European multicentre study to define disease activity criteria for systemic sclerosis.★ I. Clinical and epidemiological features of 290 patients from 19 centres

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Abstract

Objective—To investigate the existence of differences among European referral centres for systemic sclerosis (SSc) in the pattern of attendance and referral and in the clinical and therapeutical approaches.

Methods—In 1995 the European Scleroderma Study Group initiated a multicentre prospective one year study whose aim was to define the disease activity criteria in SSc. During the study period each participating European centre was asked to enrol consecutive patients satisfying American College of Rheumatology criteria for SSc and to fill out for each of them a standardised clinical chart. Patients from various centres were compared and differences in epidemiological, clinical, and therapeutical aspects were analysed.

Results—Nineteen different medical research centres consecutively recruited 290 patients. The patients could be divided into two subgroups: 173 with the limited (lSSc) and 117 with the diffuse (dSSc) form of the disease. The clinical and serological findings for the series of 290 patients seemed to be similar to data previously reported. However, when the data were analysed to elicit any differences between the participating centres, a high degree of variability emerged, in both epidemiological and clinical features and in the diagnostic and therapeutic approaches to the disease.

Conclusions—The clinical approach to SSc, not only in different countries but also in different centres within the same country, is not yet standardised. To overcome this problem, it will be necessary for the scientific community to draw up a standardised procedure for the management of patients with SSc. This would provide a common research tool for different centres engaged in research on this complex disease.

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Systemic sclerosis (SSc) is a multisystem connective tissue disorder characterised by widespread microvascular and macrovascular damage, and by fibrosis of the skin and internal organs, particularly the gut, lung, heart, and kidney.[1–6] The extent of skin and internal organ involvement, and the severity and course of the disease may vary greatly.[7–11] Moreover, the treatment for patients with SSc has not yet been standardised.[12] Thus the clinical approach may differ widely not only between doctors at outpatient clinics and those working in research oriented tertiary centres but also between centres of the same type.[13–15]

In 1995 the European Scleroderma Study Group was formed and began a multicentre study whose aim was to define a valid set of criteria for disease activity in SSc. Data were gathered on a large number of patients consecutively recruited at 19 different medical research centres in Europe. In this paper we report and discuss the preliminary data gathered at the first observation on 290 patients. In

Table 1 Demographic and patient history registered in the clinical chart

Demographic data	Historical data
● Sex	● Onset of the first manifestation
● Age	● Onset of the first non-Raynaud manifestation
● Date of first visit to the centre	● Disease duration*
● Date of enrolment in the study	
Subsetting:	Organ involvement (historical):
Clinical subset (dSSc, lSSc)	Peripheral vascular system
Serological subset (ACA†, Scl-70)	Skin
	Joints/tendons
	Muscles
	Gastrointestinal
	Lung
	Heart
	Kidney

*From either the onset of Raynaud's phenomenon or that of the first non-Raynaud manifestation.
†ACA = anticentromere antibodies.

Table 2 Main clinical, laboratory, and other diagnostic parameters investigated

Skin:	**Lung:**
Total skin score	Dyspnoea
Scleredema	Pleural rubs/pericarditis
Melanoderma	Bibasilar crackles
Telangiectasia	FVC*
Calcinosis (clinically evident)	TLCO*
Digital pitting scars	Chest *x* ray
Digital infarcts	Chest HRCT*
	Pulmonary arterial pressure (echocardiodoppler)
Joints/tendons/muscles:	**Heart:**
Arthralgias/arthritis	Pericarditis
Flexion contractures	Cardiac failure
Tendon friction rubs	Conduction defects (ECG)
Muscle weakness	Arrhythmias (ECG, Holter ECG)
Serum CK*	
Gut:	**Kidney:**
Pyrosis/dysphagia	Urine analysis (proteinuria, haematuria)
Diarrhoea	Creatinine
Oesophageal hypomotility	Systemic arterial pressure
Small bowel hypomotility	

*CK = creatine kinase; FVC = forced vital capacity; TLCO = carbon monoxide transfer factor; HRCT = high resolution computed tomography.

Table 3 Definition of some of the items recorded in the clinical chart

1 *Skin score:* recorded according to Kahaleh *et al.*[19] This score is evaluated on a four point scale (0 for normal skin, 1 for thickened skin, 2 for thickened, unpinchable skin, 3 for hidebound skin) at 22 body regions (maximal value 66)
2 *Oesophageal hypomotility:* radiologically documented hypomotility
3 *Interstitial lung disease:* signs of lung fibrosis documented by chest *x* ray and/or computed tomography (CT) scan. The standard chest *x* ray was scored 0–3: 0 = absence of interstitial lung disease; 1 = bibasilar lung fibrosis; 2 = diffuse interstitial lung fibrosis; 3 = honey combing.[20] CT was scored 0–3: 0 = absence of interstitial lung disease; 1 = ground glass appearance; 2 = subpleural septal lines; 3 = honey combing. Test of pulmonary function (forced vital capacity) and carbon monoxide transfer factor were performed, as well
4 *Cardiac disease:* signs of ischaemia and/or myocardial fibrosis or pericarditis detected by ECG and/or standard echocardiography. Holter ECG was performed to detect dysrhythmias
5 *Kidney disease:* proteinuria, haematuria, or decreased creatinine clearance, even in the absence of a typical scleroderma renal crisis

Table 4 Main demographic features of the series of 290 patients with systemic sclerosis

Number of patients	290
F/M	5.3
Age at enrolment (years)	53 (13) (range 8–87)
Age at disease onset (years)	41 (14) (range 5–80)
Disease duration at enrolment (years)*	11 (10) (range 0–56)
Disease duration at enrolment (years)†	8 (7) (range 0–51)
Time from disease onset to admission‡ (years)	8 (9) (range 0–56)
Time from admission to enrolment (years)	3 (4) (range 0–23)

*From the onset of Raynaud's phenomenon.
†From the onset of the first non-Raynaud's manifestation.
‡That is, the first visit to the centre.

Table 5 Main demographic features for the two disease subsets, limited and diffuse systemic sclerosis (SSc)

	Disease subset		
	lSSc	dSSc	p Value
Number of patients	173	117	
F/M	6.2	4.3	NS
Age at enrolment (years)	55 (range 21–87)	49 (range 8–86)	0.0002
Age at onset* (years)	42 (range 7–74)	41 (range 5–80)	NS
Mean disease duration (years)†	13 (range 0–56)	8 (range 0–47)	0.0005
Mean disease duration (years)‡	9 (range 0–51)	7 (range 0–34)	NS

*Appearance of Raynaud's phenomenon.
†From the onset of Raynaud's phenomenon.
‡From the first non-Raynaud's manifestation.

addition, by examining groups of consecutive patients from the various centres, we were able to evaluate their patterns of attendance and referral.

Materials and methods
Nineteen centres located in 11 different European countries participated in this study. Each investigator was asked to enrol a consecutive number of patients with SSc, satisfying the preliminary American College of Rheumatology (ACR, formerly American Rheumatism Association) criteria for the classification of the disease.[16]

CLINICAL CHART
A standardised clinical chart was prepared and one copy was sent to each participating centre. Table 1 summarises the demographic and epidemiological information, and table 2 the clinical, laboratory, and other parameters (radiological, etc) that were to be gathered and recorded for each patient.

The chart was made up of four sections. In section I, for each patient the participants were asked to provide demographic information and a patient history; an evaluation based on the preliminary criteria for SSc of the ACR; a classification of the patient's disease as diffuse or limited (dSSc or lSSc) according to Le Roy *et al.*[8]

At entry, each patient also had to undergo a complete evaluation, and the results (including symptoms, signs, laboratory and other diagnostic test findings) were to be recorded in section II. This section was divided into 11 parts, 10 focusing on specific categories of disease manifestations (generalised complaints; cutaneous manifestations; vascular manifestations; cardiopulmonary manifestations; articular/muscular manifestations; ocular manifestations; gastrointestinal manifestations; haematological alterations; renal alterations; and neuropsychiatric manifestations), and the 11th on aspecific inflammation and immunological features. At the end of each of the 11 subsections, an additional item was included (Δ-factor) designed to note any worsening in the relevant manifestation during the month preceding enrolment (according to the patient's report). Sections III and IV were analogous to section II (except that the Δ-factor recorded any change in the manifestation compared with the previous observation) and were to be completed for each patient at two later time points—that is, after six and 12 months, respectively. Finally, at the end of sections II–IV, the treatment prescribed
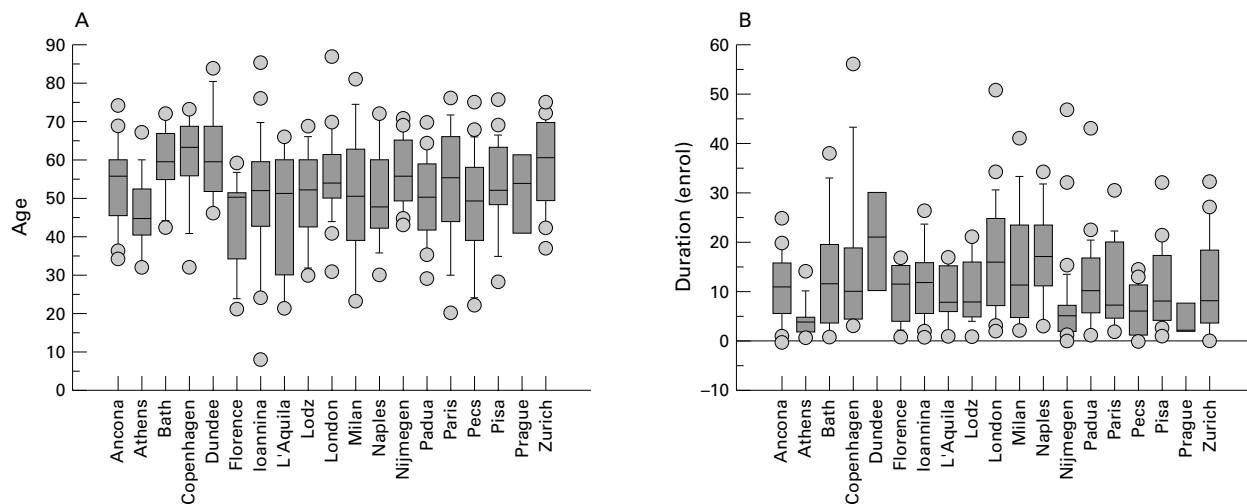

Figure 1 Distribution of the patients by (A) age at enrolment and (B) disease duration among the different centres. In the box plots the 10th, 25th, 50th (median), 75th, and 90th centiles for each variable are shown. Values above the 90th and below the 10th centiles are plotted as points.
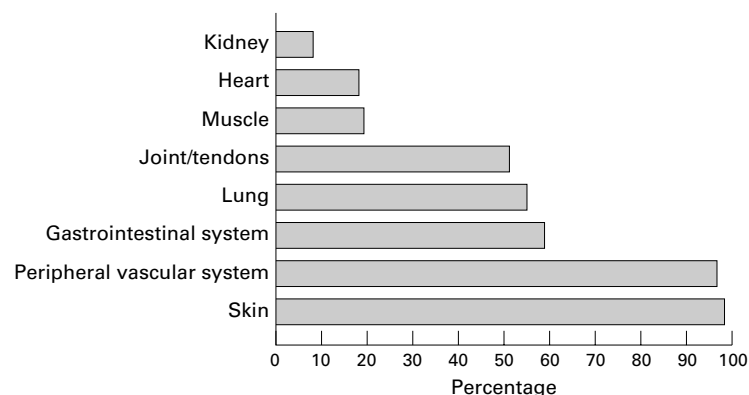
Figure 2 Cumulative prevalence of organ involvement based on data from the patient history section—that is, collected at the time of entry into the study.

at each of these time points for the patient was to be specified.

Each participant was requested to follow scrupulously the guidelines furnished by us in completing the chart. These guidelines included a precise definition of each symptom and test according to the American Rheumatism Association's *Dictionary of the Rheumatic Diseases*.[17][18] For certain items, more detailed definitions were provided by us (table 3).

DATA COLLECTION AND ANALYSIS
By the end of the enrolment period (March 1998) a total of 290 patients with SSc had been recruited, and participants had completed and returned sections I and II of the clinical charts for each of these patients. A statistical analysis of these preliminary data was carried out with the Statview program. Comparisons were made between patients attending the different centres based on analysis of variance, non-parametric tests for quantitative values, and contingency tables for proportions. In view of the high number of comparisons involved, we adopted a significance limit of 0.001.

Results

DEMOGRAPHIC AND HISTORICAL DATA
Table 4 summarises the main demographic features of the 290 patients recruited for this study. Women outnumbered men by 5.3 to 1, and there was a wide variation in the epidemiological parameters between patients. The disease duration, defined as the time elapsed from the onset of the first symptom (usually Raynaud's phenomenon), ranged from 0 to 56 years. When defined as the time elapsed from the first non-Raynaud manifestation, it ranged from 0 to 51 years. Thus a high percentage of the patients had disease of long duration. There was also in most cases a significant lapse in time between the patient's admission to the participating centre and his/her enrolment in the study; 190/290 had already been followed up at the respective centres for at least one year before being recruited into the study.

As a result of the recruitment process, all the 290 patients fulfilled the ACR criteria for SSc (165 patients met the major criterion and 125 met two of the three minor criteria). One hundred and seventeen had the diffuse and 173 the

Table 6 Main clinical and serological features for the case series (at the time of the first observation)

	No (%)	Number missing
1 Generalised complaints	163/290 (56)	0
2 Joints/tendons		
Tendon rubs	39/290 (13)	0
Myositis	17/290 (6)	0
Myalgia	62/290 (21)	0
Muscle weakness	69/290 (24)	0
Arthralgia	151/290 (52)	0
Arthritis	51/290 (18)	0
Flexion contractures	79/290 (27)	0
Acro-osteolysis	61/290 (21)	0
3 Skin		
Scleredema	157/290 (54)	0
Skin sclerosis	274/290 (94)	0
Melanoderma	100/290 (34)	0
Telangiectasia	193/290 (67)	0
Calcinosis	76/290 (26)	0
Atrophic skin ulcers	117/290 (40)	0
Vasculitic lesions	19/290 (7)	0
Sicca syndrome*	77/290 (27)	0
Sicca syndrome†	165/290 (57)	0
4 Lung		
Dyspnoea	179/290 (62)	0
Interstitial involvement	127/171 (74)	119
x Ray	84/132 (64)	158
CT¶ scan	89/105 (85)	185
Reduced T$_{LCO}$¶	144/285 (51)	5
Reduced FVC¶	69/252 (27)	38
5 Heart		
Heart involvement‡	61/290 (21)	0
Heart failure	9/290 (3)	0
6 Peripheral vascular system		
Hypertension	53/290 (18)	0
Raynaud's phenomenon	266/290 (92)	0
Digital pitting	181/290 (62)	0
Digital necrosis	50/290 (17)	0
7 Gastrointestinal apparatus		
Oesophageal involvement	229/290 (79)	0
Diarrhoea	31/290 (11)	0
8 Kidney involvement§	52/290 (18)	0
9 Nervous system		
Headache/trigeminal neuropathy	25/290 (9)	0
Depression	44/290 (15)	0
10 Laboratory parameters		
10.1 Immunological tests:		
ANA¶	233/249 (94)	41
ACA¶	57/253 (23)	37
Scl-70	116/269 (43)	21
aCL¶	22/215 (10)	75
RF¶ test	53/231 (23)	59
10.2 Routine laboratory tests:		
ESR¶ >30 mm/1st h	71/273 (26)	17
High CRP¶	34/239 (14)	51
High LDH¶	23/210 (11)	80
High CK¶	18/234 (8)	56
Low C3/C4	33/233 (14)	57

*Both xerostomia and xerophthalmia.
†Either xerostomia or xerophthalmia.
‡Either pericardial involvement or arrhythmias or conduction defects.
§Either proteinuria or haematuria or increased creatininaemia.
¶CT = computed tomography; T$_{LCO}$ = carbon monoxide transfer factor; FVC = forced vital capacity; ANA = antinuclear antibodies; ACA = anticentromere antibodies; aCL = anticardiolipin antibodies; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; LDH = lactic dehydrogenase; CK = creatine kinase.

limited form of the disease. Table 5 shows the demographic features of the patients by disease subset. A significant difference was seen in the mean disease duration, when evaluated from the onset of Raynaud's phenomenon (13 *v* 8 years), and in the mean age at enrolment (55 *v* 49 years) between patients with lSSc and dSSc.

An analysis of variance showed a significant variation between centres in epidemiological parameters (fig 1), including the age at enrolment, the disease duration from the onset of the Raynaud's phenomenon, and the male to female ratio, which ranged from 1/2 to 1/20. In addition, significant differences emerged in

Table 7 Prevalence of the different clinical and serological features among the two disease subsets

Manifestation (%)	lSSc	dSSc
1 Generalised complaints	53	60
2 Joints/tendons	70	88
Tendon rubs	*6*	*23*
Myositis	5	6
Myalgia	20	24
Muscle weakness	21	27
Arthralgia	51	60
Arthritis	17	17
Flexion contractures	*16*	*46*
Acro-osteolysis	*16*	*29*
3 Skin	100	100
Scleredema	56	51
Skin sclerosis	94	95
Melanoderma	*23*	*51*
Telangiectasia	65	68
Calcinosis	29	22
Atrophic skin ulcers	38	43
Vasculitic lesions	5	9
Sicca syndrome*	28	25
4 Heart/lung	90	93
Dyspnoea	58	67
Interstitial involvement (*x* ray)	67	72
Reduced FVC†	*16*	*44*
Reduced TLCO†	*45*	*58*
Heart failure	3	3
5 Peripheral vascular system	96	97
Arterial hypertension	19	17
Raynaud's phenomenon	92	91
Digital pitting	62	62
Digital necrosis	*13*	*22*
6 Gastrointestinal apparatus	76	81
Diarrhoea	11	10
7 Nervous system	26	19
Headache/trigeminal neuropathy	11	5
Depression	16	15
8 Routine laboratory tests		
ESR† >30 mm/1st h	25	27
High CRP†	11	19
High LDH†	10	12
High CK†	7	9
Low C3/C4	13	16

*Both xerostomia and xerophthalmia.
† FVC = forced vital capacity; TLCO = carbon monoxide transfer factor; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; LDH = lactic dehydrogenase; CK = creatine kinase.

subset distribution, the lSSc to dSSc ratio ranging from 5/1 to 1/2.5.

Figure 2 shows the prevalence of organ involvement as reported in the patients'
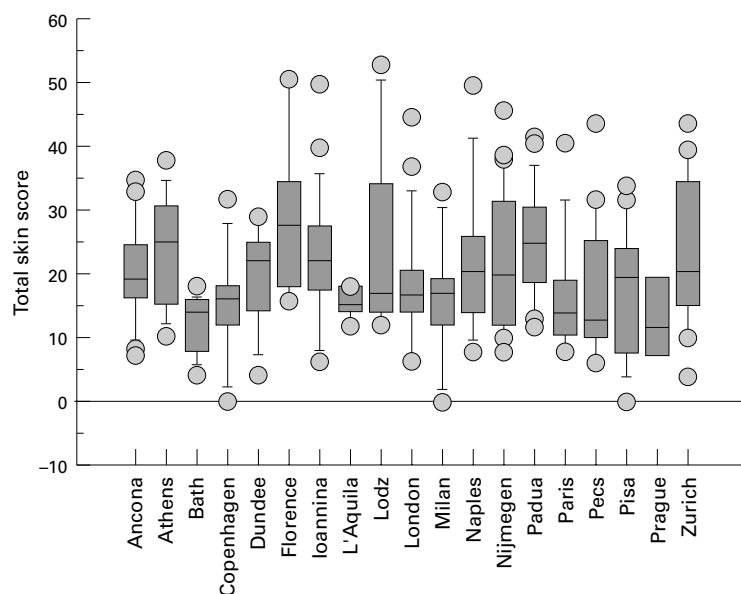

Figure 3 Distribution of the total skin score among the different centres. In the box plots the 10th, 25th, 50th (median), 75th, and 90th centiles for each variable are shown. Values above the 90th and below the 10th centiles are plotted as points.

histories collected at the time of entry into the study. Significant differences (data not shown) emerged in the prevalence of various disease manifestations—namely, gut, lung, heart, kidney, joint, and muscle involvement, while the prevalence of skin sclerosis and Raynaud's phenomenon showed a slight difference only. Of course, a number of these differences must be ascribed to different investigative methods. Nevertheless, the detected differences in sex, age, subset distribution, and clinically detectable manifestations, such as joint involvement, point to actual diversities among different centre series.

CLINICAL AND SEROLOGICAL FEATURES AT THE TIME OF ENROLMENT
Table 6 shows the clinical features reported for the 290 patients at enrolment. The most common findings were skin sclerosis, Raynaud's phenomenon, interstitial lung involvement, and oesophageal involvement. Skin sclerosis was found in 274 patients. Therefore, about 6% of the cases could be diagnosed as SSc without scleroderma. Kidney involvement (that is, either proteinuria or haematuria or increased creatininaemia) was detected in 52/290 (18%) of the patients, but no cases of renal crisis were recorded. Table 6 clearly shows that several items were characterised by a high number of missing values. This was particularly true for investigations to detect internal organ involvement. Despite these limitations, however, the figures for clinically detectable manifestations, such as scleredema, melanoderma, arthritis etc, must be considered reliable, each observer being an experienced clinician in scleroderma to whom clear cut guidelines had been provided.

When patients were compared by disease subset (dSSc *v* lSSc), statistically significant differences in some of the clinical and serological manifestations were found (table 7; data shown in italics). Patients with dSSc had more severe skin involvement, associated with a higher frequency of functional impairment (that is, flexion contractures), tendon friction rubs, melanoderma, acro-osteolysis, digital necrosis, and reduced forced vital capacity and carbon monoxide transfer factor.

An analysis was carried out to elicit any differences between the centres in the prevalence of clinically detectable manifestations. A high degree of variability was found among centres in the reported frequency of various disease manifestations (figs 3 and 4). On the whole, the greatest variation was seen in the parameters of scleredema, melanoderma, calcinosis, and digital infarcts. As already stated, these items had been so carefully defined and actually are so easy to detect that the differences which emerged are to be considered true. On the other hand, the differences which emerged in the prevalences of interstitial lung involvement, oesophageal involvement, and autoantibody profile may depend on differing investigational tools.

TREATMENT
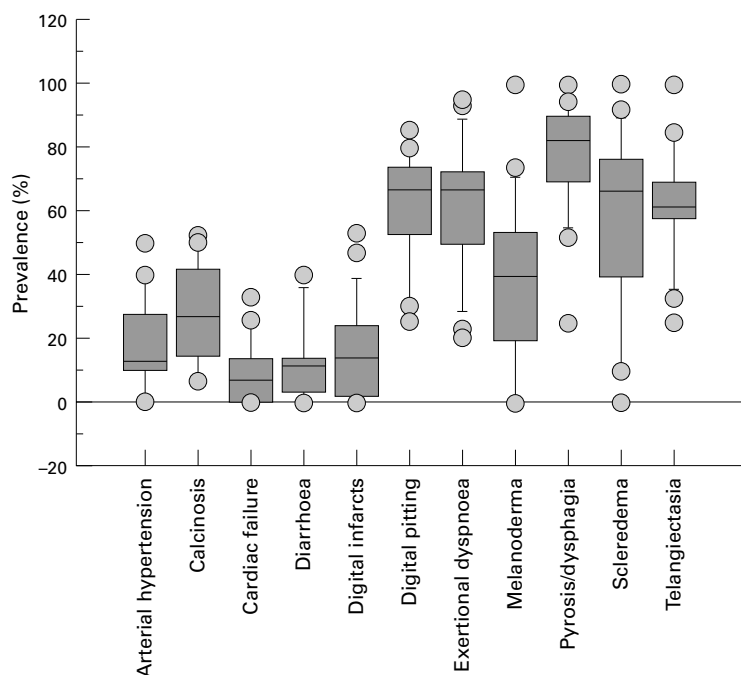Figure 5 shows the treatment prescribed by the participating clinicians at the time of the first

Figure 4   Distribution of clinical features among the different centres as emerged by data collected in section II (clinical and instrumental investigations carried out at the entry into the study). In the box plots the 10th, 25th, 50th (median), 75th, 90th centiles for each variable are shown. Values above the 90th and below the 10th centiles are plotted as points.
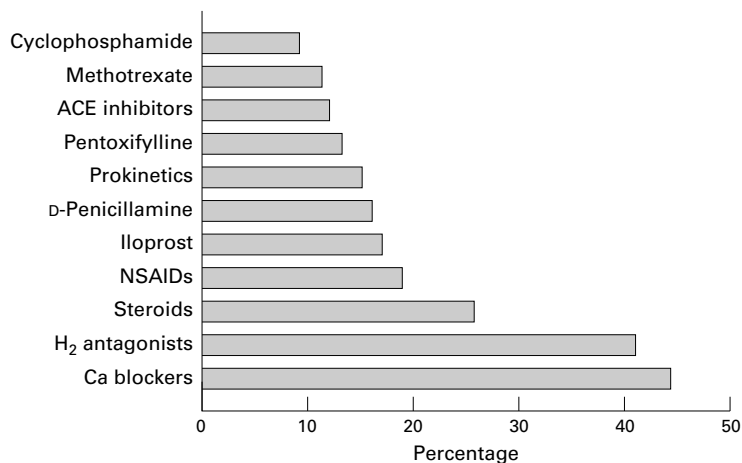

Figure 5   Drug treatment being used in the patient series at the time of enrolment.

observation. The vast majority of the patients were being treated symptomatically with calcium channel blockers or other vasodilators, H$_2$ antagonists, corticosteroids, or non-steroidal anti-inflammatory drugs. Only a small number of patients were receiving disease modifying drugs such as methotrexate, D-penicillamine, or cyclophosphamide. Considerable variation was seen in the therapeutic approach between different centres (fig 6). Only the use of H$_2$ antagonists/omeprazole was consistent across different centres. These results may depend on the differences referred to above among patients from various centres. Nevertheless, different therapeutic approaches also exist.

Discussion
The aim of this multicentre European study, which is still continuing, will be to develop a valid set of disease criteria for SSc based on

clinical data collected in a standardised manner on a large number of patients. Here we report the results of our analysis of the data gathered during the first phase of this study (patient history and evaluation at enrolment). The epidemiological and clinical serological findings for our series of 290 patients seem to be similar to data previously reported by others (tables 8 and 9). However, the data furnished by the 19 centres were far from homogeneous. The complex picture presented by SSc, characterised by a high variability in its clinical manifestations and treatment modalities, has already been discussed by other authors,[12–15 27] though not in the light of rigorously designed, large scale studies.

Our prospective study, in which all of the centres were required to follow the same clearly defined protocol, clearly demonstrates the magnitude of the problem presented by this disease. The epidemiological variability observed as well as the high variability in the reported incidence of clinical features (such as calcinosis, scleredema, scleroderma, telangiectasia) may be ascribed to differences in the nature of the participating centres. It would be hard to believe that experienced clinicians might have failed to detect single manifestations such as melanoderma, digital necrosis, etc. On the other hand, the high number of missing values concerning most investigative methods prevents us from discussing the differences detected in the internal organ involvement. Nevertheless, the absence of patients with scleroderma renal crisis in our series deserves some comments. This complication has been identified as one of the leading causes of death in the North American series.[8 28 29] However, studies conducted in Europe seem to indicate a lower prevalence.[11 23 30 31] The absence of such a manifestation in our series may depend, however, on the nature of the study protocol, which enrolled consecutive patients and therefore might have excluded more severe cases. As far as kidney disease is concerned, we detected either proteinuria or haematuria or increased creatininaemia in 18% of our patients with SSc. However, we cannot confidently ascribe these alterations to SSc itself, because we did not correct the data for the presence of diabetes, hypertension, and other causes of these alterations.

In conclusion, certain observations may be made about SSc based on the preliminary results of our multicentre study. Despite our study design—which used a standardised chart that included all of the most generally accepted diagnostic parameters for SSc, carefully defined according to authoritative sources—we still found considerable differences between centres in the use of diagnostic tests and the therapeutic approach. This reflects the as yet unstandardised approach to SSc in different countries. To overcome these problems the scientific community will need to draw up a standardised procedure for the management of patients with SSc. This should include a
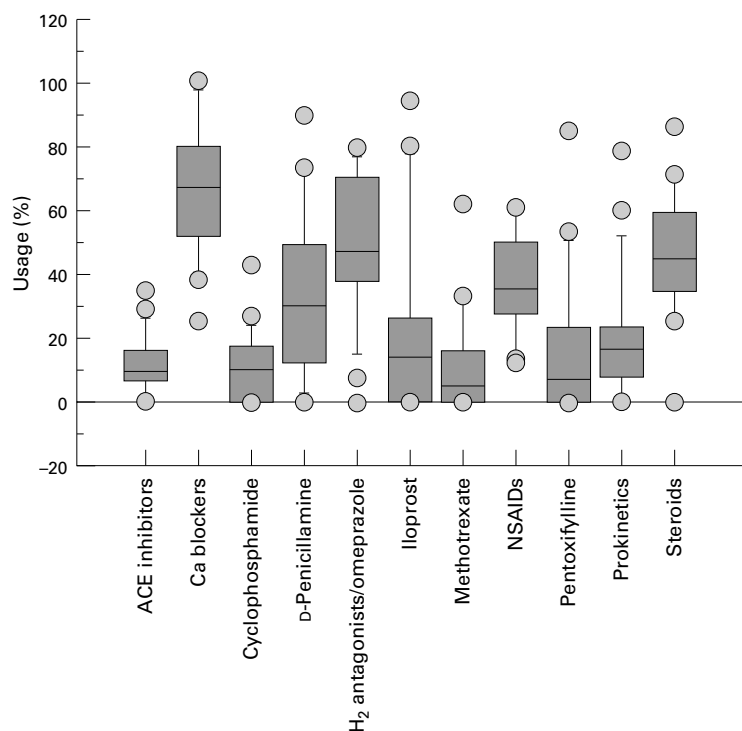
Figure 6 Treatments used by the different centres. In the box plots the 10th, 25th, 50th (median), 75th, and 90th centiles of each variable are shown. Values above the 90th and below the 10th centiles are plotted as points.

precise definition of the major clinical parameters (including the establishment of a consensus on the more controversial aspects of the disease) and the determination of a series of simple and inexpensive diagnostic tests. This would provide a common research tool for different centres engaged in research on this complex disease.

Table 8 Comparison of demographic, clinical, and serological data for the present series with similar data from other European series

	Present series	Vayssairat, et al,[21] Clin Rheumatol, 1992	Jacobsen, et al,[22] Br J Rheumatol, 1998	Nagy and Czirjak,[23] Clin Rheumatol, 1997
Number of patients	290	164	230	171
Women (%)	84	86	82	87
Limited/diffuse SSc	1.5	10	2.8	3.75
Mean age at onset	53	38	44	—
Raynaud's phenomenon (%)	92	100	96	95.3
Digital pitting (%)	62	71	—	—
Telangiectasia (%)	67	75	73	64.3
Calcinosis (%)	26	60	42	11.1
Joint involvement (%)	66	53	18	—
Scleroderma renal crisis (%)	0	—	—	1.2

Table 9 Comparison of demographic, clinical, and serological data for the present series with similar data from other, non-European countries

	Present series	Steen, et al,[24] Arthritis Rheum, 1988	Chandran, et al,[25] Aust New Z J Med, 1995	Kuwana, et al,[26] Arthritis Rheum, 1994
Number of patients	290	397	115*	275†
Women (%)	84	83	84	86
Limited/diffuse/overlap SSc	1.5/1/0	0.9/1/0	6/1/1.6	7 : 5.7 : 3
Mean age at onset	53	42	—	41
Raynaud's phenomenon (%)	92	96	—	98
Digital pitting (%)	62	66	—	25
Telangiectasia (%)	67	82	—	—
Calcinosis (%)	26	39	—	—
Joint involvement (%)	66	64	—	33
Scleroderma renal crisis (%)	0	—	1	—

*SSc was classified in three groups: dc-SSc, lc-SSc, and SSc in overlap.
†SSc was classified in three groups related to the autoantibody profile: dc-SSc, lc-SSc, and SSc in overlap.

Appendix: European Scleroderma Study Group (EScSG)

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