Mod Rheumatol (2004) 14:216–221
DOI 10.1007/s10165-004-0294-5

ORIGINAL ARTICLE

Emi Nishimagi · Yasushi Kawaguchi · Eiichi Tanaka
Masako Hara · Naoyuki Kamatani

Classification of systemic sclerosis in the Japanese population based on rapid progression of skin thickening

Received: July 11, 2003 / Accepted: February 27, 2004

Abstract In general, patients with systemic sclerosis (SSc) have been classified in two clinical subsets (diffuse and limited) based on the extent of skin thickening, and the extent of skin fibrosis is closely related to the severity of organ involvement and mortality rates. In addition, there is a rapid progression of skin thickening in diffuse cutaneous SSc (dcSSc). In this study, we classified a novel subset of SSc based on the rate of skin thickening progression, and evaluated the relationship of the subset to disease severity and laboratory markers. Thirty-three patients with dcSSc were included in the study. Participants who had a modified Rodnan's total skin thickness score higher than 15 points within a year from the first symptoms were defined as having rapidly progressive SSc (RPSSc; group 1), while all the other dcSSc patients were defined as having non-RPSSc (group 2). The frequencies of interstitial lung disease and renal crisis were significantly higher in group 1 than in group 2. The frequencies of antitopoisomerase I antibody (anti-topo I) and anti-SS-A antibody were significantly higher in group 1 than in group 2. Conversely, the frequency of anticentromere antibody was significantly higher in group 2 than in group 1. This study demonstrates the clinical significance of a new subset of SSc (defined as RPSSc), which is characterized by a markedly rapid progression of skin thickening. This new classification may be useful for predicting the prognosis of SSc at an early stage, so that patients who should receive aggressive therapy with immunosuppressants might be identified.

E. Nishimagi · Y. Kawaguchi (✉) · E. Tanaka · M. Hara · N. Kamatani
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1725; Fax +81-3-5269-1726
e-mail: y-kawa@ior.twmu.ac.jp

Key words Classification · Systemic sclerosis (SSc) · Total skin score

Introduction

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology that is characterized by fibrotic change and endothelial damage in the skin.[1] In addition, systemic organ involvement (i.e., interstitial lung disease (ILD), cardiomyopathy, and renal crisis) often accompanies the skin fibrosis. It has been reported that the extent of skin fibrosis is closely related to the severity of organ involvement and to the mortality rates for SSc.[2–6] In 1971, Bennett et al.[2] showed that the presence of truncal skin sclerosis was associated with a poor prognosis. LeRoy et al.[3] proposed two clinical subsets of SSc (diffuse and limited cutaneous types) based on the extent of skin thickening. Medsger et al.[4] and Medsger[5] demonstrated that diffuse cutaneous SSc (dcSSc) has a worse prognosis than limited cutaneous SSc (lcSSc), because dcSSc is more frequently complicated by fibrotic disorders of internal organs. They also reported that there is a significant correlation between the frequency of antitopoisomerase I antibody (anti-topo I) and the incidence of pulmonary fibrosis in dcSSc. These reports indicate that the mortality rates for SSc may be related to the extent of skin fibrosis.

We believe that the rapid progression of skin thickening, as well as its extent, may be an indication of the involvement of some internal organs. In daily clinical practice, we refer to rapid and slow progression of skin thickening in dcSSc. However, the relationship between the time course for the progression of skin fibrosis and disease severity has not been examined. In this study, we propose a novel classification based on the rate of skin thickening, and have defined rapidly progressive SSc (RPSSc) and nonrapidly progressive SSc (non-RPSSc). Our goals are to establish RPSSc as a new subset of SSc, and to clarify the relationship of RPSSc to disease severity.

Materials and methods

Patients

All 33 patients with dcSSc who were admitted to Aoyama Hospital, Tokyo Women's Medical University, between 1993 and 2000 were enrolled in this study with informed consent. All the SSc patients (31 women and 2 men; mean age 45.5 years; range 19–70 years) were Japanese and met the criteria of the American College of Rheumatology (formerly the American Rheumatism Association),[7] and they were all classified as having dcSSc according to the classification of LeRoy et al.[3] The disease duration on admission was within 60 weeks in all the SSc patients, and observations of the skin lesions were continued for at least 1 year after discharge. When admitted, they underwent several medical examinations and we estimated the likely necessity for treatment. SSc patients who were also diagnosed with systemic lupus erythematosus and/or polymyositis/dermatomyositis, or who had a history of admittance owing to treatment for SSc-related complications, were excluded from the study. The degree of skin thickness was assessed using the modified Rodnan's total skin thickness score (m-Rodnan's TSS; maximum possible score 51).[8]

Classification of a novel clinical subset

Patients who had an m-Rodnan's TSS higher than 15 within a year from the first symptoms (e.g., Raynaud's phenomenon or skin sclerosis) were categorized as having rapidly progressive SSc (RPSSc). This classification was based on the rate of skin thickening, not on the extent of skin thickness. To clarify the different clinical features of the new subset (RPSSc) from those of nonrapidly progressive SSc (non-RPSSc), we divided all the dcSSc patients into two groups: RPSSc as group 1 ($n = 14$), and nonRPSSc ($n = 19$) as group 2.

Assessment of organ involvement

Pulmonary involvement included ILD and pulmonary hypertension. ILD was assessed by chest radiography, high-resolution computed tomography of the chest, and a pulmonary functional test (functional vital volume, FVC). Pulmonary hypertension was defined as a right ventricular systolic pressure (RVSP) greater than 40 mmHg, as assessed by ultrasound cardiography (UCG). Esophageal reflux was estimated by barium esophagography using a multiphasic cine-technique. We estimated SSc-related cardiomyopathy by using the following criteria: multiple patchy defects seen on ^{201}Tl-scintigraphy or the abnormality revealed by electrocardiography (ECG) and UCG. Scleroderma renal crisis (SRC) was the only criteria for renal involvement in this study. SRC was defined as malignant arterial hypertension and/or rapidly progressive renal failure and/or microangiopathic hemolytic anemia (MHA). Patients with hypertension of recent onset without increases in serum creatinine levels or MHA were not categorized as having SRC.

Detection of autoantibodies

All patients in this study were tested for antinuclear antibodies (ANA) using indirect immunofluorescence (IIF) and HEp-2 cells as the antigen substrate (Fanawell Autoantibody Kit, Iatron Laboratory, Tokyo, Japan). The presence of anticentromere antibodies (anti-CENP) was determined by the existence of their distinctive IIF pattern on HEp-2 cells and by enzyme-immunoassay (Mesacup-2 test, MBL, Nagoya, Japan). Autoantibodies to topoisomerase I, U1-RNP, SS-A, and SS-B were determined by double immunodiffusion (DID) against calf thymus extracts using commercially available kits (Medical Biological Lab).

Statistical analysis

The frequencies of autoantibodies were evaluated by a standard χ^2 test. Other clinical laboratory variables were estimated by the Mann–Whitney rank sum test. The results are expressed as the mean SD, and differences are considered to be significant at $P < 0.05$.

Results

Characteristics of patients in each group

There were no significant differences of age or sex between groups 1 and 2 (Table 1). The clinical manifestations and laboratory findings of non-RPSSc patients before admission were confirmed from medical records, and none of the patients with non-RPSSc had a medical history that showed an increase of more than 15 points in m-Rodnan's TSS during the first year after onset. All patients were followed by rheumatologists in an out patient clinic for 1 year after

Table 1. Characteristics of systemic sclerosis (SSc) patients in each group

	Group 1 ($n = 14$)	Group 2 ($n = 19$)
Age in years, mean (range)	44.4 (20–63)	46.3 (19–70)
Sex (n)		
Male	1	1
Female	13	18
Deceased patients 1 year after onset (n)	4	0

Each group is described in Materials and methods. All diffuse cutaneous SSc (dcSSc) patients enrolled in this study were admitted to our hospital. We followed all patients for 1 year after discharge

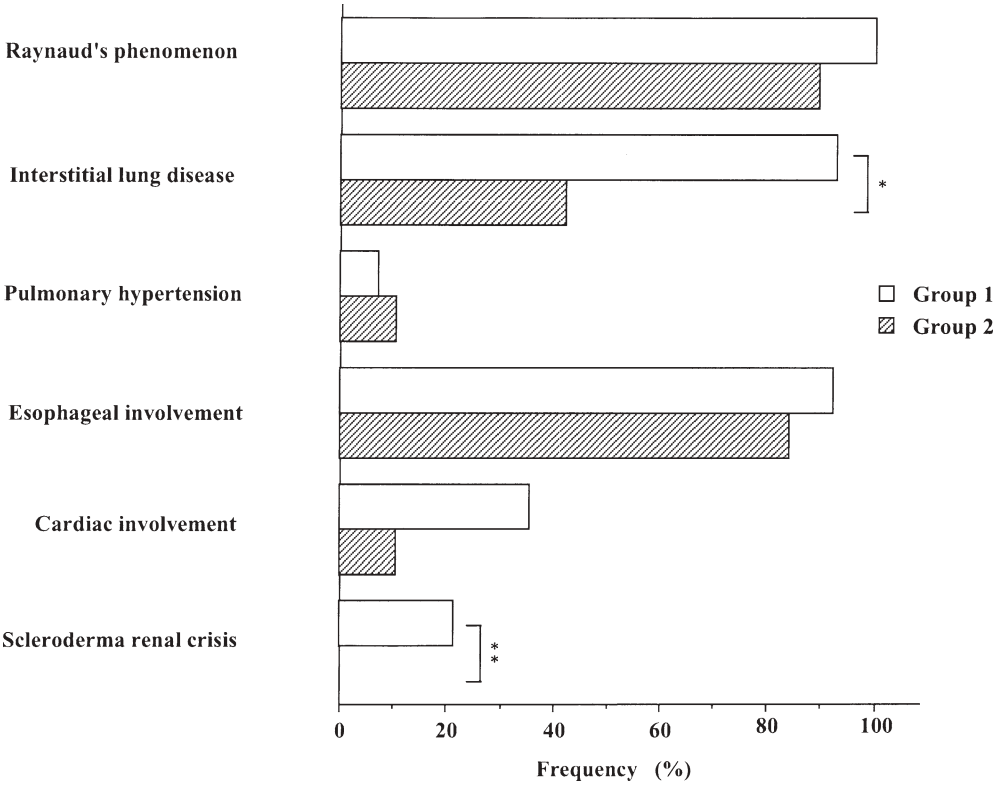

Fig. 1. Frequency of clinical features in rapidly progressive systemic sclerosis (referred to as RPSSc, group 1) and non-RPSSc (group 2). The frequencies of complications of interstitial lung disease and scleroderma renal crisis were higher in group 1 than in group 2. $*P < 0.05$, $**P < 0.0001$ by χ^2 test

discharge from our hospital. During this follow-up, four patients (28.6%) in group 1 died from complications of SSc, while none died in group 2.

Frequencies of complications in each group

To evaluate the frequency of organ involvement in the subsets of RPSSc and non-RPSSc, we compared the frequencies of pulmonary, cardiac, esophageal, and renal involvements in each subset. As shown in Fig. 1, the frequency of ILD was significantly higher in group 1 than in group 2 ($P < 0.05$). The frequency of renal crisis was also significantly higher in group 1 than in group 2 ($P < 0.0001$). Although there was no significant difference, the frequency of cardiomyopathy was much higher in group 1. Our results showed no significant difference in the frequency of Raynaud's phenomenon, pulmonary hypertension, and esophageal reflux between groups.

Comparison of laboratory parameters between groups

As shown in Table 2, WBC counts were significantly higher in group 1 than in group 2 ($P < 0.05$), and serum levels of C-reactive protein (CRP) were significantly higher in group 1 than in group 2 ($P < 0.01$). The level of functional vital capacity/predicted vital capacity (%VC) was significantly decreased in group 1 compared with group 2 ($P < 0.01$).

Table 2. Laboratory parameters

Variable	Group 1 ($n = 14$)	Group 2 ($n = 19$)
WBC ($\times 10^3$)/mm^3	7.7 ± 3.3*	6.1 ± 2.7
Hb (g/dl)	13.4 ± 6.2	11.9 ± 2.3
Plt ($\times 10^4$)/mm^3	27.4 ± 8.1	23.5 ± 7.6
BUN (mg/dl)	14.6 ± 5.4	16.5 ± 13.8
Cr (mg/dl)	0.7 ± 0.2	0.8 ± 0.5
LDH (IU/ml)	441.4 ± 402.2	268.4 ± 86.1
ICclq (g/ml)	3.1 ± 3.8	2.3 ± 1.7
CH_{50} (U/ml)	42.9 ± 6.0	40.5 ± 6.4
CRP (mg/dl)	1.6 ± 2.0**	0.5 ± 1.5
%VC	71.9 ± 18.4**	91.1 ± 13.2

Each group is described in Materials and methods
$*P < 0.05$; $**P < 0.01$ compared with Group 2
Hb, hemoglobin; BUN, blood area nitrogen; Cr, creature; LDH, lactic dehydrogenase; CRP, C-reactive protein; Plt, platelet

Frequencies of autoantibodies in each group

There were no significant differences between the two groups in the numbers of ANA-positive patients (data not shown). As shown in Table 3, the frequency of anti-topo I was significantly higher in group 1 than in group 2 ($P < 0.05$). Conversely, the frequency of anti-CENP was significantly lower in group 1 than in group 2 ($P < 0.05$), as expected. Group 1 showed a significantly higher frequency of anti-SS-A antibody (anti-SS-A) than group 2 ($P < 0.05$).

Table 3. Frequencies for autoantibodies in the SSc groups

	Topo I	U1-RNP	CENP	SS-A	SS-B
Group 1	9 (64.3)	2 (14.3)	0	7 (50)	1 (7.1)
Group 2	5 (26.3) *	4 (21.1)	5 (26.3) *	3 (15.8) *	1 (5.3)

Values are the number (%) of patients
Topo I, antitopoisomerase I antibody; CENP, anticentromere antibody
* $P < 0.05$ by Mann–Whitney rank sum test

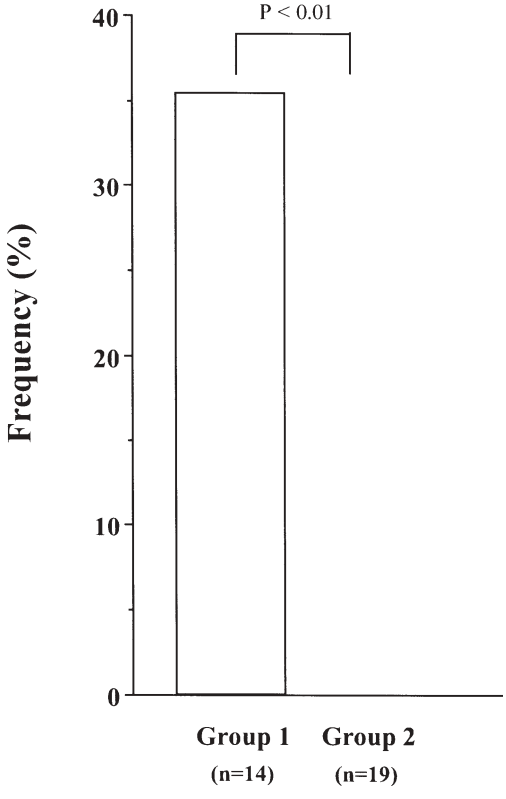

Fig. 2. Frequency of the coexistence of anti-SS-A antibody (anti-SS-A) and antitopoisomerase I antibody (anti-topo I) in rapidly progressive systemic sclerosis (referred to as RPSSc, group 1) and non-RPSSc (group 2). The frequency of coexistence of anti-SS-A and anti-topo I was significantly higher in group 1 than in group 2 ($P < 0.01$ by χ^2 test)

Furthermore, we found that there were five patients with both anti-SS-A and anti-topo I (35.7%) in group 1, which was significantly higher than in group 2 (0%, $P < 0.01$), as shown in Fig. 2.

Discussion

We have demonstrated the clinical significance of a novel subset of SSc characterized by markedly rapid progression of skin thickening, and defined as RPSSc. This is the first report that has described a subset of SSc classified by the rate of skin thickening progression. It is clear that dcSSc is composed of two clinical subsets, RPSSc and non-RPSSc, and the two subsets may exhibit different clinical features, since the frequencies of internal organ involvement in RPSSc were significantly higher than in non-RPSSc. We strongly suggest that the rapid progression of skin thickening, in addition to its extent, is an important factor in determining the prognosis of SSc patients. Clements et al.[9] demonstrated that an entry TSS up to 15 was associated with a high risk of early fatal renal and cardiac complications, and that this group had a significantly shortened survival compared with the group with an initial skin score lower than 15. Steen and Medsger[10] demonstrated that severe involvement of the heart, lung, and/or gastrointestinal organs in patients with dcSSc often developed during the first 3 years, and that the survival of patients with severe organ involvement was poor compared with that of patients without such involvement. We think that the patients with poor prognosis in the early phase of dcSSc reported in the United States may be in the same subset as the RPSSc patients we have described in this study. Although we have not shown the longitudinal study for the prognosis and survival rates, the mortality was very poor in RPSSc during the first year of follow-up; mortality rates were 28.6% in RPSSc patients versus 0% in non-RPSSc patients.

Serum CRP levels and WBC counts were significantly higher in RPSSc patients than in non-RPSSc patients. Presumably these results reflect the nonspecific inflammation of tissues in RPSSc patients experiencing the most severe complications such as ILD, arthritis, or myositis. A significant reduction in %VC was consistent with the results of the high frequency of ILD in RPSSc. Based on these findings, we speculate that the elevation of CRP and WBC may be useful indicators to distinguish RPSSc from non-RPSSc, but these indicators are not specific for RPSSc. In the future, we need to investigate which indicators are specific for RPSSc.

Our results showed that the frequency of anti-topo I was significantly higher in RPSSc than in non-RPSSc. Previous investigators showed the relationship between anti-topo I and the existence of diffuse cutaneous fibrosis with internal organ involvement such as ILD, leading to a poor prognosis.[11–14] Moreover, the frequency of anti-SS-A was also high in RPSSc that was not complicated with Sjögren's syndrome (SS) and which met the criteria of Vitali et al.[15] Most of the RPSSc patients with anti-SS-A had anti-topo I simultaneously, and the frequency of anti-SS-A and anti-topo I coexistence was significantly higher in RPSSc patients than in non-RPSSc patients. The coexistence of the two antibodies appeared to be specific to RPSSc. Interestingly, we found that RPSSc patients who were positive for both anti-topo I and anti-SS-A had an extremely high frequency (80%) of cardiomyopathy (data not shown), although the number of patients was very small and limited. Using the DID method, Fujimoto et al.[16] reported that 29 serum samples were positive for anti-SS-A in 263 Japanese patients with SSc, and that the complication of SS was found in 65% of SSc patients who were positive for anti-SS-A. They also showed that the coexistence of anti-topo I and anti-SS-

A was observed in only 9 SSc patients (3.4% of all SSc patients and 9% of anti-topo I-positive SSc patients). It was recently reported in the USA that anti-SS-A was detected in 3 of 19 patients with anti-topo I-positive sera measured by DID.[17] Those previous reports did not determine the clinical characteristics of SSc patients with coexisting anti-topo I and anti-SS-A. In contrast, Kuwana et al.[18] showed that the frequency of Japanese SSc patients positive for anti SS-A was fairly high (37%) in anti-topo I-positive SSc patients using immunoprecipitation.They also reported that the coexistence of anti-topo I and anti-SS-A was associated with the clinical subset without severe lung disease, but they did not determine whether the patients with anti-SS-A were complicated with Sjögren's syndrome. The discrepancy in the frequency of coexistence and the clinical manifestations might be explained by differences in the method of determining autoantibodies, or in the disease population selected by each research group. Immunoprecipitation is much more sensitive to the detection of autoantibodies than the DID method. This study is the first to show that the induction of both autoantibodies may be closely linked to the rapidly progressive skin thickening and severe organ complications in SSc. The contribution of SSc-related autoantibodies to the pathogenesis of the disease remains to be elucidated. It has been considered that an autoimmune response could be initiated by a cross-reaction of antibodies against exogenous infecting agents (i.e., viruses, chemical mediators, or bacteria). The unusual coexistence of anti-topo I and anti-SS-A in RPSSc strongly suggests that there may be a new subset of SSc (RPSSc) which has a pathogenesis that is different from non-RPSSc. In addition, this pattern of autoantibodies is a good indicator for predicting the poor prognosis of RPSSc.

On the other hand, our observations revealed that anti-CENP was seen only in non-RPSSc patients (26.3%). A previous report showed that dcSSc patients with anti-CENP had better prognoses than anti-CENP-negative dcSSc patients,[19] which is consistent with the results in this study. These findings suggest that anti-CENP may show an inverse correlation with the incidence of RPSSc.

Pulmonary fibrosis is now the most frequent cause of death in SSc patients, since angiotensin-converting enzyme inhibitors have reduced the mortality related to renal crisis.[20,21] There are several reports that aggressive therapies with immunosuppressive agents such as cyclophosphamide are likely to be most efficacious for ILD early in the course of the disease.[22–25] More recently, it was reported that high-dose immunosuppressive therapy combined with the infusion of autologous CD34+ peripheral stem cells was very useful for the treatment of severe SSc.[26] However, it is not clear whether these therapies should be used in all SSc patients, because severe complications due to drug toxicity may accompany immunosuppressive therapy. If the patients are classified into a subset of RPSSc in the early stage without severe ILD by the use of our proposal, they should be treated by strong immunosuppressive therapies because the rapidly progressive skin thickening is accompanied by severe multiple organ failure, resulting in an extremely poor prognosis.

In conclusion, this study strongly suggests the importance of a novel classification for the choice of an adequate therapeutic strategy for SSc patients. However, this is only a preliminary report on a new subset of severe dcSSc. In the future, we need to examine whether the severity of organ involvement or the mortality of RPSSc and non-RPSSc patients could be influenced by the progression of skin thickening for a period of more than 5 years, and we must also investigate the prospective and longitudinal trials of strong immunosuppressive therapies for RPSSc.

References

1. Medsger TA Jr. Systemic sclerosis (scleroderma): clinical aspects. In: Koopman WJ, editor. Arthritis and allied conditions. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1590–624.
2. Bennett R, Bluestone R, Holt PJ, Bywaters EG. Survival in scleroderma. Ann Rheum Dis 1971;30:581–8.
3. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification subsets and pathogenesis. J Rheumatol 1988;15:202–5.
4. Medsger TA Jr, Masi AT, Rodnan GP, Benedek TG, Robinson H. Survival with systemic sclerosis (scleroderma): a life-table analysis of clinical and demographic factors in 309 patients. Ann Intern Med 1971;75:369–76.
5. Medsger TA Jr. Scleroderma: recent advances in the treatment of progressive systemic sclerosis. Orthop Rev 1984;13:69–80.
6. Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001;44:2828–35.
7. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
8. Clements PJ, Lachenbruch P, Seibold JR, White B, Weiner S, Martin RW, et al. Inter- and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281–5.
9. Clements PJ, Lachenbruch PA, Swee Chen NG, Simmons M, Sterz M, Furst DE. A semiquantitative measure of cutaneous involvement that improves prediction of prognosis in system sclerosis. Arthritis Rheum 1990;33:1256–63.
10. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;11:2437–44.
11. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994;9:1283–9.
12. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma. Arthritis Rheum 1999;12:2660–5.
13. Diot E, Giraudeau B, Diot P, Degenne D, Ritz L, Guilmot JL, et al. Is anti-topoisomerase I a serum marker of pulmonary involvement in systemic sclerosis? Chest 1999;116:715–20.
14. Kuwana M, Kaburaki J, Mimori T, Kawakami Y, Tojo T. Longitudinal analysis of autoantibody response to topoisomerase I in systemic sclerosis. Arthritis Rheum 2000;43:1074–84.
15. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
16. Fujimoto M, Shimozuma M, Yazawa N, Kubo M, Ihn H, Sato S, et al. Prevalence and clinical relevance of 52-kDa and 60-kDa Ro/SSA autoantibodies in Japanese patients with systemic sclerosis. Ann Rheum Dis 1997;56:667–70.
17. Frank MB, McCubbin V, Trieu E, Wu Y, Isenberg DA, Targoff IN. The association of anti-Ro52 autoantibodies with myositis and scleroderma autoantibodies. J Autoimmun 1999;12:137–42.

18. Kuwana M, Kaburaki J, Arnett FC, Howard RF, Medsger TA, Wright TM. Influence of ethnic background on clinical and serologic features in patients with systemic sclerosis and anti-DNA topoisonerase I antibody. Arthritis Rheum 1999;42:465–74.
19. Muhlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. Semin Arthritis Rheum 1995;24:323–58.
20. Steen VD. Epidemiology of rheumatic disease: systemic sclerosis. Rheum Dis Clin North Am 1990;16:641–54.
21. Lee P, Langevitz P, Alderdize CA, Aubrey M, Baer PA, Baron M, et al. Mortality in systemic sclerosis (scleroderma). QJM 1992; 298:139–48.
22. Steen VD, Lanz JK Jr, Conte C, Owens GR, Medsger TA Jr. Therapy for interstitial lung disease in systemic sclerosis. Arthritis Rheum 1994;9:1290–6.
23. White B, Moore WC, Wigley FM, Xiao HQ, Wise RA. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. Ann Intern Med 2000;132:947–54.
24. Giacomelli R, Valentini G, Salsano F, Cipriani P, Sambo P, Conforti ML, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. J Rheumatol 2002;29:731–6.
25. Pakas I, Ioannidis JPA, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low- or high-dose prednisolone for systemic sclerosis lung disease. J Rheumatol 2002;29:298–304.
26. McSweeney PA, Nash RA, Sullivan KM, Storek J, Dansey R, Mayes MD, et al. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. Blood 2002;100:1602–10.