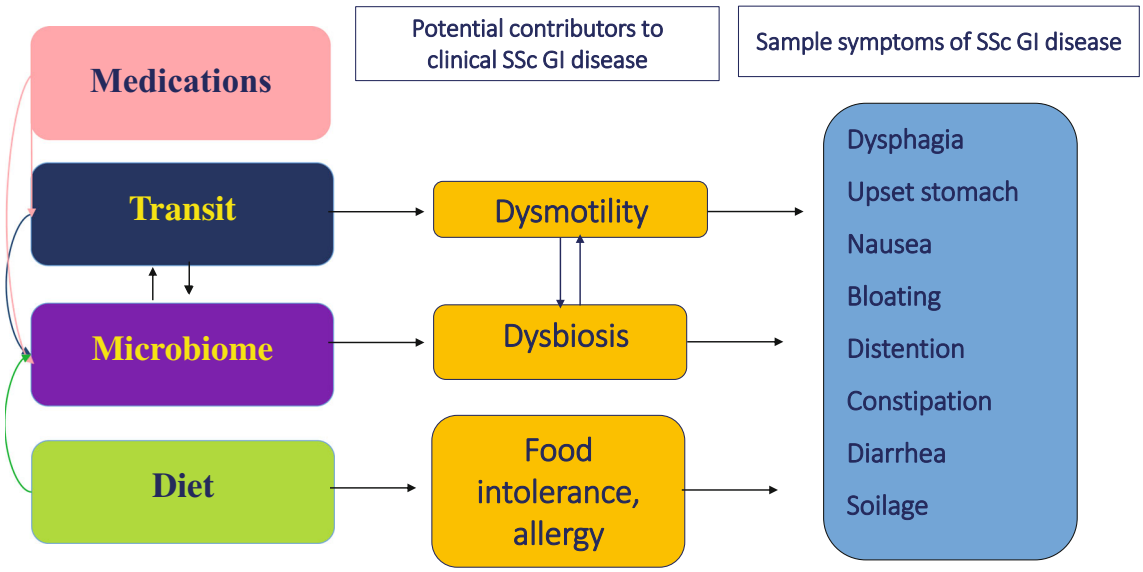

Fig. 1. The Complexity of scleroderma-associated gastrointestinal disease manifestations. This diagram illustrates the normal functions (transit and microbiome) that can be disrupted and environmental exposures (diet and medications) that are thought to most often contribute to GI dysfunction in patients with SSc. The yellow rectangles in the center of the diagram depict the objective complications that may result from disruption of normal function and/or environmental exposures on the left. On the far right some of the most common the GI symptoms in SSc that may result as a consequence of interactions on the left are listed.

Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Consensus Development Conference, Consensus Development Conference, NIH, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Randomized Controlled Trial, Review, Systematic Reviews, Validation Study, and in the last 3 years. We also searched clinicaltrials.gov using the following search terms and phrases: "scleroderma gastrointestinal," "dysphagia," "GERD," "dysmotility," "gastroparesis," "small bowel," "colon," and "fecal incontinence," and identified recent and ongoing studies in this area. In total, we identified 103 publications and clinical trials. We also manually searched the reference lists of recent reviews on this topic for additional articles. We eliminated all case reports not specifically related to the treatment of gastrointestinal complications of SSc. Ultimately, we had 58 articles remaining and we prioritized those we found to be the strongest and/or novel findings to discuss in this review.

Oropharynx

The oropharynx is commonly affected in SSc. Patients may present with a decreased oral aperture, thinning and retraction of the lips, and wrinkling around the mouth. Such changes are not only cosmetically upsetting, but they can also interfere with a patient's ability to ingest solid foods and negatively impact quality of life [12]. Effective oral hygiene and dental care may become challenging, which can negatively impact nutrition if teeth decay [13].

In order to compare educational methods in the rehabilitation of microstomia in SSc, a single-blind randomized controlled study was performed [12]. It included a control group (educational materials alone, i.e., brochures and DVD), and an experimental group (educational materials plus specific "face-to-face" interventions at follow-up visits). Patients in the experimental group were 55 (± 16) years old on average and had a median disease duration of 7 years (IQR 4–13). No measures of skin thickening or cutaneous subtype were reported, but mean mouth opening was 3.7 cm (0.7). The primary outcome was improvement in the size of the oral aperture. Overall, a significant increase in the size of the oral aperture was identified in the experimental group compared to the control group, though it was not statistically significant (p = 0.10). However, in the per-protocol analysis, which included only those patients who completed the protocol for their allocated group, the difference reached statistical significance (n = 39 patients, p = 0.02). The investigators concluded that face-to-face nursing rehabilitation training seems to improve microstomia to a greater extent, when compared to a standard intervention.

Esophagus

The esophagus is the most frequently involved region of the gut in SSc, with up to 90% of patients affected [2, 9]. GERD in SSc may be asymptomatic [14] though it is usually associated with mild to severe symptoms [15]. Patients most often experience GERD and/or dysphagia which are caused by esophageal dysmotility or lower esophageal sphincter (LES) dysfunction. When inadequately treated, these problems may lead to strictures, esophageal ulcers, or Barrett's esophagus.

The effective management of GERD is important in preventing severe GI complications [16]. Chronic uncontrolled GERD has also been tied to more severe interstitial lung disease in SSc, with chronic microaspiration of gastric acid into the lung being the proposed irritant [17–19]. Initial practices for controlling GERD such as dietary and lifestyle modifications have not been well-studied in SSc and are usually inadequate in controlling symptoms [20].

The majority of patients with SSc require acid suppression with medications such as proton pump inhibitors (PPI's) or H2 blockers to control their GERD; however, treatment with even high doses of these medications is inadequate in controlling symptoms in a subset of patients. Therefore, a group of investigators sought to identify the predictors of PPI-partial response in SSc-related GERD. Two-hundred and forty-three SSc patients were treated with omeprazole twice daily for 4 weeks. PPI-partial response GERD was defined as < 50% improvement in severity of symptoms and in acid reflux scores, and the severity of symptom-grading by Visual Analogue Scale (VAS) and frequency of symptoms (fSSG) were assessed at baseline and 4 weeks (Table 1). Fifty-four percent of SSc patients were found to have PPI-partial response (PPI-PR) GERD, and esophageal dysphagia was identified as the only predictor even after adjusting for potential confounders [21]. The results suggest that screening patients for dysphagia may identify a subpopulation who need more aggressive GERD therapy, though these results need to be validated.

A placebo-controlled trial recently evaluated the effectiveness of add-on therapy with domperidone 10 mg three times daily compared to alginic acid 1 chewing tablet three times daily in SSc patients with PPI-PR GERD on omeprazole. Alginic acid acts by precipitating as a gel and creating a relatively pH neutral mechanical barrier that floats on the surface of gastric contents. Patients were included if they were between the ages of 18 and 65 and diagnosed with GERD with a GERD-Q score ≥ 8, and they were defined as PPI-PR if they were not receiving any prokinetic drug or algycon within 2-weeks before baseline evaluation. Response was assessed by VAS and by frequency scale for symptoms of GERD and quality of life (QoL) (EuroQol five-dimensions questionnaire scoring). Eighty cases were randomized to either domperidone (n = 38) or algycon (n = 37) therapy, and at 4 weeks the severity of symptoms, frequency scale for symptoms of GERD and QoL significantly improved in both groups compared to baseline. Five patients (13.2%) in the domperidone group and 8 patients (21.6%) in the algycon groups did not respond, suggesting that both domperidone and algycon are equally effective treatments in combination with omeprazole [22].

As significant overlap exists in the neurotransmitters utilized by the central and peripheral nervous systems (CNS, PNS), medications influencing CNS neuronal signaling may also be effective in the PNS. Therefore, several agents that were initially approved for anxiety and/or depression are now being utilized to enhance upper GI motility and alleviate symptoms of PPI-PR GERD. In a 4-week open-label trial, the 5-HT1A receptor agonist buspirone was evaluated in the treatment of 30 consecutive patients with SSc and esophageal symptoms (Fig. 2). Patients underwent high-resolution manometry to assess motor function and CT chest to assess esophageal diameter. Manometric parameters (primary endpoint) and symptom severity (secondary endpoint) were documented at baseline and after 4 weeks. Of the 22 patients who completed the trial, LES resting pressure increased significantly from 7.7 ± 3.9 to 12.2 ±

Table 1. Ongoing clinical trials in SSc-related GI disease

	Phase (NCT)	Endpoints	Outcome
Esophagus			
Omeprazole + alginic acid + placebo vs. omeprazole + domperidone +placebo	3 (NCT01878526)	Primary endpoints: changing severity of heart burn of SSc-related omeprazole-resistant GERD evaluated by Visual analogue score (VAS); changing of the severity of regurgitation at 4 weeks	Primary outcome not met
Omeprazole bid (open label)	1 (NCT03561233)	Primary endpoints: changing severity of heart burn of SSc-related GERD evaluated by visual analogue score (VAS), severity of heart burn (VAS), and frequency of symptoms in SSc-related GERD evaluated by frequency scale for the symptoms of GERD (FSSG) at 4 weeks	Results pending
MMF + rituximab + belimumab vs. MMF + placebo + placebo	2 (NCT03844061)	Secondary outcome measure: change in gastrointestinal tract (GIT) in scleroderma score at 1 year	Currently recruiting
Buspirone (open label)	1 (NCT02363478)	Primary endpoints: changes from baseline in manometric parameters, changes from baseline in manometric parameters, changes from baseline in manometric parameters at 4 weeks	Primary endpoint met with significantly improved lower esophageal sphincter pressure
Double doses of proton pump inhibitors (PPI) OR standard dose of PPI + ranitidine OR double doses of PPI + domperidone OR double doses of PPI plus prucalopride /erythromycin. in patients with GERD failing standard doses of PPI	(NCT03610217)	Primary GI endpoints: change in the gastroesophageal reflux disease-health related quality of life questionnaire at 3 months	Trial ongoing
Stomach			
Transcutaneous electroacupuncture	(NCT03294616)	Primary endpoints: effect of TEA on patients symptoms at 28, 42, 70 days	Results pending
Small bowel and colon			
Anaerobically cultured human intestinal microbiota (ACHIM) vs. placebo in SSc patients with moderate to severe SSc-related lower GI symptoms	2 (NCT04300426)	Primary endpoint: change in lower GIT symptoms (UCLA GIT 2.0) in ACHIM compared to placebo at 12 weeks	Not yet recruiting (new)
ACHIM vs. placebo for SSc patients with GI symptoms	2 (NCT03444220)	Primary endpoint: clinical SSc-related GI parameters as assessed by the UCLA GIT 2.0	Trial ongoing
Rifaximin vs. placebo in SSc pseudo-obstruction	2 (NCT04118699)	Primary endpoint: improvement ratio (%) in abdominal bloating score in Global Symptomatic Score (GSS) at 4 weeks	Trial ongoing
Erythromycin vs. metronidazole vs. amoxicillin in SSc patients with SIBO	(NCT03610217)	Primary endpoint: change in the diarrhea Visual Analog Scale at 3 months	Trial ongoing
Saccharomyces boulardii oral tablet vs. Metronidazole plus S. boulardii vs. metronidazole alone in patients with SIBO	4 (NCT03692299)	Primary endpoint: presence or absence of small intestinal bacterial overgrowth (SIBO) measured by a breath test using a hydrogen monitor at 2 months	Primary endpoint met
SIBO treatment protocol or standard of care in patients with SIBO	Pilot (NCT03588845)	Primary endpoint: change in the total Gastrointestinal Symptom Scale score at 3 years	Trial ongoing
Bisacodyl vs. magnesium sulphate vs. polyethylene glycol vs. senna in patients with constipation	(NCT03610217)	Primary endpoint: change in the constipation Visual Analog Scale at 3 months	Trial ongoing

4.6 mmHg ($p = 0.00002$), though other manometric parameters did not change. Importantly, a negative correlation between individual increases in resting LES pressure and supra-aortic esophageal diameter suggested that patients with less severely affected esophageal function were more responsive to treatment. Both heartburn and regurgitation severity scores improved significantly from baseline to 4 weeks [23], suggesting that buspirone may be an effective option for patients with refractory upper GI symptoms. Large RCT's are warranted to further explore this intervention.

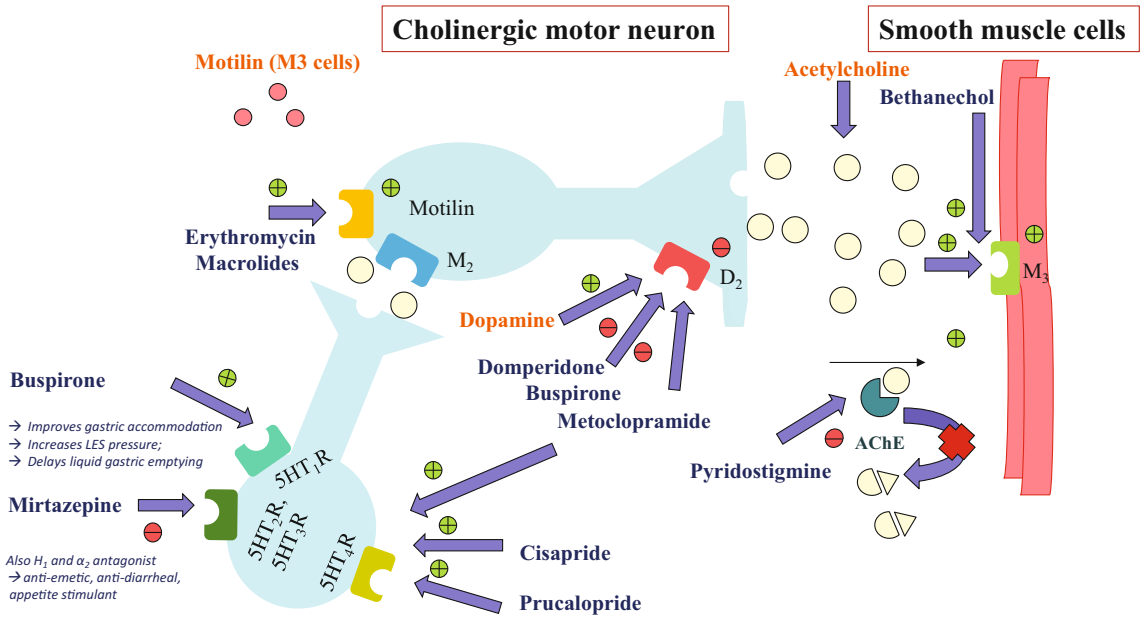

Fig. 2. SSc GI Motility: targeted pathways and promotility agents. This figure depicts different enteric neurons (blue) on the left and GI smooth muscle (pink/red) on the right. A variety of receptors and their cognate neurotransmitters are also shown. Drugs or neurotransmitters that bind these receptors are listed adjacent to the blue arrows. The plus signs represent a stimulatory action, and the minus signs represent an inhibitory action.

Stomach

Gastric abnormalities are identified in 30–50% of patients with SSc [24]. Both gastroparesis and loss of gastric accommodation may occur and cause early satiety, nausea, vomiting, and regurgitation and contribute to refractory GERD. Standard of care involves lifestyle modification with the consumption of smaller meals and avoidance of foods that aggravate symptoms. Promotility agents such as metoclopramide and erythromycin also may be initiated to alleviate symptoms. Gastric antral vascular ectasia (GAVE), gastritis and gastric ulcers may also be observed, though recent SSc GI treatment studies have focused on the management of GI dysmotility.

Several promotility agents were recently studied in the management of gastroparesis in the GI literature, and are promising for patients with SSc. One of these drugs, prucalopride, is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist and was approved by the Food and Drug Administration in 2019 for chronic idiopathic constipation (Fig. 2) [25••]. The effect of prucalopride 2 mg daily on gastric emptying rates and symptoms was recently examined in non-SSc patients with gastroparesis ($n = 34$) in a double-blind, randomized, placebo-controlled cross-over study. The primary end point was changed in symptom severity, assessed by the Gastroparesis Cardinal Symptom Index (GCSI), and secondary end points included the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index, the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life, and daily diaries. The C-octanoic acid breath test was used to assess gastric emptying rate.

Treatment with prucalopride significantly improved the total GCSI and the subscales of fullness/satiety, nausea/vomiting, and bloating/distention. Prucalopride also significantly improved the overall Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life score, and the gastric half emptying time. In a cohort of SSc patients with moderate to severe intestinal symptoms, prucalopride was also found to improve symptoms of reflux and bloating. This open-label crossover study (PROGASS) was focused primarily on the colon and is therefore described in more detail in the "Colon" section below [26••].

Mirtazapine has been shown to reduce symptoms of gastroparesis in case reports, but until recently no prospective studies have evaluated its effect on GI motility in larger groups of patients. A recent open-label prospective study sought to assess the efficacy and safety of mirtazapine in non-SSc patients with gastroparesis [27]. Thirty adults with gastroparesis and poorly controlled symptoms were enrolled and prescribed mirtazapine 15 mg PO every night. Patient-reported outcomes were assessed at baseline and 2 and 4 weeks (GCSI and the Clinical Patient Grading Assessment Scale (CPGAS)). The primary end point was nausea and vomiting response to mirtazapine using the GCSI, and the secondary end points were nausea and vomiting severity assessment using the CPGAS. Eighty percent of patients completed 4 weeks of therapy, and there was a statistically significant improvement in nausea, vomiting, retching, and perceived loss of appetite at 2 and 4 weeks compared with baseline, and a statistically significant improvement in the CPGAS score at weeks 2 and 4 as well. The data suggests that mirtazapine significantly improves nausea and vomiting in patients with gastroparesis and that studies evaluating its effects in SSc-related gastroparesis should be performed.

Finally, a randomized clinical trial was recently completed evaluating the effects of transcutaneous electroacupuncture in SSc patients with refractory upper GI symptoms and/or gastroparesis. Patients were followed for 10 weeks and patient-reported outcomes were assessed at baseline and at regular intervals throughout the study (sHAQ, UCLA GIT 2.0, SF-36). The results of this study are pending, but prior studies in SSc have shown promise (Table 1) [28].

Small bowel

Small bowel dysfunction in SSc affects approximately 8–50% of patients [29]. Abnormal small bowel transit and the development of small intestinal bacterial overgrowth (SIBO) both complicate SSc, and contribute to increased healthcare utilization, worse quality of life, bloating/diarrhea, and malnutrition [30–32]. Several different mechanisms contribute to the regulation of bacterial growth in the small bowel, including the secretion of gastric acid, bacteriostatic properties of pancreatic juice and bile, the mucosal section of immunoglobulins, intestinal peristalsis, and normal function of the ileocecal valve. Disruption of these regulatory mechanisms may result in SIBO [4, 32, 33••]. While there is no standardized approach to management, SIBO in SSc is often empirically treated with cyclic antibiotics [2, 9]. Rifaximin has been specifically studied in the treatment of SIBO among SSc patients and was demonstrated as effective in the management of diarrhea and other abdominal symptoms, and in normalizing lactulose hydrogen breathing tests following treatment [34]. After the treatment of SIBO, the management of small bowel dysmotility, when present, is likely important to reduce SIBO

recurrence though this has not been studied. Small bowel dysmotility has traditionally been managed with octreotide, though some success with pyridostigmine has also been reported [35–39].

More recently, the role of the gut microbiota in the manifestation of GI symptoms of SSc patients has been explored, and novel therapeutic strategies are in early stages of investigation. One of these interventions involves the transplantation of gut microbiota. The safety and efficacy of fecal microbiota transplantation (FMT) using commercially available anaerobic cultivated human intestinal microbiota (ACHIM) in patients with SSc was recently assessed in a single-center, randomized, double-blind, placebo-controlled 16-week pilot study [40]. FMT was completed by gastroduodenoscopy of ACHIM. Primary endpoints were safety and clinical efficacy on GI symptoms assessed at weeks 4 and 16. Efficacy on GI symptoms was measured using the UCLA GIT 2.0 score questionnaire. Patients were defined as responders if symptom improvement was equivalent to the UCLA GIT definition of "minimally clinically important difference" [41]. Ten female patients with limited cutaneous SSc and GI symptoms were randomized to ACHIM ($n = 5$) or placebo ($n = 5$). Two controls experienced procedure-related serious adverse events including one with laryngospasm at first gastroduodenoscopy, and one with duodenal perforation at final gastroduodenoscopy. FMT effects were most pronounced on diarrhea, distention/bloating, and/or fecal incontinence at baseline compared to placebo. Fecal microbiota diversity increased significantly following FMT and IgA- and IgM-coated fecal bacteria were present in the FMT but not in the placebo group. These data suggest that FMT commercially available ACHIM in patients with SSc was well-tolerated and effectively reduced lower GI symptoms, but the results need to be validated in larger trial.

The role of probiotics in managing symptoms of GI dysbiosis in SSc is a rapidly evolving field.

Several clinical trials have recently begun to look at this question (Table 1), though most of these trials are still ongoing. However, one recently published study examined the effectiveness of *Saccharomyces boulardii* for bacterial overgrowth in SSc [42••]. *Saccharomyces boulardii* was selected by the investigators as it is an antibiotic-resistant strain of yeast, which secretes proteases and phosphatases that can inactivate pathogenic toxins, favorably impact inflammatory cytokine profiles, and improve intestinal immunoglobulins [42••]. In this open-label pilot clinical trial, 40 patients with SIBO and SSc were assigned to one of three experimental groups: (1) metronidazole treatment only (M); (2) *Saccharomyces boulardii* (SB); or (3) M plus SB and followed for 2 months. The primary outcome was to evaluate the effects of intervention in GI symptoms (NIH PROMIS) and hydrogen breath test results. They found that after 2 months of treatment, SIBO was eradicated in 55% of patients on combination therapy, 33% of the patients on SB, and 25% of the patients on M. Symptoms of diarrhea, abdominal pain, and gas, bloating, and flatulence were improved in patients on SB and combination therapy but not on M. These data suggested that combination therapy or even monotherapy with SB improves GI outcomes in SSc.

Colon

Colonic dysmotility is common in SSc, affecting up to 50% of patients. Patients most often present with symptoms of constipation, which range from mild to

severe. Recurrent pseudo-obstruction is a severe complication of colonic hypomotility and is present in < 10% of SSc. Though rare, it is associated with significant morbidity and mortality [43]. Prior case reports and case series report that promotility agents such as neostigmine, prucalopride, and metoclopramide may benefit the subset of patients with more severe bowel who are refractory to standard therapies for constipation [43–45]. Importantly, patients with shorter disease duration and less severe GI manifestations are reported to have a better response to promotility agents, suggesting that these patients may have less smooth muscle atrophy. Earlier diagnosis of GI complications and the timely application of targeted therapies may be important in controlling patients' symptoms and outcomes [43].

The PROGASS study was the first study to systematically evaluate the efficacy of prucalopride in the management of SSc patients with mild to moderately severe enteric symptoms [26••]. Prucalopride is similar to its predecessor cisapride, but with a much higher affinity for the 5-HT4 receptor which largely eliminates the cardiac toxicity [46]. In this open-label crossover study, 40 SSc patients with self-reported mild to moderately severe GI symptoms were enrolled and randomized 1:1 to prucalopride 2 mg/day or no treatment for 1 month and vice-versa after a 2-week washout period. Patient-reported outcomes were collected before and after each sequence (UCLA GIT 2.0) and the number of spontaneous bowel movements was recorded. A subset of these patients completed a lactulose breath test to measure oro-cecal transit time (OCTT). In the 29 patients who completed the study, prucalopride was associated with significantly more intestinal evacuations ($p < 0.001$), improvement of UCLA GIT constipation (-0.672 ± 0.112 vs 0.086 ± 0.115; $p < 0.001$), reflux (-0.409 ± 0.094 vs 0.01 ± 0.096; $p < 0.005$), and bloating (-0.418 ± 0.088 vs -0.084 ± 0.09; $p = 0.01$) scores, and was ranked moderately to more-than-moderately effective by 72% of patients. In addition, OCTT was significantly reduced during prucalopride consumption. The data therefore suggest that prucalopride may improve symptoms of bloating and constipation, as well as reflux, in SSc patients with mild to severe gastrointestinal problems.

The results of 2 retrospective case series suggested that pyridostigmine and linaclotide may be beneficial for the treatment of patients with SSc and symptomatic gastrointestinal disease, particularly in patients with constipation [36, 47]. Other case series suggest that treatment with IVIG may also be beneficial for GI dysmotility in SSc [48, 49]. However, these reports were limited by small size and lack control groups. Larger, randomized, prospective placebo-controlled studies evaluating these interventions in patients with SSc are warranted.

Anorectum

Fecal incontinence is an underappreciated complication in SSc affecting up to 50% of patients, and it is associated with decreased quality of life [50]. Accumulating data now supports the fact that SSc-related anorectal dysfunction is attributable to a neuropathy and is associated with a decreased rectoanal inhibitory reflex (RAIR) and atrophy of the internal anal sphincter on pathology [51••]. Standard treatments for anorectal involvement in SSc have included pelvic physical therapy and biofeedback [52]. Accumulating data from small studies suggests that posterior tibial nerve stimulation (PTNS) may benefit SSc patients with fecal incontinence who fail conservative therapy [53], while sacral nerve stimulation may not be effective for

such patients [54]. A large multi-center, cross-sectional study ($n = 298$) of patients with SSc utilized a variety of validated questionnaires to examine associations between fecal incontinence and other clinical variables. They determined that controlling diarrhea, constipation, and SIBO may also be beneficial [50].

Other considerations

Updated expert consensus-derived GI treatment algorithms were recently developed in a collaborative effort between the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research group ($n = 170$). The 2012 algorithm was updated to include a broader spectrum of GI manifestations, and the new algorithm had 77% agreement; however, variance in expert opinion was notable for first-line promotility agents and for antibiotics [55••].

Controversies and hypotheses of interest

Many advances have been made in the past two decades in our understanding of SSc GI dysfunction ranging from the contributions of pathogenic autoantibodies, GI dysbiosis, and updated technologies to more comprehensively diagnose GI dysmotility. As a result, the optimal approach to managing GI complications in SSc is evolving. Currently, the standard of care is to treat GI symptoms as they arise in the clinical setting rather than to proactively prevent complications.

Role of immunomodulation in the management and prevention of SSc GI dysfunction

One area of controversy relates to the role of immunomodulation in the management and/or prevention of GI dysmotility. Accumulating data suggest that anti-muscarinic antibodies negatively impact GI motility in a subset of SSc patients [10, 11], possibly contributing to GI smooth muscle atrophy, which is a common finding in the SSc gut [2, 56, 57]. However, the screening tests for these antibodies are not yet clinically available making it challenging to identify this at-risk patient subset. In addition, the lack of objective biomarkers that define an ongoing dysfunctional immune response in the gut further limits our ability to identify patients whose GI tract might benefit from immunomodulation. This limits our ability to identify appropriate patients for GI clinical trials and accurately assess the benefits of immunosuppression for treating and/or preventing SSc-related GI dysfunction. While small case series have suggested that immunomodulators such as IVIG may benefit SSc GI patients, the treatment costs are high and the patient subset who would benefit from this treatment is poorly defined. A phase 2 double-blind RCT is planned that will assess the effects of IVIG in early SSc (NCT04138485), and the UCLA GIT 2.0 has been included to explore the beneficial impact of IVIG on GI symptoms.

Early application of promotility agents for prevention of GI dysfunction in high-risk GI subgroups

Because smooth muscle atrophy is a major finding in the SSc gut that is often associated with severe GI transit delays, another area of controversy revolves around the early application of promotility agents or transcutaneous neuromodulation. The rationale for this treatment strategy would be to

stimulate GI muscle contractions to prevent smooth muscle atrophy in patients at risk for GI poor outcomes. Key questions that need to be addressed include the following: (1) defining the patient subset that would benefit; (2) determining the overall benefit/risk ratio of early intervention with prokinetic therapy and/or neuromodulation; and (3) defining the optimal timing of initiation and the optimal duration of therapy.

Screening and treatment of SSc patients with asymptomatic GERD

A third area of controversy is related to whether or not SSc patients should be screened and treated for asymptomatic GERD. While this is not yet the standard of care, accumulating evidence suggests it may be worth considering. Several studies have now demonstrated that chronic uncontrolled GERD is associated with worse restrictive lung disease. It has been postulated that this is related to chronic microaspiration of gastric acid into the lung.

Treating GI dysmotility, GI dysbiosis, or both?

Finally, it remains to be determined whether a biologically important interaction exists between GI dysmotility to GI dysbiosis in SSc. In addition, the relative contribution(s) of each to the patient's clinical presentation remains unclear. The further characterization of this relationship will be important in development novel, targeted, therapeutic strategies.

Conclusions

Our knowledge and understanding of SSc-related GI disease continues to evolve, and several novel therapeutic strategies are now available for management of complications. Many gaps continue to exist in this area related to mechanistically important biomarkers of disease activity and the need for targeted therapies. As our understanding continues to improve with future studies, we ultimately envision the use of immunomodulatory therapies, promotility agents and/or electrostimulation, and agents that positively influence the composition of the GI microbiota to be utilized as monotherapy or in strategic combinations to treat and prevent complications of this disease.

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Compliance with ethical standards

Conflict of interest

Consultant: Acceleron, Actelion, Amgen, Bayer, Blade Therapeutics, Boehringer Ingelheim, CSL Behring, Corbus, Cytori, Galapagos, Genentech/Roche, GSK, Horizon, Merck, Mitsubishi Tanabe Pharma, Regeneron, Sanofi-Aventis,

and United Therapeutics; CME programs: Impact PH; Stocks: Eicos Sciences, Inc.; Leadership/Equity position - Medical lead, Scleroderma Development, CiviBioPharma/Eicos Sciences, Inc.

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•• Of major importance

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