Agreement with Guidelines from a Large Database for Management of Systemic Sclerosis: Results from the Canadian Scleroderma Research Group

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ABSTRACT. ***Objective.*** We determined congruence with published guidelines from the European League Against Rheumatism (EULAR)/EULAR Scleroderma Trials and Research group, for systemic sclerosis (SSc) investigations and treatment practices within the Canadian Scleroderma Research Group (CSRG).

Methods. Investigations and medication use for SSc complications were obtained from records of patients with SSc in the CSRG to determine adherence to guidelines for patients enrolled before and after the guidelines were published.

Results. The CSRG database of 1253 patients had 992 patients with SSc enrolled before publication of the guidelines and 261 after. For pulmonary arterial hypertension (PAH) treatment, there were no differences in use before and after the guidelines, yet annual echocardiograms for PAH screening were done in 95% of patients enrolled before the guidelines and in only 86% of those enrolled after ($p < 0.0001$), and fewer followup echocardiograms were done 1 year later in the latter group (88% vs 59%). No differences were found for the frequency of PAH-specific treatment; 60% had ever used calcium channel blockers for Raynaud's phenomenon, with no differences in the groups before and after the guidelines. But the use of phosphodiesterase type 5 inhibitors (which does not have guidelines) was increased in the after-guidelines group. Proton pump inhibitors were used in > 80% with gastroesophageal reflux disease before and after the guidelines. One-quarter with gastrointestinal symptoms were taking prokinetic drugs. For those with past SSc renal crisis, use of angiotensin-converting enzyme inhibitors was not different before and after the guidelines. For early diffuse SSc < 2 years, ever-use of methotrexate was similar (one-quarter of each group); and for symptomatic interstitial lung disease, 19% had ever used cyclophosphamide before the guidelines and 9% after (p = nonsignificant). CSRG practices were generally comparable to recently published guidelines; however, use of iloprost and bosentan was low for digital ulcers because these drugs are not approved for use in Canada.

Conclusion. There did not seem to be an increase in adherence to recommendations once the guidelines were published. For many guidelines, 25% to 40% of patients who would qualify received the recommended treatment. (J Rheumatol First Release Jan 15 2012; doi:10.3899/jrheum.110121)

Key Indexing Terms:
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Systemic sclerosis (SSc) is a rare connective tissue disease characterized by inflammation and fibrosis of the skin, vascular abnormalities, and variable involvement of organs including the kidneys, gastrointestinal (GI) tract, lungs, and heart[1,2]. SSc is divided into limited and diffuse disease types primarily according to the amount of skin affected. In limited SSc, skin changes are restricted to the areas distal to the elbows and knees and superior to the clavicles[3]. Diffuse cutaneous SSc (dcSSc) is progressive, has skin involvement proximal to the knees and elbows including the trunk, and is more likely to be associated with the development of renal crisis, cardiomyopathy and pulmonary fibrosis[2,4]. Raynaud's phenomenon (RP) and its complications, pulmonary arterial hypertension (PAH), and GI problems may develop in both subtypes[5].

Currently, there is some evidence to support treatment and management for particular manifestations[1,6,7,8]. The selection of therapeutic agents for the treatment of SSc-associated RP and its complications, interstitial lung disease (ILD), or PAH is supported by several metaanalyses and randomized trials[9]. For manifestations including gastroesophageal reflux disease (GERD), small bowel overgrowth, or delayed gastric empty-

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ing, various treatments are available[9]. The appropriate management for other organ involvement, such as cardiovascular disease, remains largely unconfirmed[9]. Recommendations such as performing echocardiograms annually have been made by the World Health Organization and routine screening has resulted in earlier detection of PAH, which should improve longterm outcomes[10]. Thus standardized management in SSc is essential for detection of complications that are better managed if detected earlier. However, heterogeneous clinical presentation has resulted in highly variable investigatory and treatment practices[11]. Until recently, no widely accepted clinical guidelines for the treatment of SSc have existed in Canada or elsewhere[11]. The European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research (EUSTAR) group have generated 14 evidence-based and consensus-derived treatment recommendations[12]. These guidelines addressed specific problems: SSc-related digital vasculopathy [RP, digital ulcers (DU)], SSc-PAH, SSc-related skin involvement, SSc-ILD, SSc renal crisis (SRC), and SSc-related GI disease. The final 14 recommendations are summarized in Table 1. Within the Canadian Scleroderma Research Group (CSRG), a group of rheumatologists from 15 Canadian centers who contribute to a national registry, no treatment algorithm exists for any organ involvement. Although select investigations such as chest radiography, echocardiograms, and pulmonary function tests (PFT), as well as some laboratory tests, are standardized and performed annually, additional testing and treatments are left to the discretion of the individual clinician.

The investigation and treatment practices currently followed by CSRG physicians were studied to determine how similar these practices are to the guidelines published by EULAR/EUSTAR[12].

MATERIALS AND METHODS

The CSRG annually collects prospective clinical and demographic data about adult patients with SSc. All the patients have a diagnosis of SSc as confirmed by a rheumatologist. The CSRG database from April 2011 was used, dividing data for patients enrolled before and after June 2009, when the SSc guidelines were published. Patients enrolled before June 2009 had their last visit recorded on or before this date, and patients enrolled after June 2009 had their visits recorded up to April 2011. Use of medications was "ever used" unless stated otherwise (current use). Medication use was determined by the denominator of patients at risk to be receiving the medication. For instance, patients who did not have GERD were not at risk for use of proton pump inhibitors (PPI), and similarly if ILD was absent, they were not considered for treatment of ILD. The agreement with the EULAR/EUSTAR guidelines was determined for the frequency and percentage of patients receiving specific investigations and treatment options for RP, DU, skin involvement in early dcSSc (and in a separate analysis above a certain skin score), GI involvement (GERD, small bowel overgrowth, pseudoobstruction, delayed gastric emptying, and dysphagia), renal crisis, PAH, and ILD. Use was documented for chest radiographs, high-resolution computed tomography of the chest (HRCT chest), PFT, and echocardiograms.

The physician recorded the presence of RP, DU (ever, active, or healed), inflammatory arthritis, inflammatory myositis, and a history of renal crisis. The modified Rodnan skin score (mRSS) was used as an assessment of skin involvement[6]. Standardized forms completed annually helped to determine the presence of various symptoms and complications. To assess GI involvement, patients answered yes/no to a series of questions involving dysphagia, GERD abdominal bloating, and the need for antibiotics for diarrhea. The only way to make a diagnosis of PAH is to perform right heart catheterization, but we did not record the results of these tests (if performed) in the database, so a surrogate measure was used. Suspected pulmonary hypertension (PH) was defined as an estimated systolic pulmonary artery pressure (PAP) > 45 mm Hg (PAP was measured using the Doppler flow measurement of the tricuspid regurgitation jet on echocardiography). For the purposes of our study, suspected PH was considered as possibly requiring treatment if the patient was in New York Heart Association (NYHA) class III or IV. ILD was considered present if an HRCT lung was interpreted by an experienced radiologist as showing ILD or, in the case where no HRCT was performed, if either (1) a chest radiograph was reported as showing either increased interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or (2) a study physician reported findings indicative of ILD on physical examination. ILD potentially requiring treatment was defined as reduced lung volumes (DLCO < 70% or corrected DLCO < 70% and total lung capacity < 70% and forced vital capacity < 70%) in addition to being classified as NYHA class II, III, or IV. A subset of patients had HRCT of the lungs based on the decision of the treating physician, and the proportion with HRCT evidence of ILD/pulmonary fibrosis who received treatment with cyclophosphamide and other immune suppressives was compared.

To assess adherence to guidelines and to determine whether the guideline publication may have had any effect on management, we assessed treatment and the frequency of ordering selected investigations before and after the guideline publication in June 2009.

Descriptive statistics were used to summarize the baseline characteristics of the patients. Chi-squared tests, Yates' chi-square tests, Fisher's exact tests, and Mann-Whitney U tests were used as appropriate. P values < 0.05 were considered statistically significant. The analyses were performed with SAS v.9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Data from 1253 patients within the CSRG database were analyzed. Baseline characteristics are presented in Table 2. There were 86% women; mean ± SEM age was 55.3 ± 12.2 years before June 2009 and 56.2 ± 11.9 years after June 2009. There were no significant differences in disease duration (11 years, defined as time since onset of first non-RP symptoms), age, sex, SSc subsets, RP, GI symptoms, and PH before and after June 2009. The number of DU, SRC, some cases of ILD, and the skin score were higher in the earlier group. The prevalence of various abnormalities related to the EULAR recommendations is shown for the cohorts whose baseline visits were before or after June 2009 (Table 2).

Table 3 shows the treatments ever used for various manifestations before and after the guideline publication. The frequency of only a few treatments changed. More phosphodiesterase type 5 inhibitors were used after 2009 in patients with RP (which is not in the guidelines but has some clinical trial data), and use of methotrexate (MTX) in early dcSSc was similar (but numerically higher in the preguidelines group if considering dcSSc for up to 5 years, the same if disease duration < 2 years). We did not find other treatment differences between the 2 groups.

Table 4 shows the investigations that were ordered. Surprisingly, most were ordered slightly less frequently after June 2009.

Table 1. EULAR guidelines and CSRG compatibility.

EULAR Guideline	Medication	Percentage of All CSRG Patients, n = 1253	Percentage of CSRG Patients Prior to June 2009, n = 992	Percentage of Patients in CSRG After 2009, n = 261	p
Raynaud's phenomenon (RP)					
1. Calcium channel blockers (CCB) should be first-line treatment for SSc-related RP, and intravenous iloprost should be considered for severe SSc-related RP	CCB	60.0	60.9	56.5	NS
	Iloprost	1.3	1.7	0.0	NS
Digital ulcers (DU), active					
2. Intravenous prostanoids (particularly IV iloprost) should be considered for treatment of active DU	Iloprost	4.0	4.7	0.0	NS
3. Bosentan should be considered in treatment of diffuse SSc patients with multiple DU, after failure of CCB and usually, prostanoid therapy	Bosentan	12.0*	13.0*	0.0*	NS
Pulmonary arterial hypertension (PAH)					
4. Bosentan should be strongly considered in treatment of SSc-related PAH	Bosentan	10.3	12.4	0.0	NS
5. Sitaxsentan** may be considered in treatment of SSc-related PAH	Sitaxsentan	3.5	2.1	10.5	NS
6. Sildenafil may be considered in treatment of SSc-related PAH	PDE 5 inhibitors	3.5	2.1	10.5	NS
7. Intravenous epoprostenol should be considered for treatment of severe SSc-related PAH	Epoprostenol	7.8	8.3	5.3	NS
Pulmonary hypertension (NYHA ≥ Class 3)††					
4. Bosentan should be strongly considered in treatment of SSc-related PAH	Bosentan	15.7	17.4	6.3	NS
5. Sitaxsentan** may be considered in treatment of SSc-related PAH	Sitaxsentan	3.9	2.3	12.5	NS
6. Sildenafil may be considered in treatment of SSc-related PAH	PDE5 inhibitors	3.9	2.3	12.5	NS
7. IV epoprostenol should be considered for treatment of severe SSc-related PAH	Epoprostenol	6.9	8.1	0.0	NS
Skin involvement					
8. Methotrexate (MTX) may be considered in treatment of skin involvement in early diffuse SSc		27.8*	28.4*	25.0*	NS
Percentage with early diffuse SSc taking MTX (< 2 yrs' duration)					
Percentage with early diffuse SSc taking MTX (< 5 yrs' duration)		33.1*	35.3*	22.2*	NS
Current mRSS > 10 and ever-use of MTX	MTX	32.4*	33.9*	24.0*	NS
ILD†					
9. CYC should be considered in treatment of SSc-related ILD	CYC	15.3	16.3	10.3	NS
DLCO < 70% and TLC < 70% and FVC < 70% and short of breath					
9. CYC should be considered in treatment of SSc-related ILD	CYC	16.6	19.1	8.8	NS
Renal crisis					
10. Angiotensin-converting enzyme (ACE) inhibitors should be used in treatment of scleroderma renal crisis	ACE inhibitors	83.7	86.7	50.0	NS
Gastrointestinal involvement					
12. Proton pump inhibitors (PPI) should be used for prevention of SSc-related GERD, esophageal ulcers, and strictures	PPI (GERD)	85.3	86.2	82.1	NS
13. Prokinetic agents should be used for management of SSc-related symptomatic motility disturbances (dysphagia, GERD, delayed gastric emptying, bloating, pseudoobstruction, etc.)	Promotility agents (GERD)	23.3	23.4	23.1	NS
	Promotility agents (delayed gastric emptying)	42.0	41.9	42.2	NS
	Promotility agents (pseudoobstruction)	44.7	50.0	22.2	NS
	Promotility agents (dysphagia)	26.7	25.3	31.3	NS
14. In treatment of SSc-related malabsorption, if due to bacterial overgrowth, rotating antibiotics is appropriate	Antibiotics (small bowel overgrowth) Current use	4.5#			
	Ever used	14.2#			

* Percentage of patients on select medications with the diffuse SSc subset. † CSRG definition of interstitial lung disease (ILD) is a positive HRCT lung with ILD or abnormal chest radiograph with interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or findings of ILD on physical examination. ** Sitaxsentan has been removed from the market. †† CSRG definition of suspected pulmonary hypertension is pulmonary arterial pressure (PAP) measured using the Doppler flow measurement of the tricuspid regurgitation jet on echocardiography and an estimated systolic pulmonary artery pressure > 45 mm Hg. For the subset analysis, only NYHA class ≥ III were included. # Number of patients with small bowel overgrowth is unknown, but 4.5% received antibiotics for this indication. NS: not significant; CSRG: Canadian Scleroderma Research Group; EULAR: European League Against Rheumatism; SSc: systemic sclerosis; IV: intravenous; GERD: gastroesophageal reflux disease; NYHA: New York Heart Association; TLC: total lung capacity; FVC: forced vital capacity; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; CYC: cyclophosphamide; PDE5: phosphodiesterase type 5.

Table 2. CSRG patient baseline characteristics. All data are n (%) unless otherwise indicated.

Characteristic	All Patients	Patients Before June 2009	Patients After June 2009	Comparing Patients Before and After June 2009, p
Total patients	1253	992	261	—
Age, yrs, mean ± SEM	55.45 ± 12.15	55.3 ± 12.2	56.2 ± 11.9	0.1922
Women	1080 (86.2)	854 (86.1)	226 (86.6)	0.8345
Disease duration, yrs, mean ± SEM	10.95 ± 9.50	10.9 ± 9.3	11.2 ± 10.2	0.7318
Disease subsets				0.0752
Diffuse disease	459 (37.4)	376 (38.6)	83 (32.6)	
Limited or *Sine* disease	770 (62.7)	598 (61.4)	172 (67.5)	
Raynaud's phenomenon	1198 (97.6)	952 (97.6)	246 (97.6)	0.9837
Digital ulcers ever	632 (51.7)	524 (53.9)	108 (43.2)	0.0026
Active digital ulcers	99 (8.0)	86 (8.2)	13 (5.1)	0.0484
Healed digital ulcers	378 (30.7)	318 (32.6)	60 (23.4)	0.0042
Scleroderma renal crisis	50 (4.1)	46 (4.7)	4 (1.6)	0.0221
mRSS, mean ± SEM	9.86 ± 9.50	10.3 ± 9.6	8.2 ± 8.9	0.0001
Gastrointestinal symptoms				
GERD	1036 (83.4)	824 (83.6)	212 (82.5)	0.6790
Pseudoobstruction	47 (3.8)	38 (3.9)	9 (3.5)	0.7889
Delayed gastric emptying	584 (47.0)	468 (47.5)	116 (45.1)	0.5054
Dysphagia	258 (24.5)	194 (24.3)	64 (25.0)	0.8157
Pulmonary hypertension (PH) by CSRG* definition	117 (11.2)	98 (11.8)	19 (8.9)	0.2320
PH (NYHA ≥ Class III)	102 (8.3)	86 (8.9)	16 (6.3)	0.1803
Patients with a previous CT scan indicating lung fibrosis	304 (31.0)	249 (32.3)	55 (26.2)	0.0878
Evidence of ILD on previous chest radiograph	249 (21.4)	206 (22.3)	43 (18.1)	0.1608
Velcro rales	302 (26.1)	250 (27.2)	52 (21.6)	0.0750
ILD by CSRG definition** (any ILD)	415 (34.2)	347 (36.0)	68 (27.3)	0.0100
HRCT abnormal for ILD/pulmonary fibrosis	65 (20.8)	54 (20.5)	11 (22.5)	0.7519
DLCO or corrected DLCO < 70% and TLC and FVC < 70% and short of breath	140 (11.2)	106 (10.7)	34 (13.3)	0.2854

* CSRG definition of suspected pulmonary hypertension is pulmonary arterial pressure (PAP) measured using the Doppler flow measurement of the tricuspid regurgitation jet on echocardiography and an estimated systolic PAP > 45 mm Hg. For the subset analysis, only New York Heart Association (NYHA) ≥ III were included. ** CSRG definition of ILD is a positive HRCT lung with ILD or abnormal chest radiograph with interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or findings of ILD on physical examination. CSRG: Canadian Scleroderma Research Group; mRSS: modified Rodnan skin score; GI: gastrointestinal; GERD: gastroesophageal reflux disease; NYHA: New York Heart Association; CT: computed tomography; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; TLC: total lung capacity; FVC: forced vital capacity.

Table 1 demonstrates the agreement with EULAR/EUSTAR recommendations. There was no difference in the 2 cohorts (enrolled before guidelines vs after). Sixty percent of CSRG patients with RP ever received calcium channel blockers. Although only 1.3% of patients with RP were receiving iloprost, severity of RP could not be determined in our analysis and thus comparability with the EULAR guideline could not be directly assessed. Also, iloprost is not approved for use in Canada and thus was not easy to obtain. The recommendation that intravenous prostanoids (particularly iloprost) be considered for the healing of active ulcers was thus not routine in the CSRG. In the CSRG, 12% of patients with dcSSc and a history of DU were treated with bosentan. There is no approval in Canada for use of bosentan in the prevention of DU.

CSRG medication practices mostly seemed to be in keeping with recommendations for PAH treatment. Not all the patients with our definition of PH received treatment, because some did not have PAH proven by right heart catheterization and some may have had too much ILD to qualify for coverage of PAH treatment. Others may have had PH but not PAH. One-quarter to one-third with early diffuse skin involvement received MTX. This is concordant with the recommendations. Cyclophosphamide was prescribed for about 15% of patients with ILD and use was not different before and after the guidelines. Most (84%) but not all patients with SRC were ever treated with angiotensin-converting enzyme (ACE) inhibitors and only 63% were currently treated with ACE inhibitors for previous SRC.

The recommendations state that PPI should be used for prevention of SSc-related GERD, esophageal ulcers, and strictures. PPI were used for 85% of patients with GERD. Promotility agents were used in one-quarter of patients with GERD and in > 40% if delayed gastric emptying symptoms were present, and in one-quarter of those with dysphagia. Current antibiotic use was 4.5% for presumed small bowel overgrowth and ever-use was 14.2%. However, we do not know how many patients actually had small bowel overgrowth because this was not asked of the treating physicians.

Table 3. CSRG patient medications (ever used unless otherwise stated).

Therapeutic Agent or Investigation	Before June 2009, All SSc Patients, n = 992, Frequency (%)	After June 2009, All SSc Patients, n = 261, Frequency (%)	Comparing All Before and After June 2009, p
Raynaud's phenomenon	952	246	—
Calcium channel blockers	578 (60.9)	139 (56.5)	0.2091
Iloprost	16 (1.7)	0 (0.0)	0.0820
PDE5 inhibitors	17 (1.8)	13 (5.3)	0.0018
Skin involvement in early diffuse SSc			
Methotrexate use for diffuse SSc only, < 2 yrs' duration	21 (28.4)	4 (25.0)	> 0.05
Methotrexate use for diffuse SSc only, < 5 yrs' duration	48 (35.3)	6 (22.2)	> 0.05
Skin involvement (mRSS > 10)	347	62	—
Corticosteroids	149 (43.1)	20 (32.3)	0.1117
D-penicillamine	74 (21.4)	11 (17.7)	0.5151
Methotrexate	105 (30.4)	17 (27.4)	0.6429
Cyclophosphamide	37 (10.7)	6 (9.7)	0.8103
Skin involvement (mRSS > 20)	141	25	—
Corticosteroids	63 (45.0)	5 (20.0)	0.0193
D-penicillamine	32 (22.9)	2 (8.0)	0.0907
Methotrexate	53 (37.9)	3 (12.0)	0.0119
Cyclophosphamide	16 (11.4)	4 (16.0)	0.7547
Digital ulcers	524	108	—
Calcium channel blocker	369 (70.7)	77 (71.3)	0.8996
Iloprost	15 (2.9)	0 (0.0)	0.1509
Bosentan	28 (5.4)	2 (1.9)	0.1187
Digital ulcers (active; current use)	86	13	—
Calcium channel blocker	67 (77.9)	11 (84.6)	0.8513
Ilopost	4 (4.7)	0 (0.0)	1.0000
Bosentan	7 (8.1)	0 (0.0)	0.5894
Digital ulcers (healed)	318	60	—
Calcium channel blocker	232 (73.2)	44 (73.3)	0.9812
Bosentan	18 (5.7)	2 (3.3)	0.6679
GERD	824	212	—
Gastroprotective agents	705 (86.2)	174 (82.1)	0.1316
Promotility agents	191 (23.4)	49 (23.1)	0.9422
Delayed gastric emptying	468	116	—
Promotility agents	194 (41.9)	49 (42.2)	0.9470
Dysphagia	194	64	—
Promotility agents	49 (25.3)	20 (31.3)	0.3477
Dilatation	29 (15.1)	9 (14.5)	0.9101
Inflammatory arthritis	92	32	—
Methotrexate	33 (36.3)	10 (31.3)	0.6089
Hydroxychloroquine	36 (39.6)	9 (28.1)	0.2480
D-penicillamine	17 (18.7)	4 (12.5)	0.4241
NSAID	53 (58.2)	14 (43.8)	0.1568
Corticosteroids	45 (49.5)	15 (46.9)	0.8020
Inflammatory myositis/myopathy	99	24	—
Methotrexate	39 (39.4)	13 (54.2)	0.1887
Azathioprine	15 (15.2)	6 (25.0)	0.3964
Cyclophosphamide	11 (11.1)	2 (8.3)	0.9784
Renal crisis ever	46	4	—
Hemodialysis or peritoneal dialysis	16 (34.8)	2 (50.0)	0.6123
Kidney transplant	5 (11.1)	1 (25.0)	0.4175
ACE inhibitor	39 (86.7)	2 (50.0)	0.1195
ACE inhibitor (current use)	29 (64.4)	2 (50.0)	0.6181
PH by CSRG criteria†	98	19	—
Flolan	8 (8.3)	1 (5.3)	1.0000
Trepostinil	3 (3.1)	1 (5.3)	0.5161
Iloprost	0 (0.0)	0 (0.0)	—
Bosentan	12 (12.4)	0 (0.0)	0.2273
Sitaxsentan*	2 (2.1)	2 (10.5)	0.1249
PDE5 inhibitors	2 (2.1)	2 (10.5)	0.1249
Warfarin	22 (22.7)	2 (10.5)	0.3755
Combination PAH treatment	13 (13.4)	1 (5.3)	0.5413

Table 3. Continued.

Therapeutic Agent or Investigation	Before June 2009, All SSc Patients, n = 992, Frequency (%)	After June 2009, All SSc Patients, n = 261, Frequency (%)	Comparing All Before to 2009 and After June 2009, p
PH† and NYHA ≥ Class III	86	16	—
Flolan	7 (8.1)	0 (0.0)	0.5927
Trepostinil	4 (4.7)	1 (6.3)	0.5819
Iloprost	1 (1.2)	0 (0.0)	1.0000
Bosentan	15 (17.4)	1 (6.3)	0.4497
Sitaxsentan*	2 (2.3)	2 (12.5)	0.1150
PDE5 inhibitors	2 (2.3)	2 (12.5)	0.1150
Warfarin	22 (25.6)	2 (12.5)	0.4169
Combination PAH treatment	15 (17.4)	2 (12.5)	0.9031
DLCO < 70% and TLC < 70% and FVC < 70% and short of breath	106	34	—
Corticosteroids	58 (55.2)	13 (38.2)	0.0848
Azathioprine	6 (5.7)	7 (20.6)	0.0244
Cyclophosphamide	20 (19.1)	3 (8.8)	0.1632
Mycophenolate mofetil	2 (1.9)	2 (5.9)	0.2510
ILD by CSRG criteria**	347	68	—
Corticosteroids	149 (43.4)	21 (30.9)	0.0547
Azathioprine	37 (10.8)	8 (11.8)	0.8136
Cyclophosphamide	56 (16.3)	7 (10.3)	0.2072
Mycophenolate mofetil	10 (2.9)	3 (4.4)	0.7911

* Sitaxsentan has been removed from the market. † CSRG definition of suspected pulmonary hypertension is pulmonary arterial pressure (PAP) measured using the Doppler flow measurement of the tricuspid regurgitation jet on echocardiography and an estimated systolic PAP > 45 mm Hg. For the subset analysis, only NYHA ≥ III were included. ** CSRG definition of ILD is a positive HRCT lung with ILD or abnormal chest radiograph with interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or findings of ILD on physical examination. CSRG: Canadian Scleroderma Research Group; SSc: systemic sclerosis; mRSS: modified Rodnan skin score; PDE5: phosphodiesterase type 5; GERD: gastroesophageal reflux disease; NSAID: nonsteroidal antiinflammatory drugs; ACE: angiotensin-converting enzyme; PH: pulmonary hypertension; NYHA: New York Heart Association; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; TLC: total lung capacity; FVC: forced vital capacity.

Table 4. CSRG investigatory practices for baseline and followup visits.

Investigation	All SSc Patients Before June 2009, n = 992 (%)	All SSc Patients After June 2009, n = 261 (%)	Comparing All Before 2009 and After June 2009, p	Year 1 Followup and No PAH at Baseline for Echocardiogram Before June 2009, n = 662 (%)	Year 1 Followup and No PAH at Baseline for Echocardiogram After June 2009, n = 106 (%)
HRCT	264 (26.6)	49 (18.8)	0.0092	62 (9.4)	6 (5.7)
Chest radiograph	762 (76.8)	173 (66.3)	0.0005	442 (66.8)	58 (54.7)
PFT	843 (85.0)	206 (78.9)	0.0184	476 (71.9)	63 (59.4)
ECG	677 (68.2)	185 (70.9)	0.4136	406 (61.3)	61 (57.5)
Echocardiogram	943 (95.1)	224 (85.8)	< 0.0001	582 (87.9)	63 (59.4)

CSRG: Canadian Scleroderma Research Group; SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; HRCT: high-resolution computed tomography; PFT: pulmonary function tests; ECG: electrocardiogram.

DISCUSSION

Prescribing practices of rheumatologists who follow SSc were documented in our analysis without differences before and after the guidelines were published. Not all guidelines were analyzed for compatibility with CSRG practices because some data were not collected within the CSRG, and definitions varied (e.g., ILD needing cyclophosphamide and proven PAH were studied only through a surrogate). The published guidelines did not consider contraindications or cost-effectiveness and the absence of a recommendation was not indicative of opposition to its use[12]. Thus, a discrepancy between guidelines and CSRG practice is not necessarily a failing of the CSRG because different indications or approvals for medications may exist in Canada compared to Europe, and some guidelines had to be eminence-based if literature was lacking. The majority of CSRG patients were followed and treated

before publication of the guidelines. In the pre-June 2009 group, concordance with guidelines offers face validity for the recommendations.

Annual echocardiogram screening was part of the CSRG protocol, and missing data are queried so that the rate of annual testing is a best-case scenario. Echocardiogram use did not increase after the guidelines were published (it actually declined), but echocardiograms in the group enrolled after June 2009 may not have been recorded yet in the database (they were ordered but not yet performed or entered; this is especially true for followup tests). It does not appear that adherence to guidelines for annual echocardiograms has improved.

The use of MTX in SSc could be considered controversial as trials have shown at most modest effects and 1 study had a p value not < 0.05[8,13]. Therefore, the rate of use in early dcSSc is about one-quarter to one-half of patients. Currently, there is a lack of evidence to support D-penicillamine use in the treatment of skin fibrosis and thus it is not recommended[4,6]. We documented "ever-use," which was low. Few studies have investigated the efficacy of mycophenolate mofetil (MMF) in the treatment of SSc skin. One retrospective study of its efficacy in treating dcSSc found no significant difference in mean mRSS between patients taking MMF and controls[14]. Another study found that in patients with recent-onset dcSSc, MMF in combination with antithymocyte globulin resulted in a decrease of mean skin score[15].

Intravenous iloprost is not available in Canada and thus must be obtained by special access from another country and consequently its use would be low. Bosentan is not approved in Canada for prevention of DU.

Since the patients enrolled over the last 2 years were included in the post-guidelines era, it may be too soon to determine whether the SSc recommendations will change practice over time.

Evidence from other etiologies must often be applied to treatment of SSc-associated GI disturbances due to a lack of randomized controlled trials[9]. Within the CSRG, treatment with PPI and promotility agents was reasonable. Some patients with GERD may not have been very symptomatic and others may have had sufficient treatment with lifestyle modification or other medications (such as H2 blockers). Some promotility agents have been removed from the market, a change that could affect prescribing patterns. Additionally, small bowel overgrowth was not defined by the physician, so we could not determine how concordant antibiotic prescription was with respect to this indication.

A limitation of our study was that the CSRG database did not contain a record of PAH diagnoses after the baseline visit, which limited our ability to accurately identify patients with PAH. Assuming that all who were diagnosed with PAH were treated would result in 9% of patients identified as having PAH. This percentage may be lower than in other reports, therefore it is possible that not all patients with PAH were identified. Applying a definition of PAH at echocardiogram PAP > 45 mm Hg would yield some false positives. This is likely what happened, because bosentan was prescribed in only about 15% of patients who met our case definition of PH. However, the CSRG definition correlates strongly with right heart catheter studies[16]. Bosentan has been associated with improved survival in patients with advanced SSc-associated PAH[12,17,18]. From the CSRG database, reasons for prescribing a particular agent could not be determined. In addition, the reason a patient did not take a medication could have been lack of a prescription, side effects, deliberate nonadherence, or other factors such as limited finances for relatively expensive therapies. Patients might have also been awaiting coverage for treatments such as those for PAH. These factors may have led to an overestimation or underestimation in the number of patients receiving treatment for a particular SSc-associated manifestation. For instance, sildenafil may have been prescribed for PAH, RP, or DU.

Within the CSRG database, patients were not definitively classified as having symptomatic ILD. Thus, various definitions of ILD were applied. Not all patients with ILD are symptomatic and thus not all will require treatment. Cyclophosphamide use within the CSRG varied among centers regardless of the ILD definition applied, although the subset in which it varied was dependent on the definition. Use of azathioprine was also inconsistent depending on the definition of ILD used.

Guidelines are generally not followed at high rates. For instance, steroid-induced osteoporosis guidelines are followed 10% of the time[19]. Thus there is often a gap between ideal practice and real practice.

It has been previously demonstrated that treatment of SSc varies in that experts are less likely to use treatments that have been proven ineffective and more apt to consider treatments that are under investigation. Further, rheumatologists who see a greater number of patients with SSc will see a particular organ manifestation more often, which might allow for more thorough identification of complications[11]. In general rheumatology practices, there could be wide variability because of the small number of patients, or because a practice is not enrolled in a database, resulting in a lack of feedback about whether echocardiograms should be performed annually and lack of awareness of the guidelines[11].

Overall, it does not appear that guidelines have changed the behavior of rheumatologists in the CSRG, but the patients with SSc enrolled after June 2009 had long disease duration and we studied ever-treatment. The guidelines would only potentially affect a 2-year period, from June 2009 until April 2011.

APPENDIX

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