The Collaborative National Quality and Efficacy Registry for Scleroderma: association of medication use on gastrointestinal tract symptoms in early disease and the importance of tobacco cessation

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Abstract

Objective

Systemic Sclerosis (SSc) is frequently associated with gastrointestinal tract (GIT) involvement. The Collaborative National Quality and Efficacy Registry (CONQUER) is a US-based collaborative study collecting longitudinal follow up data on SSc patients with less than 5-years disease duration enrolled at Scleroderma centres of excellence. This manuscript presents the GIT natural history and outcomes in relation to other scleroderma manifestations and medication exposures.

Methods

CONQUER participants that had completed a minimum of two serial Scleroderma Clinical Trials Consortium GIT Questionnaires (GIT 2.0) were included in this analysis. Patients were categorised by total GIT 2.0 severity at baseline, and by category change: none-to-mild (0.49); moderate (0.50-1.00), and severe-to-very severe (1.01-3.00) at the subsequent visit. Based on this data, four groups were identified: none-to-mild with no change, moderate-to-severe with no change, improvement, or worsening. Clinical features and medications, categorised as gastrointestinal tract targeted therapy, anti-fibrotic, immunosuppression, or immunomodulatory drugs, were recorded. Analysis included a proportional odds modelaccounting for linear and mixed effects of described variables.

Results

415 enrolled CONQUER participants met project inclusion criteria. Most participants had stable mild GIT symptoms at baseline and were on immunomodulatory and anti-reflux therapy. In most patients, anti-reflux medication and immunosuppression initiation preceded the baseline visit, whereas anti-fibrotic initiation occurred at or after the baseline visit. In the proportional odds model, worsening GIT score at the follow-up visit was associated with current tobacco use (odds ratio: 3.48 (1.22, 9.98, p 0.020).

Conclusion

This report from the CONQUER cohort, suggests that most patients with early SSc have stable and mild GIT disease. Closer follow-up was associated with milder, stable GIT symptoms. There was no clear association between immunosuppression or anti-fibrotic use and severity of GIT symptoms. However, active tobacco use was associated with worse GIT symptoms, highlighting the importance of smoking cessation counselling in this population.

Key words

systemic sclerosis, gastrointestinal tract, immunosuppression, tobacco use

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Introduction

Gastrointestinal tract (GIT) symptoms are common in systemic sclerosis (SSc) (1). While there are established longitudinal markers for pulmonary and skin involvement in scleroderma including the modified Rodnan skin score (mRSS) and pulmonary function tests (PFT), serial assessment of the gastrointestinal tract is more challenging (2, 3).

The Scleroderma Clinical Trials Consortium University of California Los Angeles Gastrointestinal Tract Questionnaire (GIT 2.0) is a validated, patient-reported outcome measure to assess Health Related Quality of Life (HRQOL) and gastrointestinal symptom severity in SSc (4, 5). The 34-item GIT 2.0 allows a clinician to assess to the preceding seven days of reflux, bloating/distention, diarrhoea, constipation, soilage as well as the emotional and social impact of gastrointestinal symptoms into an absent-to- mild, moderate, or severe categorisation, which can then be trended over subsequent care visits. Similar to trending mRSS and PFT, the clinician may alter therapy in response to changes in GIT 2.0. Possible interventions may include initiation of anti-reflux therapy, pro-motility therapy, or laxative initiation; modifying medications known to have side effects on the GIT, such as mycophenolate mofetil or nintedanib; or referring the patient for procedural diagnostics such as motility studies or endoscopy. Many gastrointestinal symptoms such as dyspepsia, diarrhoea, and constipation may either be due to SSc pathogenesis or may be a potential adverse side effect of immunosuppressive and antifibrotic treatments for SSc. The GIT 2.0 can be a powerful instrument to guide initiation and response to therapy as well as to assess whether there is need for procedural referrals. Serial monitoring of the GIT 2.0 can thus be harnessed to identify patients in whom further intervention is warranted.

The Collaborative National Quality and Efficacy Registry (CONQUER) is a collaborative longitudinal study collecting data on a large cohort of early scleroderma patients followed at SSc centres of excellence in the United States (6). This registry enrols patients that meet classification for SSc (7) within 5 years of their first non-Raynaud's symptom. CONQUER collects clinical data, biorepository specimens, and patient reported outcomes at six-month intervals with a manual of procedures that minimises missing data (6, 8, 9). In this manuscript, we describe the natural history of SSc gastrointestinal tract symptoms in the CONQUER cohort.

Materials and methods

The inclusion criteria for this analysis included CONQUER participants who had completed a minimum of two serial GIT 2.0 (10). Each SCTC GIT 2.0 total score collected on or after the patient's baseline visit was categorised in a GIT status of none/mild (0–0.49) or moderate/severe (0.5–3.0). Chronological order of the GIT statuses was then used to categorise patients into the following GIT status change groups: none/mild with no change (no change mild), moderate/severe with no change (no change severe), went from none/mild to moderate/severe (worsened), or went from moderate/severe to none/mild (improved) with the last observation determining the analysis of the trajectory. Sankey diagrams were created to illustrate the changes in GIT scores across the visits.

Medications were categorised as gastrointestinal tract targeted therapy or immunomodulatory drugs. Gastrointestinal tract medications included reflux medications (proton pump inhibitors, antacids, oesophageal guardian, and histamine-2 blockers); anti-diarrheal (loperamide); anti-constipation (polyethylene glycol); pro-motility (metoclopramide and domperidone), and small intestinal bacterial overgrowth)-specific prescribed antibiotics). Immunomodulatory drugs included hydroxychloroquine, methotrexate, mycophenolate, rituximab, azathioprine, tocilizumab, cyclophosphamide, intravenous immunoglobulin (IVIG), and prednisone; and anti-fibrotic drugs included pirfenidone and nintedanib. Analysis included a proportional odds model accounting for linear and mixed effects of described variables.

Medications taken within 90 days of any survey were summarised using frequencies and percentages for each GIT

Table I. Patient characteristics by type of first change in GIT score. Baseline sociodemographic and disease characteristics of the 415 CONQUER participants included in this analysis.

	Overall (n=415)	Type of first change in GIT score				*p*-value
		No change (none/mild) (n=214)	No change (moderate/severe) (n=64)	Improved (n=64)	Worsened (n=73)	
Age (years) at baseline visit: n, mean (SD)	415, 51.8 (13.78)	214, 52.1 (13.65)	64, 51.4 (13.58)	64, 50.6 (13.54)	73, 52.2 14.71)	0.856[1]
Sex: Female	344 (82.9%)	168 (78.5%)	55 (85.9%)	56 (87.5%)	65 (89.0%)	0.101[2]
BMI at baseline (kg/m^2): n, mean (SD)	401, 26.0 (5.20)	206, 25.7 (4.63)	64, 27.1 (5.58)	62, 26.2 (5.44)	69, 25.9 (6.13)	0.268[1]
Race						0.221[2]
White	336 (81.0%)	171 (79.9%)	53 (82.8%)	49 (76.6%)	63 (86.3%)	
Black or African American	42 (10.1%)	18 (8.4%)	8 (12.5%)	9 (14.1%)	7 (9.6%)	
Other	35 (8.4%)	24 (11.2%)	2 (3.1%)	6 (9.4%)	3 (4.1%)	
Ethnicity: Hispanic or Latino	39 (9.4%)	18 (8.4%)	8 (12.5%)	8 (12.5%)	5 (6.8%)	0.523[2]
Employment status[3]						0.002[2]
Full-time	202 (48.7%)	117 (54.7%)	27 (42.2%)	30 (46.9%)	28 (38.4%)	
Retired	75 (18.1%)	41 (19.2%)	10 (15.6%)	7 (10.9%)	17 (23.3%)	
Disabled	48 (11.6%)	11 (5.1%)	14 (21.9%)	13 (20.3%)	10 (13.7%)	
Other	85 (20.5%)	43 (20.1%)	11 (17.2%)	13 (20.3%)	18 (24.7%)	
Smoking status						0.569[2]
Never	281 (67.7%)	143 (66.8%)	42 (65.6%)	44 (68.8%)	52 (71.2%)	
Former	118 (28.4%)	65 (30.4%)	19 (29.7%)	15 (23.4%)	19 (26.0%)	
Current	16 (3.9%)	6 (2.8%)	3 (4.7%)	5 (7.8%)	2 (2.7%)	
Disease duration (years) from date of first non-Raynauds symptom to baseline visit: n, mean (SD)	415, 2.6 (1.40)	214, 2.6 (1.42)	64, 2.7 (1.34)	64, 2.7 (1.30)	73, 2.3 (1.45)	0.296[1]
Disease duration (years) from date of first Raynauds symptom to baseline visit: n, mean (SD)	403, 4.8 (7.18)	207, 4.6 (5.99)	64, 6.1 (10.54)	61, 5.2 (8.55)	71, 3.9 (5.01)	0.389[1]
SSc subtype at baseline						0.721[2]
Limited cutaneous	161 (38.8%)	85 (39.7%)	26 (40.6%)	26 (40.6%)	24 (32.9%)	
Diffuse cutaneous	254 (61.2%)	129 (60.3%)	38 (59.4%)	38 (59.4%)	49 (67.1%)	
ANA status	380 (91.6%)	199 (93.0%)	60 (93.8%)	56 (87.5%)	65 (89.0%)	0.180[2]
ANA pattern - any visit (accounting for changing patterns and anticentromere, collapsed)						0.057[2]
Centromere	70 (16.9%)	36 (16.8%)	14 (21.9%)	15 (23.4%)	5 (6.8%)	
Nucleolar	61 (14.7%)	34 (15.9%)	12 (18.8%)	5 (7.8%)	10 (13.7%)	
Other	215 (51.8%)	108 (50.5%)	28 (43.8%)	34 (53.1%)	45 (61.6%)	
Anti-centromere positive	64 (15.4%)	33 (15.4%)	11 (17.2%)	15 (23.4%)	5 (6.8%)	0.146[2]
Anti-Scl-70 positive	121 (29.2%)	66 (30.8%)	13 (20.3%)	18 (28.1%)	24 (32.9%)	0.328[2]
Anti-RNA polymerase III positive	112 (27.0%)	57 (26.6%)	14 (21.9%)	16 (25.0%)	25 (34.2%)	0.429[2]
Anti-U1-RNP positive	27 (6.5%)	11 (5.1%)	4 (6.3%)	5 (7.8%)	7 (9.6%)	0.785[2]
Modified Rodnan Skin Score (mRSS) at baseline: n, mean (SD)	415, 13.0 (10.67)	214, 12.6 (10.39)	64, 14.0 (11.77)	64, 11.5 (10.12)	73, 14.4 (10.92)	0.296[1]
Digital pitting scars	93 (22.4%)	43 (20.1%)	16 (25.0%)	18 (28.1%)	16 (21.9%)	0.546[2]
Ischemic digital ulcers at baseline	28 (6.7%)	14 (6.5%)	6 (9.4%)	3 (4.7%)	5 (6.8%)	0.765[2]
Gastric antral vascular ectasia[5]	38 (9.2%)	16 (7.5%)	7 (10.9%)	2 (3.1%)	13 (17.8%)	0.016[2]
GI tract: not normal[6]						<.001[2]
Normal oesophagram; normal small bowel series; not GI symptoms	115 (27.7%)	74 (34.6%)	5 (7.8%)	16 (25.0%)	20 (27.4%)	
Distal oesophageal hypoperistalsis; small bowel abnormal (*e.g.*, reflux, bloating, distension)	285 (68.7%)	136 (63.6%)	53 (82.8%)	44 (68.8%)	52 (71.2%)	
Antibiotics required for bacterial overgrowth	8 (1.9%)	1 (0.5%)	3 (4.7%)	3 (4.7%)	1 (1.4%)	
Malabsorption syndrome; episodes of pseudo-obstruction	2 (0.5%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	
Hyperalimentation required	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	
GI tract: not normal[6]	296 (71.3%)	137 (64.0%)	58 (90.6%)	48 (75.0%)	53 (72.6%)	<.001[2]
Baseline supplemental oxygen use	13 (3.1%)	6 (2.8%)	2 (3.1%)	4 (6.3%)	1 (1.4%)	0.414[2]
Creatine kinase (CK)	289, 164.7 (457.15)	152, 191.1 (586.34)	45, 109.1 (94.53)	42, 109.9 (83.17)	50, 180.9 (383.73)	0.494[1]
HRCT performed at baseline	286 (68.9%)	140 (65.4%)	47 (73.4%)	45 (70.3%)	54 (74.0%)	0.430[2]
Medications at baseline						
Azathioprine	5 (1.2%)	3 (1.4%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0.778[2]
Cyclophosphamide	2 (0.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.4%)	0.250[2]
Hydroxychloroquine	98 (23.6%)	56 (26.2%)	20 (31.3%)	14 (21.9%)	8 (11.0%)	0.024[2]
Methotrexate	32 (7.7%)	19 (8.9%)	4 (6.3%)	5 (7.8%)	4 (5.5%)	0.774[2]
Mycophenolate	219 (52.8%)	102 (47.7%)	33 (51.6%)	38 (59.4%)	46 (63.0%)	0.091[2]
Nintedanib	7 (1.7%)	2 (0.9%)	0 (0.0%)	3 (4.7%)	2 (2.7%)	0.122[2]
Prednisone	76 (18.3%)	32 (15.0%)	14 (21.9%)	17 (26.6%)	13 (17.8%)	0.166[2]
Rituximab	7 (1.7%)	3 (1.4%)	1 (1.6%)	3 (4.7%)	0 (0.0%)	0.184[2]
Tocilizumab	8 (1.9%)	4 (1.9%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	0.884[2]
Proton pump inhibitor	252 (60.7%)	113 (52.8%)	50 (78.1%)	41 (64.1%)	48 (65.8%)	0.002[2]

Cohort contains subjects with at least two GIT surveys. [1]Kruskal-Wallis test. [2]Chi-squared test. [3]Employment status of 'Other' includes part-time, homemaker, student or unemployed. [4]ANA pattern of 'Other' includes speckled, homogenous and mixed pattern. [5]GAVE displays counts and percent of Yes out of No/Missing with missings assuming no GAVE. [6]GI Tract not normal: distal oesophageal hypoperistalsis; small bowel abnormal (*e.g.* reflux, bloating, distension) or antibiotics required for bacterial overgrowth or malabsorption syndrome; episodes of pseudo-obstruction or hyperalimentation required.

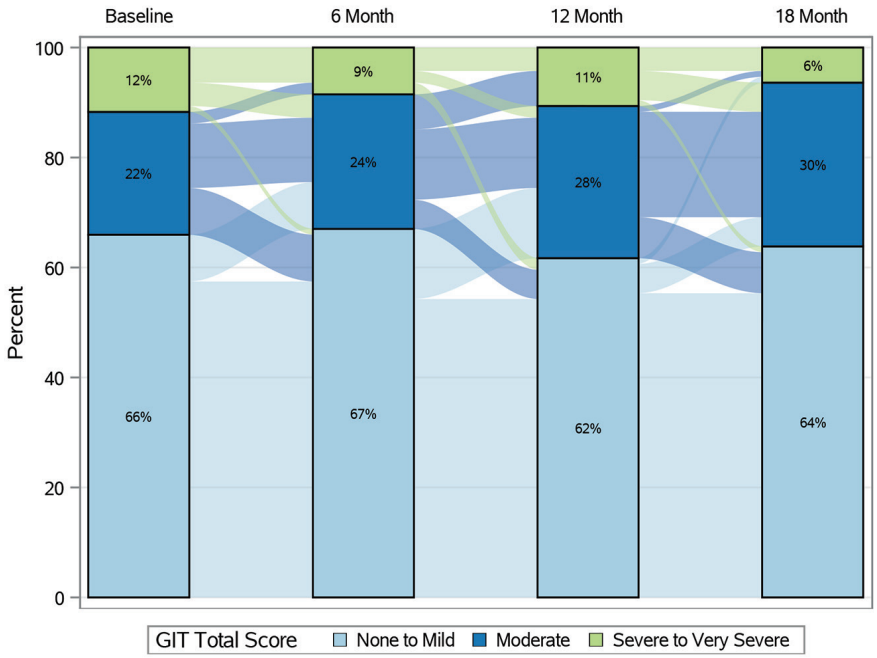

Fig. 1. Change between GIT total severity score by category over an 18-month period.

status change group. For the no change groups, medication use was summarised before and after the baseline visit. For the improved group, medication use was summarised before and after the date of the last survey prior to improvement. For the worsened group, medication use was summarised before and after the date of the last survey prior to worsening. Medications started after the last recorded survey date were excluded from analysis.

Medications and survey timing were summarised for each of the GIT status change groups using a bar plot overlaid by a bubble plot to indicate number of patients in each category on the specific treatment. For patients with no change in GIT status, the length of the bar indicates the median time from baseline to last GIT recorded. For patients with improved GIT status, the length of the bar

Table II. Medication use for GIT groups.

	No change (none/mild) (n=214)	No change (moderate/severe) (n=64)	Improved (n=64)		Worsened (n=73)	
			Moderate/severe	None/mild	None/mild	Moderate/severe
Immune targeted therapy	172 (80.4%)	54 (84.4%)	53 (82.8%)	53 (82.8%)	58 (79.5%)	64 (87.7%)
Cyclophosphamide	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Mycophenolate mofetil	123 (57.5%)	38 (59.4%)	41 (64.1%)	40 (62.5%)	49 (67.1%)	56 (76.7%)
Rituximab	3 (1.4%)	2 (3.1%)	5 (7.8%)	3 (4.7%)	0 (0.0%)	1 (1.4%)
Prednisone	45 (21.0%)	15 (23.4%)	18 (28.1%)	15 (23.4%)	12 (16.4%)	15 (20.5%)
Methotrexate	22 (10.3%)	7 (10.9%)	8 (12.5%)	6 (9.4%)	7 (9.6%)	8 (11.0%)
Azathioprine	2 (0.9%)	1 (1.6%)	2 (3.1%)	2 (3.1%)	1 (1.4%)	1 (1.4%)
Tocilizumab	11 (5.1%)	4 (6.3%)	2 (3.1%)	3 (4.7%)	1 (1.4%)	3 (4.1%)
Hydroxychloroquine	74 (34.6%)	17 (26.6%)	20 (31.3%)	22 (34.4%)	13 (17.8%)	15 (20.5%)
Antifibrotic	6 (2.8%)	2 (3.1%)	4 (6.3%)	5 (7.8%)	5 (6.8%)	5 (6.8%)
Nintedanib	6 (2.8%)	2 (3.1%)	4 (6.3%)	5 (7.8%)	5 (6.8%)	5 (6.8%)
Constipation	3 (1.4%)	2 (3.1%)	0 (0.0%)	1 (1.6%)	1 (1.4%)	5 (6.8%)
Polyethylene glycol	3 (1.4%)	2 (3.1%)	0 (0.0%)	1 (1.6%)	1 (1.4%)	5 (6.8%)
Anti-diarrheal	2 (0.9%)	1 (1.6%)	2 (3.1%)	3 (4.7%)	2 (2.7%)	2 (2.7%)
Loperamide	2 (0.9%)	1 (1.6%)	2 (3.1%)	3 (4.7%)	2 (2.7%)	2 (2.7%)
Small bacterial overgrowth treatment	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (3.1%)	0 (0.0%)	1 (1.4%)
Rifaximin	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (3.1%)	0 (0.0%)	1 (1.4%)
Promotility	3 (1.4%)	3 (4.7%)	2 (3.1%)	1 (1.6%)	2 (2.7%)	4 (5.5%)
Metoclopramide	2 (0.9%)	3 (4.7%)	2 (3.1%)	1 (1.6%)	2 (2.7%)	4 (5.5%)
Domperidone	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reflux	147 (68.7%)	59 (92.2%)	52 (81.3%)	50 (78.1%)	52 (71.2%)	59 (80.8%)
Antiacid	17 (7.9%)	3 (4.7%)	4 (6.3%)	4 (6.3%)	7 (9.6%)	7 (9.6%)
Famotidine	28 13.1%)	17 (26.6%)	13 (20.3%)	15 (23.4%)	8 (11.0%)	15 (20.5%)
Esomeprazole	18 (8.4%)	6 (9.4%)	7 (10.9%)	5 (7.8%)	8 (11.0%)	10 (13.7%)
Omeprazole	93 (43.5%)	28 (43.8%)	28 (43.8%)	27 (42.2%)	31 (42.5%)	35 (47.9%)
Dexlansoprazole	6 (2.8%)	2 (3.1%)	4 (6.3%)	2 (3.1%)	0 (0.0%)	0 (0.0%)
Lansoprazole	4 (1.9%)	6 (9.4%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	2 (2.7%)
Rabeprazole	1 (0.5%)	5 (7.8%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Pantoprazole	22 (10.3%)	20 (31.3%)	16 (25.0%)	14 (21.9%)	9 (12.3%)	11 (15.1%)

[1]Change is referring to the first change for a patient (*i.e.*, if patient improved and then later worsened just the first change is used here).
[2]For the no change groups the medication was marked as taken if they ever took it from before baseline to last GIT date.
[3]For improved patients, the medication counts in the the Moderate/Severe section if they ever started the medication before the change to mild. For the Mild section, the subject was on the medication anytime after the change to mild to last GIT.
[4]For worsened patients, the medication counts in the Mild section if they ever started the medication before or on the last mild GIT date. For the Moderate/severe section, the subject was on the medication anytime after the last mild GIT to the last GIT.
[5]No patients were on Alginate.

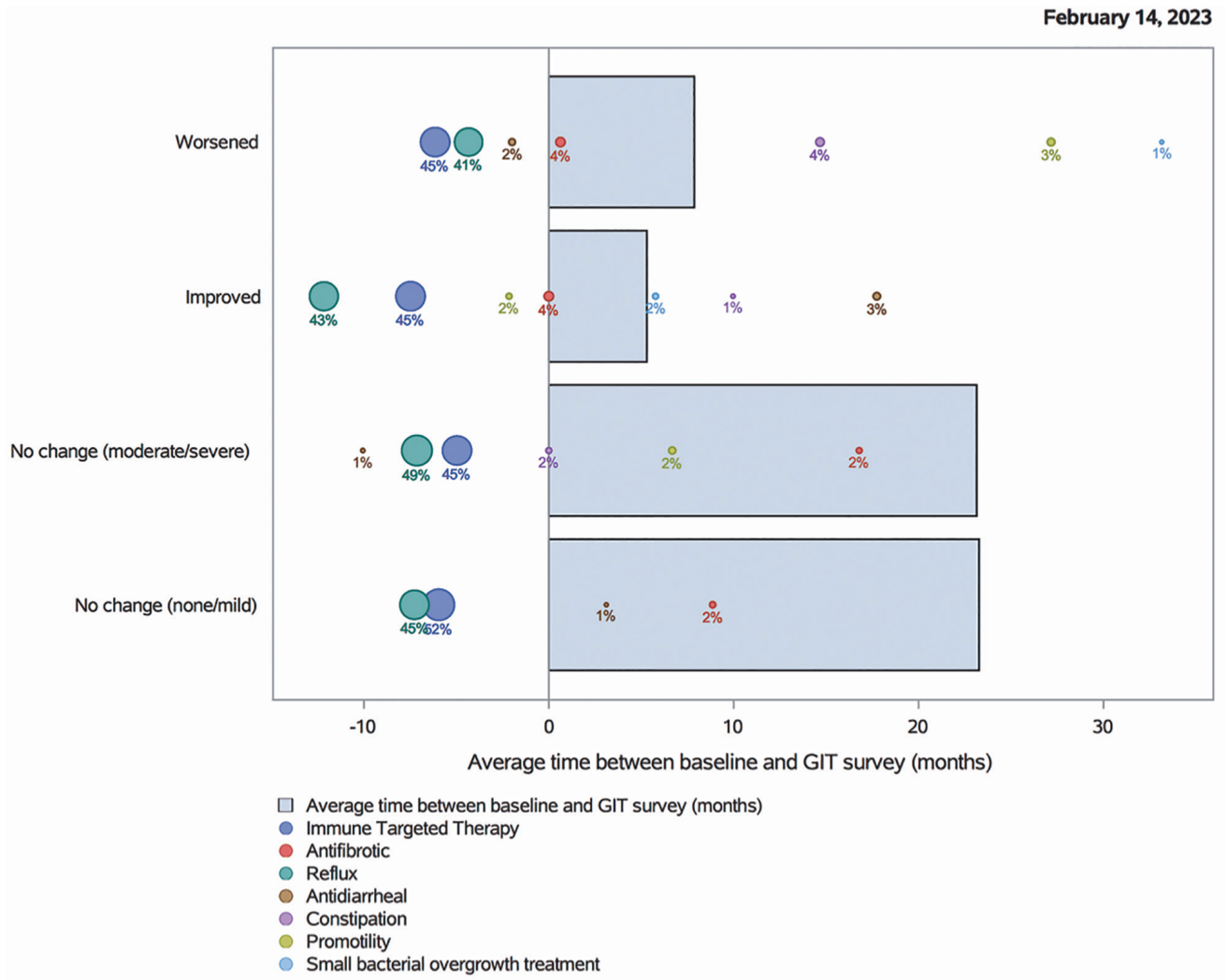

Fig. 2. Medications and survey timing for each of the GIT status change groups.
For patients with no change in GIT scores, GIT survey time = time from baseline to last GIT recorded. For patients with improved GIT scores, GIT survey time = time from baseline to date of last moderate GIT score.
For patients with worsened GIT scores, GIT survey time = time from baseline to date of last mild GIT score. Location of the bubble is the median start time of the medication for each GIT group and medication category. Size of medication bubbles indicates the percentage of patients in that GIT group who have taken that medication.

indicates the median time from baseline to the date of last moderate/severe GIT status. For patients with worsened GIT status, the length of the bar represents the median time from baseline to the date of last mild GIT status. Medication usage is summarised by medication category, prevalence, and start date. The size of each bubble represents the percentage of patients in the GIT change group who have taken the medication. The location of each bubble is the median start time of the medication relative to baseline.

Results

At the time of data analysis, the 415 CONQUER participants met the inclusion criteria with follow-up to 42 months. The sociodemographic and disease characteristics of those 415 participants are shown in Table I. Most participants were female (n=344, 83%), white race (n=366, 81%), and employed full-time (n=202, 49%) with a mean age of 52 years (SD 13.78), non-Raynaud's symptom duration of 2.6 years (SD 1.40), and Raynaud's symptoms duration of 4.8 years (SD 7.18). There was not a predominant SSc auto-antibody pattern in participants and GIT severity categories did not show differing antibody profiles. There was no significant difference in body mass index (BMI) across GIT severity categories. In this cohort, 286 (69%) had high resolution computed tomography chest performed at baseline. Over half of the patients were on mycophenolate (n=219, 52%) with the indication in 97 patients ILD. There were 16 (3.9%) current smokers. Most patients (n=252, 61%) were on a proton pump inhibitor for reflux disease. There were 38 patients (9.2%) with gastric antral vascular ectasia.

Over 50% of patients had mild GIT symptoms that did not change between assessments. The change between GIT total severity score by category over an 18-month period is shown in Figure 1. Patients with shorter interval follow-up was associated with stable, mild GIT 2.0 scores. Medication use by GIT severity group is shown in Table II. The most

Table III. Modelling the odds of having a worse GIT score.

	GIT score	
	Odds ratio (95% CI)	*p*-value
Sex		0.034
Male	Reference	
Female	1.89 (1.05, 3.42)	
Number of days the first PRO that was completed from this visit is from baseline (days)	1.00 (1.00, 1.00)	0.747
Race/ethnicity		0.230
Hispanic	1.03 (0.50, 2.11)	
Non-Hispanic White	Reference	
Non-Hispanic Black	2.17 (1.09, 4.33)	
Non-Hispanic Asian	0.79 (0.30, 2.09)	
Non-Hispanic Other	0.75 (0.16, 3.55)	
SSc subtype at baseline		0.946
Limited cutaneous	Reference	
Diffuse cutaneous	1.02 (0.61, 1.69)	
Anti-Centromere		0.901
Negative or not done	Reference	
Positive	1.04 (0.53, 2.06)	
Anti-Scl-70		0.098
Negative or not done	Reference	
Positive	0.64 (0.38, 1.08)	
Anti-RNA Polymerase III		0.464
Negative or not done	Reference	
Positive	0.82 (0.48, 1.40)	
Currently smoking cigarettes		0.020
No	Reference	
Yes	3.48 (1.22, 9.98)	
Anti-diarrheal		0.851
No	Reference	
Yes	0.87 (0.19, 3.88)	
Antifibrotic		0.064
No	Reference	
Yes	2.51 (0.95, 6.65)	
Constipation		0.327
No	Reference	
Yes	1.90 (0.53, 6.86)	
Immune Targeted Therapy		0.576
No	Reference	
Yes	1.19 (0.64, 2.22)	
Promotility		0.032
No	Reference	
Yes	3.55 (1.11, 11.31)	
Reflux		<.001
No	Reference	
Yes	3.82 (2.25, 6.50)	

commonly prescribed immunosuppressive drug in all groups was mycophenolate, and the most used gastrointestinal tract targeted therapy was omeprazole. In most patients these medications were initiated prior to the baseline CONQUER visit (Fig. 2). Initiation of antifibrotic therapy, rifaximin for small-intestinal bowel overgrowth, promotility agents, and constipation treatment typically occurred after the initial baseline visit with the expert rheumatologist. There were no patients on antibiotics other than rifaximin for small-intestinal bowel overgrowth, and no use of IVIG or pirfenidone in this cohort.

As shown in Table III, female sex, current tobacco use, promotility drugs, and anti-reflux medications were significantly associated with a longitudinally worse GIT 2.0 total score. However, SSc subtype by skin involvement or auto-antibody, immunosuppressive drugs, and nintedanib were not significantly associated with longitudinal GIT 2.0 score worsening.

Discussion

Gastrointestinal tract symptoms influence HRQOL and medication utilisation in SSc patients. Apart from diffuse cutaneous patients with low body mass index, the natural history of gastrointestinal tract symptoms has previously been reported to demonstrate longitudinal stability over five years in an established cohort of SSc patients (11). The purpose of the present analysis was to investigate GIT symptoms in the CONQUER cohort, which represents patients with disease less than 5 years duration. We found that more than half of the CONQUER patients showed stability of gastrointestinal disease irrespective of SSc-targeted therapy. Patients followed at the closest time intervals between appointments had the mildest GIT symptoms. Current tobacco use was associated with worse GIT survey scores. This finding is important since it emphasises the need for smoking cessation in patients with SSc.

While immunosuppressive and antifibrotic therapies have been shown to have disease-modifying effect on skin and lung disease, the effects of these drugs on the gastrointestinal tract are less clear. It is known that alterations in cell-mediated immunity are important for development of SSc-related gastrointestinal disease, but reports have not examined the timing of these cellular changes, and whether symptoms correlate with disease duration (12, 13). The current data suggest that immunosuppressive and anti-fibrotic drugs do not correlate with GIT 2.0 scores, however this is an early disease cohort and may not apply to SSc patients with more long-standing GIT disease Additionally, close follow-up of SSc patients is the standard of care at CONQUER centres, which highlights the importance of short-interval GIT symptom tracking on immunomodulatory therapy.

The CONQUER cohort is a valuable resource to investigate multiple different phenotypes of early SSc (6). Longitudinal cohorts such as CONQUER can inform clinical trial design since they allow better understanding of the natural history of SSc 88, 14). The CONQUER cohort allows integration of pharmacologic and other therapeutic interventions with longitudinal outcome data to identify interventions that are associated with stabilisation of the more difficult to evaluate manifestations of SSc. We identified that tobacco

cessation is imperative in SSc patients with GIT symptoms. The data presented shows that immunosuppression and antifibrotic therapies do not worsen GIT manifestations and may well contribute to GIT 2.0 stabilisation in most SSc patients. The natural history of gastrointestinal tract disease activity and damage in response to standard of care therapeutics is best characterised in longitudinal cohorts, such as CONQUER. Ongoing follow-up of the CONQUER cohort is planned and this will provide important data to discern damage and disease progression indices.

References

1. ZHU J, FRECH T: Gut disease in systemic sclerosis - new approaches to common problems. *Curr Treatm Opt Rheumatol* 2019; 5(1): 11-9. https://doi.org:10.1007/s40674-019-00117-x
2. KHANNA D, NAGARAJA V, GLADUE H, CHEY W, PIMENTEL M, FRECH T: Measuring response in the gastrointestinal tract in systemic sclerosis. *Curr Opin Rheumatol* 2013; 25(6): 700-6. https://doi.org:10.1097/01.bor.0000434668.32150.e5
3. HASEGAWA M, ASANO Y, ENDO H *et al*.: Investigation of prognostic factors for skin sclerosis and lung function in Japanese patients with early systemic sclerosis: a multicentre prospective observational study. *Rheumatology* 2012; 51(1): 129-33. https://doi.org:10.1093/rheumatology/ker333
4. KHANNA D, FURST DE, MARANIAN P *et al*.: Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *J Rheumatol* 2011; 38(9): 1920-4. https://doi.org:10.3899/jrheum.110225
5. KHANNA D, HAYS RD, MARANIAN P *et al*.: Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum* 2009; 61(9): 1257-63. https://doi.org:10.1002/art.24730
6. SHANMUGAM VK, FRECH TM, STEEN VD *et al*.: Collaborative National Quality and Efficacy Registry (CONQUER) for Scleroderma: outcomes from a multicenter US-based systemic sclerosis registry. *Clin Rheumatol* 2020; 39(1): 93-102. https://doi.org:10.1007/s10067-019-04792-y
7. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65(11): 2737-47. https://doi.org:10.1002/art.38098
8. FRECH TM, VANBUREN JM, STARTUP E *et al*.: Does hand involvement in systemic sclerosis limit completion of patient-reported outcome measures? *Clin Rheumatol* 2021; 40(3): 965-71. https://doi.org:10.1007/s10067-020-05467-9
9. CASTELINO FV, VANBUREN JM, STARTUP E *et al*.: Baseline characteristics of systemic sclerosis patients with restrictive lung disease in a multi-center US-based longitudinal registry. *Int J Rheum Dis* 2022; 25(2): 163-74. https://doi.org:10.1111/1756-185X.14253
10. BERNATSKY S, PANOPOLIS P, HUDSON M *et al*.: Demographic and clinical factors associated with physician service use in systemic sclerosis. *J Rheumatol* 2009; 36(1): 96-8. https://doi.org:10.3899/jrheum.080623
11. BERING J, GRIFFING WL, CROWELL M, UMAR SB: Progression of gastrointestinal symptoms over time in patients with systemic sclerosis. *Rheumatol Int* 2021; 41(7): 1281-7. https://doi.org:10.1007/s00296-021-04806-6
12. KUMAR S, SINGH J, RATTAN S, DIMARINO AJ, COHEN S, JIMENEZ SA: Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. *Aliment Pharmacol Ther* 2017; 45(7): 883-98. https://doi.org:10.1111/apt.13963
13. KUMAR S, SINGH J, KEDIKA R *et al*.: Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIG. *Am J Physiol Gastrointest Liver Physiol* 2016; 310(11): G1052-60. https://doi.org:10.1152/ajpgi.00034.2016
14. GORDON JK, DOMSIC RT: Clinical trial design issues in systemic sclerosis: an update. *Curr Rheumatol Rep* 2016; 18(6): 38. https://doi.org:10.1007/s11926-016-0582-z