# Best practices in scleroderma: an analysis of practice variability in SSc centres within the Canadian Scleroderma Research Group (CSRG)

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**ABSTRACT**

**Objective.** *There is currently no consensus on best practice in systemic sclerosis (SSc). To determine if variability in treatment and investigations exists, practices among Canadian Scleroderma Research Group (CSRG) centres were compared.*

**Methods.** *Prospective clinical and demographic data from adult SSc patients are collected annually from 15 CSRG treatment centres. Laboratory parameters, self-reported socio-demographic questionnaires, current and past medications and disease outcome measures are recorded. For centres with >50 patients enrolled, treatment practices were analysed to determine practice variability.*

**Results.** *Data from 640 of 938 patients within the CSRG database met inclusion criteria, where 87.3% were female, the mean ± SEM age was 55.3±0.5, 48.9% had limited SSc and 47.8% had diffuse SSc (and 3.3% uncharacterised). Some investigation and treatment practices were inconsistent among 6 centres including proportion receiving: PDE5 (phosphodiesterase type 5) inhibitors for Raynaud's phenomenon (p=0.036); cyclophosphamide (p=0.037) and azathioprine (p=0.037) for treatment of ILD; and current use of D-penicillamine, although uncommon, varied among sites. Annual echocardiograms and PFTs were frequently done and did not vary among sites but the rate of pulmonary arterial hypertension (PAH) was directly related to site size and this was not the case for other organ involvement.*

**Conclusions.** *Despite routine tests within a database, site variation in SSc with respect to investigations and management among CSRG centres exists suggesting a need for a standardised approach to the investigation and treatment of SSc. One can speculate that larger centres are more expert in detecting PAH.*

## Introduction

Systemic sclerosis (SSc, scleroderma) is a rare (2 per 10,000) connective tissue disease characterised by inflammation and fibrosis of the skin, vascular abnormalities and variable involvement of visceral organs including the kidneys, gastrointestinal tract, lungs and heart (1, 2). Currently, there is some evidence to support treatment and disease management (1, 3-5). Also, the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research group (EUSTAR) recently published guidelines for investigations and management of SSc, but these were not published until after these data were collected (6). The selection of therapeutic agents for the treatment of SSc-associated Raynaud's phenomenon and its complications, interstitial lung disease and pulmonary arterial hypertension (PAH) is aided by several randomised trials and meta-analyses (7). For manifestations, including gastroesophageal reflux disease (GERD), small bowel overgrowth and delayed gastric emptying, the treatment practices of distinct etiologies are often applied (7). The appropriate management of other associated organ conditions, including some aspects of cardiovascular involvement, remains largely unconfirmed (7). Recommendations such as performing echocardiograms annually have been made by the World Health Organisation and routine screening has resulted in earlier detection of pulmonary arterial hypertension (PAH), which should improve long term outcomes (8). Thus standardised 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 practice (9). Inconsistent disease management is exacerbated by the limited availability of proven or indicated treatments in SSc (7). Within the Canadian Scleroderma Research Group (CSRG), no treatment algorithm exists for any organ involvement and although select investigations such as chest x-rays (CXR), echocardiograms and pulmonary function tests (PFT), as well as some laboratory tests are agreed to be performed annually by participants in the study, additional testing and treatments are left to the discretion of the individual clinician.

In order to eventually contribute to a consensus on best practice in SSc, we evaluated the consistency and variabilityof practices among SSc treatment centres, which see a 'critical mass' of SSc patients in Canada.

**Materials and methods**

The Canadian Scleroderma Research Group (CSRG) is comprised of a group of rheumatologists from 15 Canadian centres that contribute to a national registry. Prospective clinical and demographic data from adult SSc patients are collected annually. The CSRG database contains numerous variables including: self-reported questionnaires (demographics, Health Assessment Questionnaire (HAQ), Short Form-36 Health Survey (SF36), dates of symptom onset such as Raynaud's phenomenon (RP) and first non-RP symptom, current and past medications, physical examination characteristics, modified Rodnan Skin Score (MRSS), organ based examination parameters, disease activity, severity and damage scores, autoantibodies and laboratory parameters.

All patients had a diagnosis of SSc as confirmed by a rheumatologist. Medication use was documented if a patient had ever taken or was currently taking that therapeutic agent. Disease duration was calculated as time since onset of first non-Raynaud's symptom. The CSRG database from June 2009 was used. The patients included in the analysis were those whose baseline visit took place between 18/8/2004 and 31/3/2009 and follow-up by 25/3/2009. All statistical analyses were performed with PASW Statistics 17 Software.

For centres enrolling more than fifty patients with SSc, investigation and treatment for various organ systems were compared to determine if a site effect existed using Chi squared, Mantel-Haenszel and *t*-tests. Treatment practices for Raynaud's phenomenon, digital ulceration, immunomodulation, gastrointestinal involvement (GERD, delayed gastric emptying and dysphagia), renal crisis, PAH, interstitial lung disease (ILD), renal crisis, inflammatory arthritis, myositis and cardiac involvement were compared where data was available. Chest x-ray, high resolution computed tomography (HRCT) chest scan, PFT, electrocardiogram (ECG) and echocardiogram use were documented. It should be noted that the CSRG members agreed to perform annual ECGs, PFTs, CXR and echocardiogram and lab tests (such as complete blood count (CBC), creatinine, and creatinine kinase (CK)) on all patients.

Baseline and follow-up data were used to classify patients as having a particular organ manifestation. Standardised forms completed annually helped to determine the presence of various symptoms and complications. The presence of Raynaud's phenomenon, digital ulcers (ever, active or healed), inflammatory arthritis, inflammatory myositis and a history of renal crisis were recorded by the physician. The MRSS was used as an assessment of skin involvement (3), and for some analyses, we divided the score of MRSS between 0 to 10 and MRSS >10. We arbitrarily decided that we would study the use of immune suppressive agents and D-penicillamine for those with MRSS >10; and patients with the diffuse subset who had less than 3 years disease duration were studied with respect to use of methotrexate. Gastroesophageal reflux disease was assumed if a patient reported having woken up at night choking, having food or acid-tasting liquid coming back into their mouth or nose on most days, or having a burning feeling rise from their stomach or lower chest to their neck on most days (from standardised questionnaires). A patient was classified as having other bowel complaints if a physician reported malabsorption or a patient reported on most days having visible swelling of the abdomen or bloating. The physician indicated a history of pseudo-obstruction. A diagnosis of delayed gastric emptying was assumed if a patient recorded feeling full shortly after starting a meal on most days or having a poor appetite on most days. Dysphagia was assumed to be present if a patient reported having difficulty swallowing on most days. PAH was reported at the baseline visit by the physician. In subsequent visits, a diagnosis of PAH was assumed if a patient had a right systolic pressure of >40 mmHg on an echocardiogram and a diagnostic right heart catheterisation was performed. The presence of an SSc related arrhythmia was determined from the standardised CSRG annual ECG. Arrhythmias were scored as mild (ECG conduction deficit), moderate (arrhythmia) or severe (arrhythmia requiring treatment). A patient was classified as having ILD if lung fibrosis was seen on a CT or CXR or if typical Velcro rales were detected. Treatment necessary for ILD was considered by the definition of FVC <70% predicted. Another analysis was performed for ILD with FVC<70% predicted and disease duration of less than 5 years.

*Reasons for medications*

It was difficult to determine if some medications were used due to skin involvement, lung involvement or both. Likewise for those with inflammatory arthritis, we could not always determine if the medications were used for the joint disease or for disease modification (such as use of methotrexate). Prescription of a medication commonly used in treatment of a particular organ manifestation was assumed to be treatment for that manifestation. Thus, although potentially flawed, the bias of our assumptions would not have added to site variability, as the error in accuracy would be consistent across sites. The current rate of use of D-penicillamine was compared between sites as it is not recommended (6).

**Results**

Data from 640 patients within the CSRG database were analysed: 87.3%

were female, the mean ± SEM age was 55.3±0.5; 48.9% had limited SSc; 47.8% had diffuse SSc; and 3.3% were uncharacterised. Disease duration ± SEM was long at 13.5±0.4 years. Patient characteristics are presented in Table I. Nearly all rates of organ involvement did not differ significantly from those from smaller sites (n=298). Data from the 6 CSRG treatment centres with >50 patients are displayed in Table II.

Treatment of digital ulcers, scleroderma renal crisis, GERD, pseudo-obstruction, delayed gastric emptying, PAH, and arrhythmia did not vary among centres as assessed by prescriptions for each manifestation (Table II). Use of PFTs and echocardiograms did not differ significantly among centres.

*Raynaud's phenomenon*

There was a significant difference in the number of patients with RP receiving PDE5 inhibitors ($p$=0.036).

*Skin involvement*

Although uncommon, use of D-penicillamine differed significantly among centres for all patients with an MRSS >10 ($p$=0.004). When comparing methotrexate in the early diffuse subset, there were no differences. The use of D-penicillamine currently was 2.5% but at one site was higher than the others (9%).

*GI involvement*

Use of hyperalimentation ($p$=0.000) differed significantly among centres for patients with other bowel complaints. Esophageal dilatation ($p$=0.000) use differed significantly among centres for patients with dysphagia.

*Interstitial lung disease*

Utilisation of cyclophosphamide ($p$=0.037) and azathioprine (0.037) was significantly different among centres. There were no differences in those with <5 years disease duration for all the immune suppressives and steroids but the numbers were small. Data is only shown in the latter group for cyclophosphamide.

*PAH*

Echocardiogram rates did not differ between sites (>90%), nor did treatment. However, prevalence of PAH seemed to be higher in the larger centres with the rate of PAH increasing with site size.

**Table I.** CSRG patient characteristics for centres with n>50.

| Characteristic | Patients not included in this analysis (from smaller sites) (n=298) | Patients included in the analysis (n=640) | $p$-value between patients included and excluded from the analysis |
|---|---|---|---|
| Age, mean ± SEM years | 55 .4 ± 0.7 | 55.3 ± 0.5 | 0.977 |
| Female (%) | 248 (83.2) | 559 (87.3) | 0.090 |
| Disease duration, mean ± SEM years | 13.7 ± 0.6 | 13.5 ± 0.4 | 0.909 |
| Raynaud's phenomenon (%) | 275 (97.9) | 629 (98.9) | 0.222 |
| Digital ulcers ever (%) | 135 (45.3) | 278 (43.4) | 0.592 |
| Active digital ulcers (%) | 28 (9.8) | 110 (17.3) | 0.003 |
| Healed digital ulcers (%) | 132 (46.3) | 254 (39.9) | 0.070 |
| Renal crisis (%) | 12 (4.3) | 37 (5.8) | 0.329 |
| MRSS, mean ± SEM | 11.1 ± 0.4 | 11.2 ± 0.3 | 0.921 |
| GERD (%) | 208 (70.0) | 467 (73.0) | 0.352 |
| Other bowel complaints (%) | 143 (48.8) | 329 (51.6) | 0.434 |
| Delayed-gastric emptying (%) | 162 (54.5) | 350 (54.7) | 0.968 |
| Dysphagia (%) | 165 (55.6) | 369 (57.7) | 0.546 |
| PAH (%) | 20 (7.9) | 42 (7.2) | 0.739 |
| Abnormal ECG (%) | 36 (15.5) | 71 (16.6) | 0.704 |
| Patients with a previous CT scan indicating lung fibrosis (%) | 75 (32.8) | 171 (31.6) | 0.756 |
| Evidence of ILD on previous CXR (%) | 64 (26.2) | 169 (28.1) | 0.587 |
| Velcro rales (%) | 87 (34.1) | 172 (27.5) | 0.051 |
| FVC % predicted <70 (%) | 42 (17.9) | 108 (19.3) | 0.642 |

$p$-values indicate the difference within a variable between patients included and not included in the analysis.

CSRG: Canadian Scleroderma Research Group; CT: computed tomography; CXR: chest x-ray; ECG: electrocardiogram; FVC: forced vital capacity; GERD: gastroesophageal reflux disease, ILD: interstitial lung disease; MRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension; SEM: standard error of the mean.

*Inflammatory arthritis and myositis*

Use of hydoxychloroquine ($p$=0.023), D-penicillamine ($p$=0.008) and corticosteroids ($p$=0.039) differed significantly among centres for patients with inflammatory arthritis. There was a significant difference in the number of patients with myositis receiving cyclophosphamide ($p$=0.019) among centres.

*Chest x-rays and high resolution lung CT scan*

Among centres, the frequency with which chest x-rays were performed differed significantly for all patients ($p$=0.000). CT scans were performed at different rates among centres for all patients ($p$=0.000) and when studying those with FVC<70% predicted ($p$=0.000).

*ECGs*

ECG use differed among centres for all patients with SSc ($p$=0.000).

## Discussion

Several of these investigation and treatment practices varied between sites. The results of this study are not surprising given the lack of standardisation for treatment of some organ systems in SSc and this may be similar to practices in other connective tissue diseases. One could gain consensus beyond treatment guidelines for standardisation in second and third line treatment to help decrease practice variability but standardisation would only be important if using a specific therapy over another would differentially effect outcomes. D-penicillamine has negative randomised controlled trial results, so data do not support D-penicillamine in the treatment of skin fibrosis (3, 10) but it is currently used more at one site. PDE5 inhibitors varied for Raynaud's which has two positive trials (11, 12) although one trial is unpublished and the other is a single site RCT. This demonstrates the lack of consensus or lack of access for PDE5 inhibitors in RP (7). The rates of treatment with mycophenylate mofet-

**Table II.** Treatment and investigation practice frequency and variation among centres with n>50.

| | Centre (n=640) | | | | | | |
|---|---|---|---|---|---|---|---|
| | A (n=52) Frequency (%) | B (n=65) Frequency (%) | C (n=86) Frequency (%) | D (n=98) Frequency (%) | E (n=154) Frequency (%) | F (n=185) Frequency (%) | *p*-value |
| Raynaud's phenomenon | | | | | | | |
| n. (%) with RP | 52 (100) | 65 (100) | 86 (100) | 91 (94.8) | 152 (100) | 183 (98.9) | 0.002 |
| Calcium channel blocker | 25 (48.1) | 25 (38.5) | 41 (47.7) | 50 (54.9) | 62 (40.8) | 85 (46.4) | 0.280 |
| Iloprost | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0.7) | 0 (0) | 0.678 |
| PDE5 Inhibitors | 5 (9.6) | 2 (3.1) | 1 (1.2) | 0 (0) | 8 (5.3) | 6 (3.3) | 0.036 |
| Digital ulcers (DU) (ever) | | | | | | | |
| n. (%) with DU ever | 28 (53.8) | 31 (47.7) | 56 (65.1) | 47 (48.0) | 56 (36.4) | 60 (32.4) | 0.000 |
| Calcium channel blocker | 15 (53.6) | 11 (35.5) | 28 (50) | 28 (59.6) | 28 (50.0) | 39 (65.0) | 0.131 |
| Iloprost | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n/a |
| Bosentan | 2 (7.1) | 3 (9.7) | 2 (3.6) | 1 (2.1) | 2 (3.6) | 4 (6.7) | 0.650 |
| Digital ulcers (DU) (active) | | | | | | | |
| n. (%) with DU active | 4 (7.7) | 12 (18.5) | 22 (25.6) | 14 (14.4) | 20 (13.2) | 38 (20.5) | 0.46 |
| Calcium channel blocker | 2 (50.0) | 7 (58.3) | 15 (68.2) | 11 (78.6) | 10 (50.0) | 28 (73.7) | 0.403 |
| Iloprost | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n/a |
| Bosentan | 0 (0) | 2 (16.7) | 2 (9.1) | 0 (0) | 1 (5.0) | 4 (10.5) | 0.650 |
| Skin involvement (MRSS>10) | | | | | | | |
| n. (%) with MRSS>10 | 21 (40.4) | 42 (64.6) | 54 (62.8) | 47 (48.0) | 76 (49.4) | 88 (47.6) | 0.020 |
| Corticosteroids | 3 (14.3) | 8 (19.0) | 8 (14.8) | 15 (31.9) | 16 (21.3) | 23 (26.1) | 0.299 |
| D-penicillamine | 0 (0) | 1 (2.4) | 6 (11.1) | 0 (0) | 1 (1.3) | 1 (1.1) | 0.004 |
| Methotrexate | 2 (9.5) | 9 (21.4) | 8 (14.8) | 8 (17.0) | 6 (8.0) | 15 (17.0) | 0.387 |
| Cyclophosphamide | 3 (14.3) | 0 (0) | 1 (1.9) | 5 (10.6) | 3 (4.0) | 8 (9.1) | 0.062 |
| Stem Cell Transplant | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n/a |
| Diffuse SSc <3 years Methotrexate use | | | | | | | |
| 18/90 using Methotrexate (20%) | 17% (1/6) | 43% (3/7) | 8% (1/13) | 29% (4/14) | 20% (3/15) | 17% (6/35) | 0.496 |
| Current use of D-penicillamine for any reason (n=16) 2.5% of entire group | 2% | 3% | 9% | 1% | 1% | 1% | 0.001 |
| GERD | | | | | | | |
| n. (%) with GERD | 41 (78.8) | 55 (84.6) | 56 (65.1) | 69 (70.4) | 112 (72.7) | 134 (72.4) | 0.134 |
| Gastroprotective Agents | 38 (92.7) | 50 (90.9) | 44 (78.6) | 61 (88.4) | 96 (85.7) | 112 (83.6) | 0.294 |
| Promotility Agents | 10 (24.4) | 8 (14.5) | 19 (33.9) | 14 (20.3) | 32 (28.6) | 29 (21.6) | 0.159 |
| Other bowel complaints | | | | | | | |
| n. (%) with other bowl complaints | 29 (55.8) | 37 (56.9) | 59 (68.6) | 39 (39.8) | 66 (43.4) | 99 (53.5) | 0.001 |
| Hyperalimentation | 3 (10.3) | 1 (2.7) | 19 (32.2) | 3 (7.9) | 4 (6.1) | 2 (2.0) | 0.000 |
| Antibiotics (for bacterial overgrowth) | 3 (10.3) | 7 (18.9) | 8 (13.6) | 8 (21.1) | 15 (22.7)) | 9 (9.1) | 0.167 |
| Delayed gastric emptying | | | | | | | |
| n. (%) with delayed gastric emptying | 34 (65.4) | 38 (58.5) | 48 (55.8) | 47 (48.0) | 77 (50.0) | 106 (57.3) | 0.262 |
| Promotility agents | 8 (23.5) | 8 (21.1) | 16 (33.3) | 8 (17.0) | 30 (39.0) | 27 (25.5) | 0.084 |
| Dysphagia | | | | | | | |
| n. (%) with dysphagia | 31 (59.6) | 41 (63.1) | 55 (64.0) | 54 (55.1) | 94 (61.0) | 94 (50.8) | 0.236 |
| Promotility agents | 8 (25.8) | 8 (19.5) | 16 (29.1) | 12 (22.6) | 29 (30.9) | 26 (27.7) | 0.768 |
| Esophageal dilatation | 7 (22.6) | 11 (26.8) | 8 (14.5) | 12 (22.6) | 35 (37.2) | 4 (4.3) | 0.000 |
| Inflammatory arthritis | | | | | | | |
| n. (%) with inflammatory arthritis | 19 (37.3) | 23 (35.4) | 71 (83.5) | 42 (44.7) | 32 (21.2) | 39 (21.1) | 0.000 |
| Methotrexate | 1 (5.3) | 7 (30.4) | 10 (14.1) | 9 (21.4) | 4 (12.5) | 8 (20.5) | 0.259 |
| Hydroxychloroquine | 5 (26.3) | 0 (0) | 10 (14.1) | 11 (26.2) | 7 (21.9) | 13 (33.3) | 0.023 |
| D-penicillamine | 0 (0) | 0 (0) | 7 (9.9) | 0 (0) | 0 (0) | 0 (0) | 0.008 |
| NSAIDs | 9 (47.4) | 5 (21.7) | 26 (36.6) | 21 (50.0) | 15 (46.9) | 12 (30.8) | 0.174 |
| Corticosteroids | 4 (21.1) | 8 (34.8) | 10 (14.1) | 16 (38.1) | 6 (18.8) | 13 (33.3) | 0.039 |
| Inflammatory myositis | | | | | | | |
| n. (%) with inflammatory myositis | 3 (5.9) | 11 (17.2) | 42 (50.6) | 11 (11.7) | 6 (3.9) | 18 (10.1) | 0.000 |
| Methotrexate | 1 (33.3) | 4 (36.4) | 8 (19.0) | 2 (18.2) | 1 (16.7) | 5 (27.8) | 0.826 |
| Azathioprine | 1 (33.3) | 3 (27.3) | 2 (4.8) | 1 (9.1) | 1 (16.7) | 2 (11.1) | 0.268 |
| Cyclophosphamide | 1 (33.3) | 0 (0) | 1 (2.4) | 3 (27.3) | 0 (0) | 1 (5.6) | 0.019 |
| Renal crisis ever | | | | | | | |
| n. (%) with renal crisis ever | 3 (5.8) | 3 (4.6) | 6 (7.0) | 5 (5.2) | 12 (7.9) | 8 (4.3) | 0.787 |
| ACE inhibitor | 2 (66.7) | 2 (66.7) | 5 (83.3) | 5 (100.0) | 7 (58.3) | 7 (87.5) | 0.463 |
| Haemodialysis or peritoneal dialysis | 1 (33.3) | 2 (66.7) | 2 (33.3) | 2 (40.0) | 2 (16.7) | 3 (37.5) | 0.670 |
| Kidney transplant | 1 (33.3) | 0 (0) | 0 (0) | 0 (0) | 2 (16.7) | 0 (0) | 0.338 |

| | Centre (n=640) | | | | | | |
|---|---|---|---|---|---|---|---|
| | A (n=52) Frequency (%) | B (n=65) Frequency (%) | C (n=86) Frequency (%) | D (n=98) Frequency (%) | E (n=154) Frequency (%) | F (n=185) Frequency (%) | *p*-value |
| PAH | | | | | | | |
| n. (%) with PAH | 1 (2.2) | 2 (3.3) | 1 (1.3) | 4 (4.2) | 10 (7.4) | 24 (14.4) | 0.001 |
| Epoprostinil | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (10.0) | 1 (4.2) | 0.961 |
| Trepostinil | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (10.0) | 3 (12.5) | 0.955 |
| Iloprost | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | n/a |
| Bosentan | 1 (100.0) | 1 (50.0) | 0 (0) | 1 (25.0) | 2 (20.0) | 4 (16.7) | 0.383 |
| Sitaxentan# | 0 (0) | 1 (50.0) | 0 (0) | 0 (0) | 1 (10.0) | 7 (29.2) | 0.516 |
| Warfarin | 1 (100.0) | 0 (0) | 0 (0) | 1 (25.0) | 2 (20.0) | 5 (20.8) | 0.476 |
| PDE5 Inhibitors | 1 (100.0) | 1 (50.0) | 0 (0) | 0 (0) | 3 (30.0) | 3 (12.5) | 0.150 |
| Arrhythmia | | | | | | | |
| n. (%) with arrhythmia | 4 (12.5) | 9 (15.3) | 20 (26.3) | 11 (14.3) | 21 (15.2) | 6 (13.0) | 0.255 |
| Anti-arrhythmics | 0 (0) | 1 (11.1) | 3 (15.0) | 0 (0) | 3 (14.3) | 0 (0) | 0.643 |
| ILD | | | | | | | |
| n. % with ILD | 13 (25.0) | 28 (44.4) | 36 (43.4) | 35 (36.1) | 38 (25.5) | 83 (45.4) | 0.001 |
| Corticosteroids | 3 (23.1) | 7 (25.0) | 4 (11.1) | 12 (34.3) | 11 (28.9) | 25 (30.1) | 0.284 |
| Cyclophosphamide | 4 (30.8) | 1 (3.6) | 2 (5.6) | 3 (8.6) | 1 (2.6) | 10 (12.0) | 0.037 |
| Azathioprine | 2 (15.4) | 6 (21.4) | 4 (11.1) | 2 (5.7) | 3 (7.9) | 2 (2.4) | 0.037 |
| Mofetil mycophenylate | 1 (7.7) | 0 (0) | 2 (2.8) | 1 (2.9) | 1 (2.6) | 8 (9.6) | 0.269 |
| ILD with FVC<70% and SSc <5 years | | | | | | | |
| Cyclophosphamide (8/32 using cyclophosphamide) 25% | 100% (2/2) | 20% (1/5) | 0 (0/1) | 14% (1/7) | 20% (1/5) | 25% (3/12) | 0.229 |
| Investigations | | | | | | | |
| CXR | 34 (72.3) | 63 (96.9) | 81 (97.6) | 90 (93.8) | 118 (78.7) | 179 (97.8) | 0.000 |
| HRCT | 5 (10.6) | 20 (30.8) | 33 (41.3) | 27 (30.7) | 22 (14.8) | 66 (37.3) | 0.000 |
| PFT | 40 (85.1) | 61 (93.8) | 74 (92.5) | 85 (96.6) | 134 (89.9) | 166 (93.8) | 0.171 |
| ECG | 38 (80.9) | 59 (90.8) | 61 (76.3) | 81 (92.0) | 112 (75.2) | 174 (98.3) | 0.000 |
| Echocardiogram | 47 (100.0) | 59 (90.8) | 75 (92.6) | 93 (96.9) | 141 (94.6) | 170 (96.0) | 0.205 |

*$p$-values measure variation among centres.
ACE: angiotensin-converting enzyme; CXR: chest x-ray; DU: digital ulcer; ECG: electrocardiogram; GERD: gastroesophageal reflux disease; HRCT; high resolution computed tomography chest scan; MRSS: modified Rodnan skin score; NSAID: non-steroidal anti-inflammatory drug; PAH: pulmonary arterial hypertension; PDE5: phosphodiesterase type 5; PFT: pulmonary function test; RP: Raynaud's phenomenon; #Sitaxsentan has been withdrawn from the market.

il (MMF) were low and there are no RCTs in SSc. Case series have yielded conflicting results (13, 14). Thus where treatment is unproven where there is a lack of RCTs, then more site to site variability would be expected. Intravenous iloprost is not approved in Canada and must be obtained by special access from another country and consequently it is logical that its use would be low. Evidence for treatment from other diseases is often applied to SSc, such as for the treatment of inflammatory arthritis and gastrointestinal complications due to a lack of randomised controlled trials (7).

A limitation of the study was that the CSRG database did not record the results of the right heart catheterisation. If we assume all who were diagnosed with PAH were treated then 9.0% of patients would have had PAH and this is similar to other published rates of proven PAH in SSc (15). The frequency of PAH increasing with site size, which is not the case for the other organ complications, leads us to speculate that there is under-detection at smaller centres (such as a lack of reading of the PA pressure on the screening echocardiogram as the rate of echocardiograms was not different between centres, or an inability to obtain a right heart catheterisation or PAH expertise) or it could be due to referral bias (sicker patients referred to larger centres which is less likely as lung, skin and GI involvement did not vary by site size) or it could be a spurious finding. The site is queried if an annual echocardiogram has not been performed so the rate of echocardiograms is a 'best case' scenario and likely higher than in usual rheumatologic care of scleroderma patients.

A clinician's reasons for prescribing any drug could not be confirmed. In addition, a patient not taking a medication could have been due to lack of prescription, side effects, non-adherence or other factors such as limited finances for relatively expensive therapies. These factors may have lead to an over- or under-estimation in the rate of treatment for a particular manifestation. For instance sildenafil may have been prescribed for PAH, Raynaud's or digital ulcers.

The need for ILD treatment was arbitrary (FVC of <70% predicted overall and in those with disease of <5 years). This definition was done to compare treatment rates across centres. This post hoc definition should not have caused between-site variability as it was applied to all sites. The frequency of missing data could have differed among sites, but with our quality control of data and queries, this should not

have been the case. In addition, the medications should have been entered accurately as there is a standardised medication form completed at each visit. Multiple statistical tests were performed so there could have been spurious associations. Our results may not be generalisable to other practices as only patients within a database from relatively large SSc practices were studied. However, the patient characteristics were similar to the smaller centres, but we did not study the practices within smaller centres.

Practice variability was found despite ideal conditions: a critical mass of patients, standardised forms with database queries when tests are not entered and rheumatologists who are interested in SSc. The reason for less PAH in smaller centres is not explained by lack of ordering screening echocardiograms. This study demonstrates practice patterns in a large group of SSc patients before the EULAR/EUSTAR guidelines were published so practice may change due to the guidelines.

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