The Belgian Systemic Sclerosis Cohort: Correlations Between Disease Severity Scores, Cutaneous Subsets, and Autoantibody Profile

MARIE VANTHUYNE, VANESSA SMITH, ELLEN DE LANGHE, JENS VAN PRAET, SEHER ARAT, GENEVIÈVE DEPRESSEUX, RENE WESTHOVENS, DANIEL BLOCKMANS, VALÉRIE BADOT, ELIE COGAN, FILIP DE KEYSER, and FRÉDÉRIC A. HOUSSIAU

ABSTRACT. ***Objective.*** To report baseline and followup data on the first 438 patients with systemic sclerosis (SSc) included in the Belgian Systemic Sclerosis Cohort.

Methods. According to LeRoy and Medsger's classification, 73 patients with limited SSc (lSSc), 279 with limited cutaneous SSc (lcSSc), and 86 with diffuse cutaneous SSc (dcSSc) were included. History was collected and clinical examination, blood tests, and paraclinical investigations were repeated. The Disease Activity Score (DAS) and Disease Severity Score (DSS) of several organ systems were computed. An organ system was considered to demonstrate SSc if the corresponding DSS was ≥ 1.

Results. At baseline, patients with dcSSc had more general, joint/tendon, muscle, gastrointestinal, and kidney involvement. Mean DLCO was below normal in patients with lSSc, indicating unsuspected lung involvement. Patients with anti-Scl-70 had more vascular, skin, joint/tendon, and lung involvement. Patients with anti-RNA polymerase III had more skin and joint/tendon involvement compared to patients with anticentromere. Time to death was statistically shorter for patients with dcSSc. New-onset lung disease was the most common complication over time. No changes in DAS were observed. By contrast, the general and the skin DSS worsened in patients with lcSSc and lSSc, respectively. Fifteen percent of patients with lSSc shifted to lcSSc at Month 30, but neither serology nor capillaroscopy findings at baseline were helpful in identifying those at risk.

Conclusion. Our data indicate that the DSS can be used to define organ involvement in SSc. Differences can be seen between subsets classified not only according to cutaneous subtypes but also to autoantibody profile. (First Release Sept 15 2012; J Rheumatol 2012;39:2127–33; doi:10.3899/jrheum.120283)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SUBSETS OUTCOME DISEASE SEVERITY SCORE AUTOANTIBODIES MORTALITY

Systemic sclerosis (SSc) is a rare and possibly life-threatening multisystemic disease purportedly resulting from 3 injuries: immune dysregulation with production of autoantibodies, microvascular damage leading to capillary loss, and fibrosis contributing to organ dysfunction and late disease phenotype[1]. The low disease prevalence (± 150/million individuals)[2] leads to the regrouping of patients into large cohorts to study disease progression, to perform genetic and pathophysiological studies on *ex-vivo* samples, and to test new therapies. Since the pioneering initiative launched by the Pittsburgh group more than 3 decades ago[3], several other large cohorts of patients with SSc have been gathered

From the Rheumatology and Internal Medicine Departments, Cliniques Universitaires Saint-Luc, and Centre Hospitalier Universitaire (CHU) Mont Godinne, Université Catholique de Louvain, Brussels; Ghent University Hospital, Universiteit Gent, Ghent; UZ Gasthuisberg, Katholieke Universiteit Leuven, Leuven; CHU Brugmann, Brussels; and Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

Supported by the Association des Patients Sclérodermiques de Belgique and by Actelion, both through the Société Royale Belge de Rhumatologie/Koninklijke Belgische Vereniging for Reumatologie and the Fonds pour la Recherche Scientifique en Rhumatologie/Fons voor Wetenschappelijk Onderzoek in de Reumatologie.

M. Vanthuyne, MD, PhD, Rheumatology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, CHU Mont Godinne; V. Smith, MD, PhD, Rheumatology, Ghent University Hospital, Universiteit Gent; E. De Langhe, MD, Rheumatology Department, UZ Gasthuisberg, Katholieke Universiteit Leuven; J. Van Praet, MD, PhD, Rheumatology Department, Ghent University Hospital, Universiteit Gent; S. Arat, RN, MSc, Rheumatology Department, UZ Gasthuisberg, Katholieke Universiteit Leuven; G. Depresseux, MD, Rheumatology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain; R. Westhovens, MD, PhD, RN, MSc, Rheumatology Department, UZ Gasthuisberg, Katholieke Universiteit Leuven; D. Blockmans, MD, PhD, Internal Medicine Department, UZ Gasthuisberg, Katholieke Universiteit Leuven; V. Badot, MD, PhD, Rheumatology Department, CHU Brugmann; E. Cogan, MD, PhD, Internal Medicine Department, Hôpital Erasme, Université Libre de Bruxelles; F. De Keyser, MD, PhD, Rheumatology Department, Ghent University Hospital, Universiteit Gent; F.A. Houssiau, MD, PhD, Rheumatology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain.

Address correspondence to Dr. F.A. Houssiau, Rheumatology Department, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium. E-mail: frederic.houssiau@uclouvain.be

Accepted for publication July 11, 2012.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

worldwide[4,5], with recent European input through the European League Against Rheumatism/Scleroderma Trials and Research group (EUSTAR)[6].

Since April 2006, prevalent and incident cases of SSc fulfilling LeRoy and Medsger's classification criteria[7] were included in the Belgian Systemic Sclerosis Cohort (BSSC). The originality of our approach stems from a standardized longitudinal protocol for clinical assessments using well-defined outcome measures, such as the SSc Disease Activity Score (DAS)[8] and Medsger's Disease Severity Score (DSS)[9], the latter to define organ involvement using homogeneous criteria. Clinical and paraclinical investigations were systematically repeated at fixed intervals to reveal organ involvement.

We report the baseline and 30-month data of the first 438 patients with SSc included in the BSSC.

MATERIALS AND METHODS

Between April 2006 and November 2011, all consecutive patients with SSc examined in Belgian teaching hospitals, including those referred by many private rheumatologists who agreed to participate, and fulfilling LeRoy and Medsger's classification criteria[7], were asked to participate in the Belgian Systemic Sclerosis Cohort. This observational study was approved by the Ethics Committee of all participating hospitals and signed informed consent was obtained. Five percent of the patients declined to participate. All patients but 1 were white. Seventy-three patients with limited SSc (lSSc), 279 with limited cutaneous SSc (lcSSc), and 86 with diffuse cutaneous SSc (dcSSc) were recruited. At baseline, medical history was collected, with special emphasis on SSc-related organ involvement, including various skin signs, calcinosis, sicca syndrome, arthritis and tendonitis, myositis, interstitial lung disease (ILD), pulmonary arterial hypertension, esophageal dysmotility, small bowel disease, and renal crisis. Past drug intake was recorded. At each visit (baseline, Months 6, 18, and 30), standard clinical examination was performed, and a modified Rodnan skin score (mRSS) was measured[10]. Chest computerized tomography was performed at baseline in all patients. Standard blood tests, electrocardiography, chest radiography, echocardiography, pulmonary function tests, and a 6-min walking distance test were done at every visit. Besides these required tests, optional investigations, such as right heart catheterization, were left to the discretion of the physician, based on the clinical symptoms and signs and on the results of the other tests.

Patients were asked to complete the Health Assessment Questionnaire (HAQ)[11]. The SSc DAS and DSS were computed as described[8,9]. Briefly, each of the following items of the DAS (maximum score of 10) was valued as follows: mRSS > 14 (1), scleroedema (0.5), at least 1 active digital ulcer (0.5), arthritis (0.5), erythrocyte sedimentation rate (ESR) ≥ 30 mm/h (1.5), hypocomplementemia (1), DLCO < 80% of predicted values (0.5), worsening of cutaneous involvement (2), worsening of vascular symptoms (0.5), and worsening of cardiopulmonary symptoms (2), the last 3 items being assessed by the patient only. By definition, SSc is considered to be active if the DAS is ≥ 3. The DSS were calculated for 9 different organ systems: general, peripheral vascular, skin, joints and tendons, muscle, gastrointestinal, lung, heart, and kidney. Each DSS is graded from 0 (no involvement) to 4 (major involvement), based on strictly defined criteria[9]. We considered that an organ system was involved by SSc if the corresponding DSS was ≥ 1.

Serological tests were centrally performed on baseline samples at the University of Ghent on the first 319 patients included in the cohort. Sera were screened for these antibodies: (1) antinuclear (ANA) by indirect immunofluorescence (IIF) on Hep-2 cells; (2) anti-Scl-70, anti-CENP-B [anticentromere antibodies (ACA)], anti-RNP, anti-SSA (52/60), anti-SSB, and anti-Sm by line immunoassay[12,13]; and (3) anti-RNA polymerase III (anti-RNAP) by ELISA (MBL International). Local serotyping was performed on the 119 remaining samples (ANA by IIF on Hep-2 cells; anti-Scl-70 antibodies, anti-RNP antibodies, anti-SSA antibodies, anti-SSB antibodies, and anti-Sm antibodies by ELISA; ACA were detected by the centromeric pattern on IIF; anti-RNAP were not screened).

For statistical analyses, Fisher's exact test was used to compare (1) baseline DSS according to SSc subtypes; (2) autoantibody status according to SSc subtypes; (3) baseline DSS according to autoantibody status; and (4) progression of DSS and DAS over time. Bonferroni's correction was applied to counteract the problem of multiple comparisons (Tables 1, 2, 3). Therefore, a p value of 0.017 was considered significant. Survival curves were computed by Kaplan-Meier analyses and statistically tested by log rank.

RESULTS

Baseline data. Baseline clinical and functional data of the 438 patients with SSc included in this analysis are described in Table 4, according to subtypes. Not surprisingly, more patients with dcSSc met the American College of Rheumatology (ACR) classification criteria, disease duration was longer in patients with lcSSc, and mRSS, DAS and HAQ were higher in patients with dcSSc.

History of SSc was retrievable in 355 patients. Before inclusion in the BSSC, the following disease manifestations had been recorded: sclerodactyly (71% of the patients), telangiectasias (58%), sicca syndrome (51%), digital tip ulcers (41%), digital pitting scars (39%), esophageal dysmotility (35%), arthritis (26%), ILD (23%), calcinosis (23%), digital gangrene (10%), pulmonary arterial hypertension (8%), myositis (8%), palpable tendon friction rub (7%), small bowel involvement (5%), and renal crisis (3%).

Drug intake before inclusion was available by chart review in 355 patients. The most commonly prescribed drugs were calcium channel blockers (59%), proton pump inhibitors (44%), oral glucocorticoids (42%), aspirin (28%), methotrexate (25%), prostaglandin analogs (19%), d-penicillamine (17%), angiotensin-converting enzyme inhibitors (16%), and intravenous (IV) methylprednisolone pulses (13%). Azathioprine, IV cyclophosphamide (CYC), oral CYC, and bosentan had been prescribed in 6%, 5%, 3%, and 1.7%, respectively.

Table 1 compares baseline DSS for each of the 9 systems across SSc subtypes. Data are percentages of patients with a DSS ≥ 1, i.e., with involvement of that component. Logically, the percentage of patients with a DSS ≥ 1 in the general, joint/tendon, muscle, gastrointestinal, and kidney systems was statistically higher in patients with dcSSc compared to patients with lcSSc. This was, however, not the case for the lung component. Conversely, few patients with lSSc had system involvements except peripheral vascular, and more surprisingly, lung. The latter was not related to reduced lung volumes (vital capacity: mean/median 105/105% of predicted values), nor to subclinical pulmonary arterial hypertension (mean/median tricuspid regurgitation 23/22 mm Hg). Rather, it was related to Hb-adjusted DLCO values, which were lower than predicted

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

Table 1. Baseline Disease Severity Score according to systemic sclerosis subtype.

System	Percentage of Patients with DSS ≥ 1				p*		
	All, n = 438	dcSSc, n = 86	lcSSc, n = 279	ISSc, n = 73	dcSSc vs lcSSc	dcSSc vs ISSc	lcSSc vs ISSc
General	20.3	33.3	16.7	19.2	**0.002**	**0.049**	0.604
Peripheral vascular	63.4	72.9	66.3	41.1	0.291	**< 0.0001**	**< 0.0001**
Skin	82.8	100	100	0	> 0.999	**< 0.0001**	**< 0.0001**
Joint/tendon	34.3	72.6	28.7	11.0	**< 0.0001**	**< 0.0001**	**0.001**
Muscle	10.1	22.4	7.6	5.5	**0.0005**	**0.003**	0.798
Gastrointestinal tract	31.1	48.2	29.7	16.7	**0.002**	**< 0.0001**	0.026
Lung	73.4	82.1	76.0	53.4	0.297	**0.0001**	**0.0003**
Heart	12.5	16.5	11.6	11.0	0.266	0.361	> 0.999
Kidney	3.7	10.7	2.2	1.4	**0.002**	**0.021**	> 0.999

* Fisher's exact test. P values in bold type are considered statistically significant (p < 0.017; Bonferroni correction). DSS: Disease Severity Score; SSc: systemic sclerosis; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; lSSc: limited SSc.

Table 2. Autoantibody status according to systemic sclerosis subtype. Data are percentages of patients.

Autoantibodies	SSc Subsets				p*		
	All SSc, n = 428	dcSSc, n = 84	lcSSc, n = 273	ISSc, n = 71	dcSSc vs lcSSc	dcSSc vs ISSc	lcSSc vs ISSc
ANA	95.6	94.2	96.4	94.5	0.361	> 0.999	0.502
ACA	41.3	14.5	44.9	59.2	**< 0.0001**	**< 0.0001**	0.034
Anti-Scl-70	23.9	37.3	23.5	9.9	**0.016**	**< 0.0001**	**0.013**
Anti-RNAP	6.1	15.5	4.8	0	**0.003**	**0.0002**	0.079
Anti-RNP	4.5	3.6	4.8	4.2	> 0.999	> 0.999	> 0.999
Other anti-ENA**	4.9	4.8	5.1	4.2	> 0.999	> 0.999	> 0.999

* Fisher's exact test; p values in bold type are considered statistically significant (p < 0.017; Bonferroni correction). ** Anti-SSA (52/60) or anti-SSB or anti-Sm. SSc: systemic sclerosis; lSSc: limited SSc; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ANA: antinuclear antibodies; ENA: extractable nuclear antigens; ACA: anticentromere antibodies; RNAP: RNA polymerase antibodies.

Table 3. Baseline Disease Severity Score according to autoantibody status.

System	Percentage of Patients with DSS ≥ 1					
	Autoantibody Subset*			p**		
	Scl-70, n = 94	ACA, n = 170	RNAP, n = 23	Scl-70 vs ACA	Scl-70 vs RNAP	ACA vs RNAP
General	16.3	16.6	26.1	> 0.999	0.364	0.255
Peripheral vascular	77.4	58.8	47.8	**0.003**	**0.009**	0.372
Skin	92.6	72.4	100	**< 0.0001**	0.342	**0.001**
Joint/tendon	54.3	20.1	43.5	**< 0.0001**	0.363	0.018
Muscle	14.0	6.5	4.3	0.071	0.296	> 0.999
Gastrointestinal tract	34.4	29.2	22.7	0.404	0.325	0.622
Lung	84.9	68.5	69.6	**0.0032**	0.127	> 0.999
Heart	14.0	8.8	8.7	0.213	0.732	> 0.999
Kidney	5.4	3.5	8.7	0.524	0.626	0.244

* Data concern patients whose serum contains only 1 of the 3 autoantibodies. ** Fisher's exact test. P values in bold type are considered statistically significant (p < 0.017; Bonferroni correction). DSS: Disease Severity Score; RNAP: RNA polymerase antibodies; ACA: anticentromere antibodies.

(mean/median 79.7/80.0% of predicted values), without a smoking effect (data not shown).

Autoantibody status across SSc subtypes is summarized in Table 2. As expected, anti-Scl-70 and ACA were significantly more frequently detected in patients with dcSSc and patients with lcSSc, respectively. ACA were also frequently detected in patients with lSSc. By contrast, anti-RNAP were never found in patients with lSSc; they were statistically more frequent in patients with dcSSc compared to patients with lcSSc. We next examined whether the frequencies of system involvement, again defined by a DSS ≥ 1, differed between autoantibody subgroups. As indicated in Table 3, more patients with anti-Scl-70 had vascular, skin, joint/tendon, and lung involvement. Interestingly, lung involvement differed more between subgroups of patients with SSc when they were classified according to their autoantibody status

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

Table 4. Baseline clinical and functional status.

Characteristic	All, n = 438	SSc Subsets dcSSc, n = 86	lcSSc, n = 279	lSSc, n = 73
Female, %	80.3	70.9	80.6	89.0
ACR, %	57.0	92.8	57.5	13.9
Age, yrs, mean ± SD	54.4 ± 13.2	54.2 ± 12.2	55.3 ± 13.1	51.6 ± 14.6
Disease duration since RP, yrs, median (range)	7.5 (0–68)	4.8 (0–36)	9.8 (0–68)	3.7 (0–55)
Disease duration since first non-RF, yrs, median (range)	4.4 (0–41)	3.5 (0–36)	5.5 (0–41)	2.2 (0–39)
mRSS, median (range)	4 (0–40)	18 (2–40)	4 (1–20)	0 (0–0)
DAS, median (range)	1.5 (0–8)	3.5 (0–8)	1.0 (0–7)	0.5 (0–6)
HAQ, median (range)	0.500 (0–3.000)	0.875 (0–2.875)	0.375 (0–3.000)	0.375 (0–2.750)

SSc: systemic sclerosis; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; lSSc: limited SSc; ACR: American College of Rheumatology (fulfill ACR criteria for SSc); RP: Raynaud's phenomenon; RF: Raynaud's feature; mRSS: modified Rodnan skin score; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

(Table 3) than on a clinical basis (Table 1). Patients with anti-RNAP had less peripheral vascular disease compared to patients with anti-Scl-70, but more skin and joint/tendon involvement compared to patients with ACA. Two of the 10 patients with a history of scleroderma renal crisis were anti-RNAP-positive.

Followup data. Between April 2006 and November 2011, 39 of the 438 patients (9%) died (29 females; 15 dcSSc, 21 lcSSc, 3 lSSc), after a mean followup period (after inclusion in the cohort) of 23.0 (SD 16.8) months. As depicted in Figure 1, time to death, computed by Kaplan-Meier analysis, was statistically shorter for patients with dcSSc compared to patients with lcSSc and lSSc. Mean age at death was 59.0 (SD 10.1) and 69.2 (SD 10.3) years for patients with dcSSc and lcSSc, respectively. Of note, mean age at death was 79.8 years for the Belgian general population in 2009[14], while it was 65.1 (SD 11.0) years for all cases of SSc. Causes of death fell into 3 categories: not SSc-related (n = 15), possibly SSc-related (n = 7), and SSc-related (n = 17). Among the latter group, the causes of death were digestive tract involvement (n = 4), scleroderma renal crisis (n = 3), pulmonary arterial hypertension (n = 3), multiple organ involvement (n = 3), ILD (n = 2), and cardiac disease (n = 2). Three, 9, and 10 patients who died had serum anti-RNAP, ACA, or anti-Scl-70, respectively. Of note, ACA-positive patients represent only 23% of the fatal cases,

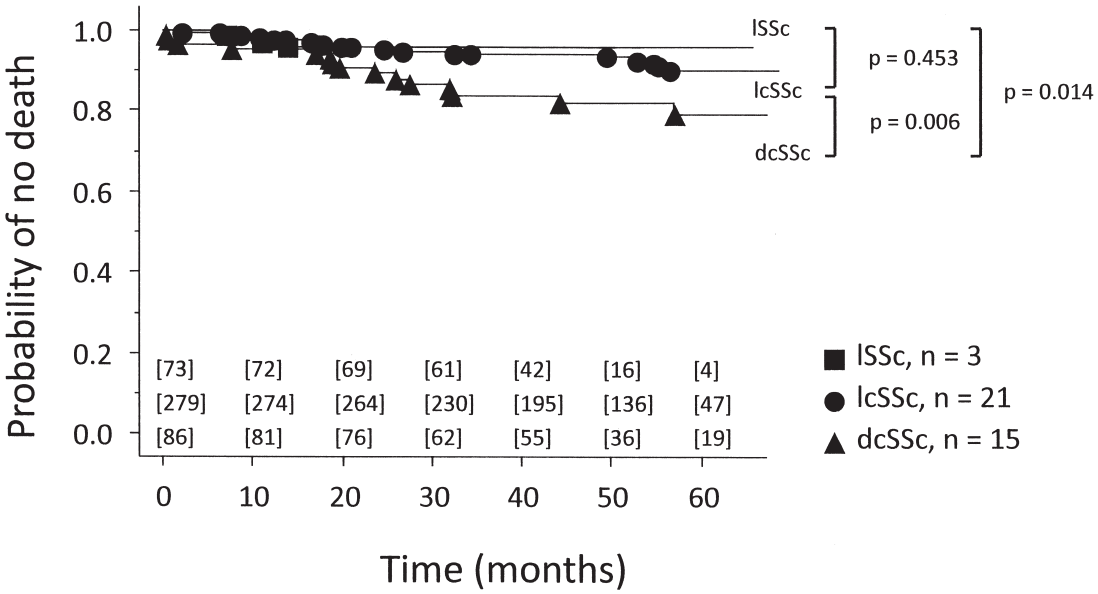

Figure 1. Kaplan-Meier probability of survival according to systemic sclerosis (SSc) subsets. Survival curves were statistically tested with the log-rank test. Numbers in brackets along the X axis indicate the numbers of patients at risk in each group. lSSc: limited systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

while these antibodies are detected in 41.3% of all our SSc cases.

We investigated whether the simple EUSTAR prognostic model for survival prediction[15] could be replicated in our cohort of 86 patients with dcSSc, of whom 15 had died and 71 survived after a mean followup period of 43 (SD 18) months. As suggested, 3 risk factors were assessed at baseline: proteinuria (by dipstick), ESR ≥ 25 mm/h, and Hb-adjusted DLCO < 70%. Interestingly, mortality rates were 0%, 7%, 36%, and 50% if none, 1, 2, or 3 risk factors was/were present at baseline, respectively.

During followup (mean 16.2 ± SD 11.7 mo), several SSc-related major clinical events were recorded that led to treatment changes. Thus, new-onset ILD was diagnosed in 12 patients, of whom 7 received IV CYC, 2 azathioprine, 1 mycophenolate mofetil, and 2 glucocorticoids alone. Pulmonary arterial hypertension was diagnosed in 9 patients, of whom 5 were treated with endothelin receptor blockers. The single new case of renal crisis was observed in a patient with anti-RNAP.

Progression of the HAQ, DSS, and the DAS over time was available for 152 patients. No statistically significant HAQ changes were observed. Table 5 indicates the percentages of patients with a DSS ≥ 1 (for each of the 9 components) or with a DAS ≥ 3. The 2 statistically significant changes at Month 30 were a worsening of the general DSS in patients with lcSSc and of the skin DSS in patients with lSSc. The former was not explained by weight loss (mean 65 ± 15 kg at baseline and 67 ± 15 at Month 30) but by a fall in hemoglobin (from 13.3 ± 1.3 g/dl at baseline to 12.9 ± 1.4 at Month 30; $p < 0.0001$) and hematocrit (from 40.2% ± 3.7% at baseline to 39.5% ± 4.0% at Month 30; $p = 0.008$), the other 2 components of the general DSS.

Worsening of the skin DSS in patients with lSSc was obviously due to an increase in mRSS over time. Taking into account a difference of at least 4 points (to avoid slight and questionable variations), 11 out of the 73 patients with lSSc (15%) had clearly shifted from lSSc to lcSSc at Month 30. Of note, neither the serological status nor the capillaroscopic findings at baseline could predict which patients with lSSc would progress to lcSSc (data not shown).

Table 5. Progression of Disease Severity Score (DSS) and Disease Activity Score (DAS) over time.

DSS	Subtype	Percentage of Patients (n) with DSS ≥ 1 Baseline	Month 30	p*
General	dcSSc	33.3 (28/84)	18.8 (6/32)	0.257
	lcSSc	**16.7 (46/276)**	**25.5 (27/106)**	**0.007**
	lSSc	19.2 (14/73)	7.1 (1/14)	0.596
Peripheral vascular	dcSSc	72.9 (62/85)	90.6 (29/32)	0.708
	lcSSc	66.3 (183/276)	64.2 (68/106)	0.772
	lSSc	41.1 (30/73)	50.0 (7/14)	> 0.999
Skin	dcSSc	100 (86/86)	100 (32/32)	> 0.999
	lcSSc	100 (265/265)	91.7 (88/96)	> 0.999
	lSSc	**0 (0/73)**	**57.1 (8/14)**	**0.002**
Joint/tendon	dcSSc	72.6 (61/84)	64.5 (20/31)	0.582
	lcSSc	28.7 (79/275)	30.8 (32/104)	> 0.999
	lSSc	11.0 (8/73)	28.6 (4/14)	> 0.999
Muscle	dcSSc	22.4 (19/85)	18.8 (6/32)	0.732
	lcSSc	7.6 (21/277)	2.9 (3/103)	> 0.999
	lSSc	5.5 (4/73)	0.0 (0/14)	> 0.999
GI tract	dcSSc	48.2 (40/83)	51.6 (16/31)	0.795
	lcSSc	29.7 (82/276)	34.6 (36/104)	0.456
	lSSc	16.7 (12/72)	14.3 (2/14)	> 0.999
Lung	dcSSc	82.1 (69/84)	82.1 (23/28)	> 0.999
	lcSSc	76.0 (209/275)	83.7 (87/104)	0.065
	lSSc	53.4 (39/73)	42.9 (6/14)	> 0.999
Heart	dcSSc	16.5 (14/85)	13.3 (4/30)	0.731
	lcSSc	11.6 (32/275)	9.6 (10/104)	> 0.999
	lSSc	11.0 (8/73)	0.0 (0/13)	> 0.999
Kidney	dcSSc	10.7 (9/84)	0.0 (0/32)	0.492
	lcSSc	2.2 (6/277)	3.8 (4/106)	0.683
	lSSc	1.4 (1/73)	7.1 (1/14)	> 0.999
		Percentage of Patients (n) with DAS ≥ 3		
DAS	dcSSc	57.6 (49/85)	40.6 (13/32)	0.145
	lcSSc	21.9 (61/278)	27.4 (29/106)	0.282
	lSSc	11.1 (8/72)	7.1 (1/14)	> 0.999

* Fisher's exact test. Data in bold type are considered statistically significant. SSc: systemic sclerosis; lSSc: limited SSc. lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; GI: gastrointestinal.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

DISCUSSION

SSc is the most medically demanding connective tissue disease because of its chronicity, its severity, and the absence of efficacious disease-modifying therapy. The picture is further complicated by its heterogeneity: the spectrum of the disease spans from late diagnosed cases characterized by longstanding Raynaud's phenomenon (RP) associated with some subtle cutaneous changes to rapidly progressing forms with diffuse cutaneous thickening and multiorgan dysfunction. The aim of the BSSC, launched in 2006, was to determine the natural history of SSc subtypes, to identify prognostic markers, and to optimize the quality of care by boosting the creation of specialized clinics in Belgian teaching hospitals. The need for more standardized care is well illustrated in our cohort by the variety of drugs prescribed before inclusion. The strength of our approach stems from a standardized prospective followup protocol, using appropriate clinimetrics.

The decision to use LeRoy and Medsger's classification was justified to include the full spectrum of SSc cases, including the pre-SSc and the early patients. The presence of a relatively large cohort of lSSc cases likely explains that the overall ACR criteria positivity is on the lower side (57%) compared to other series in the literature. Of note, this percentage is very similar to that observed in a French cohort[2] (64%), with a similar proportion of SSc subsets.

To our knowledge, this is the first attempt to use the 9 DSS to define organ involvement and to correlate them across SSc subsets defined either clinically, according to LeRoy and Medsger[7] (Table 2), or serologically (Table 4). Thus, using the DSS, we confirm that patients with dcSSc have more frequent organ involvement than patients with lcSSc and that the same holds true for anti-Scl-70 compared to ACA patients. Interestingly, the percentage of patients with a lung DSS ≥ 1 differed statistically when anti-Scl-70 patients were compared to ACA patients, but not when patients with dcSSc were compared to patients with lcSSc. In this respect, it should be stressed that the clinical classification is more subject to change over time (because of skin score fluctuations), not to mention possible intraobserver variability, whereas autoantibody positivity is stable over time and not physician-dependent.

An unexpected finding at baseline was that half of the patients classified as lSSc had a lung DSS ≥ 1, mainly due to Hb-adjusted DLCO values < 80% (one of the cutoffs for a grade 1 lung DSS). This reduction of lung diffusion capacity, which had already been shown in patients with lSSc by Poormoghim, *et al*[16], was not linked to smoking, nor to reduced lung volumes, nor to subclinical pulmonary arterial hypertension. We therefore hypothesize the presence of lung RP, as suggested by Emmanuel, *et al*, who showed seasonal variations of DLCO values in patients with SSc that were independent of lung volumes[17].

Special attention was paid to the patients with anti-RNAP. The frequency of this autoantibody in our series, even at a relatively low level, is closely in agreement with that observed in other Western European SSc cohorts. Thus, Meyer, *et al*[18], Mierau, *et al*[19], and Bardoni, *et al*[20] reported frequencies of 9.4%, 3.8%, and 7.8% in the French, German, and Italian SSc cohorts, respectively. Previously reported associations include malignancy, diffuse cutaneous disease, tendon friction rubs, and renal crisis. In our series, 27% of the 11 patients with renal crisis (10 with a history and 1 incident case) were anti-RNAP-positive, a figure contrasting with the 6.1% anti-RNAP positivity in our general SSc population. Of note, renal crisis was a rare event in our patients, in contrast with some other series, mainly from the United States[21]. Whether this discrepancy is related to different ethnic backgrounds (all our patients but 1 were white) is not too far-fetched.

The death rate was high (9%), mainly in the dcSSc subset (15/86; 17%), despite a relatively short followup period. These high figures are probably because our cohort was not an inception cohort but also included prevalent cases. Many patients with longstanding severe dcSSc were recruited. If this assumption turns out to be correct, mortality figures should decrease with further followup.

Relatively few changes in DSS were observed over time. Anemia explained worsening of the general DSS in patients with lcSSc, possibly related to occult gastrointestinal blood loss due to chronic peptic esophagitis. Comparison of the skin DSS at baseline and Month 30 revealed that 15% of patients with lSSc shifted to lcSSc, thereby further emphasizing that these presystemic sclerosis cases truly belong to the SSc spectrum[15]. Of note — and quite consistently — more than half the patients with lSSc were ACA-positive. Further studies are clearly needed to identify patients with lSSc who will progress to lcSSc, as neither serology nor capillaroscopic findings were helpful in this respect.

Our data indicate that the 9 DSS can be used to define organ involvement in SSc and that differences can be seen between subgroups classified not only according to cutaneous subtypes but also by autoantibody profile. Whether DSS will be sensitive to change to identify progression of visceral disease needs to be addressed by a longer followup study.

REFERENCES

1. Abraham DJ, Krieg T, Distler J, Distler O. Overview of pathogenesis of systemic sclerosis. Rheumatology 2009;48 Suppl 3:iii3-7.
2. Le Guern V, Mahr A, Mouthon L, Jeanneret D, Carzon M, Guillevin L. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology 2004;43:1129-37.
3. Steen VD, Powell DL, Medsger TA Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum 1988;31:196-203.
4. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, et al. The registry of the German Network for Systemic Scleroderma: Frequency of disease subsets and patterns of organ

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

involvement. Rheumatology 2008;47:1185-92.
5. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Ramos-Casals M, Campillo-Grau M, et al. Registry of the Spanish network for systemic sclerosis: Clinical pattern according to cutaneous subsets and immunological status. Semin Arthritis Rheum 2012;41:789-800.
6. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: A report from the EULAR Scleroderma Trials and Research Group database. Ann Rheum Dis 2007;66:754-63.
7. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.
8. Valentini G, Della Rossa A, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, et al. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. Ann Rheum Dis 2001;60:592-8.
9. Medsger TA Jr, Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003;21 Suppl 29:S42-6.
10. Clements PJ, Lachenbruch PA, Seibold JR, Zee B, Steen VD, Brennan P, et al. Skin thickness score in systemic sclerosis: An assessment of interobserver variability in 3 independent studies. J Rheumatol 1993;20:1892-6.
11. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346-53.
12. Meheus L, Van Venrooij WJ, Wiik A, Charles PJ, Tzioufas AG, Meyer O, et al. Multicenter validation of recombinant, natural and synthetic antigens used in a single multiparameter assay for the detection of specific anti-nuclear autoantibodies in connective tissue disorders. Clin Exp Rheumatol 1999;17:205-14.
13. Peene I, Meheus L, Veys EM, De Keyser F. Detection and identification of antinuclear antibodies (ANA) in a large and consecutive cohort of serum samples referred for ANA testing. Ann Rheum Dis 2001;60:1131-6.
14. Statistics Belgium. Tables de mortalité et espérance de vie. [Internet. Accessed July 13, 2012.] Available from: http://statbel.fgov.be/fr/statistiques/chiffres/population/deces_mort_esp_vie/tables/
15. Fransen F, Popa-Diaconu D, Hesselstrand R, Carreira P, Valentini G, Beretta L, et al. Clinical prediction of 5-year survival in systemic sclerosis: Validation of a simple prognostic model in EUSTAR centres. Ann Rheum Dis 2011;70:1788-92.
16. Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum 2000;43:444-51.
17. Emmanuel G, Saroja D, Gopinathan K, Gharpure A, Stuckey J. Environmental factors and the diffusing capacity of the lung in progressive systemic sclerosis. Chest 1976;69 Suppl:304-7.
18. Meyer O, De Chaisemartin L, Nicaise-Roland P, Cabane J, Tubach F, Dieude P, et al. Anti-RNA polymerase III antibody prevalence and associated clinical manifestations in a large series of French patients with systemic sclerosis: A cross-sectional study. J Rheumatol 2010;37:125-30.
19. Mierau R, Moinzadeh P, Riemekasten G, Melchers I, Meurer M, Reichenberger F, et al. Frequency of disease-associated and other nuclear autoantibodies in patients of the German network for systemic scleroderma: Correlation with characteristic clinical features. Arthritis Res Ther 2011;13:R172.
20. Bardoni A, Rossi P, Salvini R, Bobbio-Pallavicini F, Caporali R, Montecucco C. Autoantibodies to RNA-polymerases in Italian patients with systemic sclerosis. Clin Exp Rheumatol 2003; 21:301-6.
21. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437-44.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org