

Scleroderma: Health Services Utilization from Patients' Perspective

SINDHU R. JOHNSON, SIMON CARETTE, and JAMES V. DUNNE

ABSTRACT. Objectives. To evaluate utilization of the health care system by patients with scleroderma by determining which physicians are diagnosing and following patients, what tests are being used, and what is the time to diagnosis, as measured over the past 3 decades.

Methods. A self-administered questionnaire (available in English and French) was mailed up to twice to 1437 members of 12 provincial chapters of the Scleroderma Society of Canada.

Results. The overall response rate was 63%. Eighty-nine percent of respondents were female. Sixty percent were between the ages of 30 and 59 years. Forty-three percent were diagnosed by a rheumatologist. Among patients with diffuse disease, 90% have been followed by a rheumatologist; however just over half of patients have seen a gastroenterologist (54%), cardiologist (51%), respirologist (67%), and less than half have seen a dermatologist (42%), nephrologist (13%), physiotherapist (46%), or occupational therapist (34%). The mean time to diagnosis over the last 3 decades is 2.4 years. At diagnosis less than 50% of patients had an electrocardiogram, echocardiogram, gastroscopy, thorax CT, or skin thickness measurements, whereas over 50% of patients had a chest radiograph and pulmonary function testing.

Conclusion. Less than half of patients were diagnosed by a rheumatologist, and time to diagnosis from onset of symptoms has remained unchanged over the last 3 decades. Despite their complex, multisystemic disease, less than 50% of patients see sub-specialists or had baseline screening tests for organ involvement of their systemic sclerosis. Further research is needed on health services utilization and on determinants of access to care by patients with scleroderma. (J Rheumatol 2006;33:1123-7)

Key Indexing Terms:

SYSTEMIC SCLEROSIS
ACCESS TO CARE

SCLERODERMA

HEALTH SERVICES UTILIZATION
PATIENT SURVEY

Systemic sclerosis (SSc) is a complex, multisystem, autoimmune disease characterized by fibrotic infiltration of the skin that also often affects the internal organs including the lungs, kidneys, gastrointestinal (GI) tract, and vasculature. It has a prevalence of 2.6 cases per 10,000 and an incidence of up to 18.7 per million people per year^{1,2}.

Internal organ involvement is frequent and can have several manifestations. GI involvement occurs in up to 90% of patients, 50% of whom can be symptomatic³. Pulmonary

manifestations include interstitial lung disease and pulmonary arterial hypertension (PAH) characterized by dyspnea, physical limitation, and untimely death. Indeed, in an observational cohort of 309 patients with SSc, PAH was the leading cause of death in these patients⁴. Although the classically described renal manifestation has been scleroderma renal crisis⁵, mild proteinuria, renal insufficiency, and hypertension can occur in up to 50% of patients^{5,6}. Other systemic manifestations include cardiac disease (myocardial and pericardial disease, arrhythmias)⁷ and erectile dysfunction^{8,9}.

A number of reviews have advocated optimal care for patients with SSc¹⁰⁻¹². Recommendations included specialist care for patients with multisystem disease, baseline and annual target organ testing (pulmonary function tests^{10,11}, echocardiogram, electrocardiogram^{10,11}, and renal function testing^{11,13}), and physical rehabilitation¹⁴, as needed. At face value, these recommendations should be relatively easy to implement in a health care system with universal health care coverage. In Canada, all citizens and landed immigrants have access to primary care, specialist care, and medically necessary investigations, free of cost to the patient. Thus access to appropriate care should not be constrained for socioeconomic reasons.

Our objective was to evaluate use of the health care system by patients with SSc. In particular, we wanted to determine which physicians are diagnosing and following patients and

From the Division of Rheumatology, University Health Network, University of Toronto, Toronto, Ontario and the Division of Rheumatology and Internal Medicine, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

Dr. Johnson is the recipient of a research fellowship award from The Arthritis Society of Canada and the Institute for Musculoskeletal Health and Arthritis, Canadian Institutes for Health Research. Actelion Canada provided financial support to the Scleroderma Society of Canada for costs incurred for questionnaire mailing and French translation of the questionnaire.

S.R. Johnson, MD, FRCPC; S. Carette, MD, FRCPC, Division of Rheumatology, University Health Network, University of Toronto; J.V. Dunne, MB, FRCPC, Division of Rheumatology and Internal Medicine, Department of Medicine, St. Paul's Hospital, University of British Columbia.

Address reprint requests to Dr. J. Dunne, Department of Medicine, St. Paul's Hospital, Vancouver, BC, Canada, V6Z 1Y6.

E-mail: James.Dunne@VCH.ca

Accepted for publication January 5, 2006.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2006. All rights reserved.

what tests are being used and to assess time to diagnosis over the past 3 decades.

MATERIALS AND METHODS

Patients. The Scleroderma Society of Canada (SSC) is the largest patient driven, volunteer, scleroderma advocacy group in Canada. Membership includes patients, family members and friends of patients, and health care professionals with an interest in SSC. Questionnaires were mailed to all members of 12 of the 13 provincial chapters of the SSC (n = 1437). One chapter declined participation. Only questionnaires from patients were included in the analysis.

Questionnaire. After consultation with key stakeholders (patients, pharmacists, physicians, scleroderma researchers) English and French versions of a questionnaire were created to ascertain the demographic profile of patients with SSc, their subset of SSc (limited versus diffuse), family history, type of physician making the diagnosis, and their baseline investigations. The questionnaire was pretested in 30 patients with SSc representing 12 regional chapters of the SSC. Respondents were debriefed to evaluate clarity, face, and content validity. Based on patient feedback, the questionnaire was modified to its final form. Education was categorized as grade school, high school, and post-secondary education (trade school, college, university). Proximity of the patient was dichotomized as living within 100 km versus further than 100 km from a SSc expert. Family history was defined as having a blood relation (first and second degree) with a specified condition. Time to diagnosis was calculated by subtracting year of onset of symptoms from year of SSc diagnosis. Baseline was defined as at the time of or within the same year of diagnosis. Followup was defined as at least one year after diagnosis. A copy of the questionnaire is available on request.

Survey methods. Questionnaire packages containing the questionnaire, prepaid return envelopes, and a cover letter from the SSC or Sclérodémie Québec (containing society letterhead and president's endorsement) were mailed to its 1437 members. Patients self-administered the questionnaire at home. To increase the response rate, a second mailing was sent to non-responders. Professional mailers (CSH Consulting) handled all mail outs. All data were coded and entered into a computer database.

Statistical analysis. Descriptive statistics were used to analyze the data. All data were analyzed using Number Cruncher Statistical System and SAS (version 8.0, Cary, North Carolina, USA).

RESULTS

A response rate of 63% (n = 813/1290) was achieved, excluding patients who were deceased or had moved and were not traceable and members of the organization who were not patients. Eighty-nine percent of respondents were female. Sixty percent of patients were between the ages of 30 and 59 years. Fifty-four percent of respondents had completed a post-secondary education. Fifty-four percent of respondents lived within 100 km of a SSc specialist. The majority (54%) had limited scleroderma, 18% had diffuse disease, and 23% did not know what type of scleroderma they had. Seventy-four percent of patients were between the ages of 30 and 59 years at the time of diagnosis, 28% of whom were 40 to 49 years of age. A family history of scleroderma, rheumatoid arthritis (RA), Raynaud's phenomenon, and pulmonary hypertension were reported in 8%, 27%, 20%, and 9%, respectively (Table 1). A family history of thyroid disease, cancer, psoriasis, heart disease, inflammatory bowel disease, hypertension, obstructive lung disease, and hyperlipidemia were reported in less than 2% of respondents.

Table 1. Demographic characteristics of questionnaire respondents (n = 813).

Characteristic	Percentage
Female	89.4
Current age, yrs	
Under 30	1.5
30–39	5.7
40–49	21.7
50–59	32.1
60–69	25.7
Over 70	13.4
Education level	
Grade school	5.1
High school	41.1
Post secondary education (college/university/trade school)	53.8
Proximity to a scleroderma specialist	
Within 100 km	54.4
Further than 100 km	45.6
Type of scleroderma	
Limited	53.8
Diffuse	18.0
Don't know	23.2
Age at diagnosis, yrs	
Under 30	12.4
30–39	21.5
40–49	27.6
50–59	25.2
60–69	11.0
Over 70	2.4
Family history	
Scleroderma	8.1
Pulmonary hypertension	9.3
Raynaud's phenomenon	19.7
Rheumatoid arthritis	26.8

Forty-three percent of respondents were diagnosed by a rheumatologist. The remaining patients were diagnosed by a family physician (12%), general internist (12%), dermatologist (12%), vascular specialist (3%), or respirologist (1%). Less than 1% of respondents were diagnosed by a gastroenterologist, surgeon, cardiologist, nephrologist, immunologist, oncologist, or dentist. Mean time to diagnosis over the last 3 decades was 2.4 years with no significant change in time to diagnosis over this time period (Table 2). At diagnosis less than 50% of patients had an electrocardiogram, echocardiogram, gastroscopy, computed tomography (CT) of the thorax, or skin thickness measurements (Table 3). Among patients with diffuse disease, 90% have been followed by a rheumatologist; however just over 50% of patients have seen a gastroenterologist (54%), cardiologist (51%), and respirologist (67%) and less than 50% have seen a dermatologist (42%), nephrologist (13%), physiotherapist (46%), or occupational therapist (34%) in consultation (Table 4).

DISCUSSION

The demographic profile of the respondents provides interesting insights. Eighty-nine percent of respondents in this study

Table 2. Average time to diagnosis by decade of questionnaire respondents.

Decade	Number of Patients When Symptoms Developed	Number of Patients When Diagnosis Made	Mean Time to Diagnosis, yrs
1970–1979	88	55	2.0
1980–1989	193	187	2.9
1990–1999	375	381	2.2
> 2000	90	153	2.7
Sub-total	746	776	2.4

Table 3. Proportion of patients with SSc who had a specific investigation at diagnosis.

Investigation	Percentage (n = 813)
Skin thickness measurement	21.6
Chest CT scan	25.0
Bone density	30.2
Gastroscopy	33.7
Barium swallow	38.7
Echocardiogram	44.3
Electrocardiogram	48.5
Pulmonary function tests	61.1
Chest radiograph	67.9

CT: computed tomography.

were female. Although a female preponderance in scleroderma has been described¹, the significantly higher percentage of females in our study may reflect the notion that females tend to participate in support groups more than males^{15,16}. Nearly three quarters of the patients developed SSc between the ages of 30 and 59 years, and this is consistent with the literature¹⁷. This finding highlights that SSc predominantly occurs during the prime of one's working life.

Interestingly, 8% of patients reported a blood relative with SSc. Although there has been some evidence to suggest familial aggregation of SSc^{2,18}, such a high percentage has not been reported to our knowledge. Genetic analysis of the Choctaw Indians suggests a genetic component to SSc¹⁹. However,

Assassi, *et al* point out that a shared environmental factor may also be partly responsible for familial aggregation²⁰. Furthermore, in our study 9% of respondents reported a blood relation with pulmonary hypertension. A recent registry study of patients with familial primary pulmonary hypertension has suggested that familial primary pulmonary hypertension is under-diagnosed²¹. This may also be the case with family members of patients with SSc. Due to the anonymity of the questionnaire responses, we were unable to perform a clinic chart review or patient interview to confirm the validity of responses that study participants reported. Further investigation into these findings is needed. If indeed true, screening of family members may allow for early intervention that could affect prognosis.

Less than 50% of the respondents underwent skin thickness measurement, CT thorax, gastroscopy, barium swallow, echocardiography, or electrocardiogram at diagnosis. Similarly, less than 50% of the respondents with diffuse disease have seen a nephrologist, dermatologist, or physio- or occupational therapist, and just over half of respondents have seen a cardiologist or gastroenterologist in consultation. The low numbers of patients with SSc receiving baseline screening tests or specialist consultation may partially reflect the fact that testing/consultation was not required. For example, a patient with normal serum creatinine and urinalysis would not require consultation with a nephrologist. Alternatively, these low percentages may also reflect under utilization and inadequate access to care for patients with SSc. This is concerning in light of recent guidelines regarding the optimal care of

Table 4. Proportion of patients with SSc who have seen a health professional.

Specialty	Limited Scleroderma (n = 397)		Diffuse Scleroderma (n = 178)		Don't Know (n = 238)	
	Baseline n (%)	Followup n (%)	Baseline n (%)	Followup n (%)	Baseline n (%)	Followup n (%)
Family physician	322 (81)	323 (81)	144 (81)	143 (80)	182 (76)	180 (76)
Dermatologist	209 (53)	150 (38)	57 (32)	74 (42)	85 (36)	79 (33)
Rheumatologist	266 (67)	327 (82)	142 (80)	161 (90)	151 (63)	164 (69)
Respirologist	75 (19)	195 (49)	55 (31)	119 (67)	63 (26)	94 (40)
Cardiologist	44 (11)	123 (31)	30 (17)	90 (51)	29 (12)	53 (22)
General internist	116 (29)	141 (36)	51 (29)	60 (34)	36 (23)	8 (3)
Nephrologist	15 (4)	30 (8)	11 (6)	24 (13)	4 (2)	14 (6)
Gastroenterologist	57 (14)	173 (44)	23 (13)	96 (54)	18 (12)	76 (32)
Physiotherapist	–	126 (32)	–	82 (46)	–	74 (31)
Occupational therapist	–	67 (17)	–	61 (34)	–	37 (16)

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2006. All rights reserved.

patients with SSc. Indeed, the American College of Chest Physicians evidence-based clinical practice guidelines, also endorsed by the American College of Rheumatology, suggest that all patients with SSc should have annual echocardiograms and pulmonary function testing (PFT)²². Furthermore, because of the clinically important risk of interstitial lung disease in these patients, PFT for the first 5 years of followup should be done. Further research is needed into potential determinants of access to care by patient with SSc, particularly at the patient, primary care physician, and specialist levels.

Our results suggest that concerted efforts are needed to improve management of patients with SSc, and this can begin at the level of the patient. Patient advocacy groups have begun^{23,24} and should continue to promote education of their members. Ninety-five percent of respondents in our study had at least high school education and were predominantly Caucasian women. Patient advocacy groups should consider methods of extending education and support to other segments of the SSc population. Potential interventions include gender specific educational material (e.g., discussion of erectile dysfunction as a manifestation of SSc) and provision of non-English educational material for centers with a multicultural population. A French multicenter study of patients with ankylosing spondylitis (AS) found the need for disease specific education was greater in those patients with limited formal schooling²⁵. This may also be the case for patients with SSc. These issues should be taken into consideration during the preparation of educational and support resources.

Concerted efforts should also be directed at the primary care physician. A 1993 survey of primary care physicians showed low rates of referral to medical and non-medical specialists for patients with RA and low confidence in performing a comprehensive musculoskeletal examination. Indeed, in many countries, there is little exposure to rheumatology training in either medical education or post-graduate medical training^{26,27}. Gaps in training may result in suboptimal management practices including delays in diagnosis, investigation, and intervention^{28,29}. Effects of delayed referral have been documented in other connective tissue diseases including AS and RA³⁰. Specialist care is usually indicated as disease modifying agents are most often initiated and monitored by rheumatologists³¹. Lack of referral or late referral of patients with SSc may have implications for response to therapy and prognosis.

Primary care physicians may also face barriers in access to specialized care for SSc patients. More than 50% of respondents in a physician survey reported access barriers to obtaining timely consultation with medical and rehabilitation specialists for patient with RA. Barriers to services for patients with SSc may include situations where services are not available, services are available but waiting or travel times are unacceptably long, or services are available but physicians have no confidence in them³². Future research and policy implications may include the need to improve primary care training and expand access to specialist care.

Finally, efforts should also be directed at the specialist.

Although no disease modifying agent has yet been shown to cure SSc, there are now effective treatments to prevent or slow down complications. Morbidity and mortality of scleroderma renal crisis has improved with the use of angiotensin-converting enzyme inhibitors³³. The use of proton pump inhibitors has improved the morbidity of reflux esophagitis. The use of prostacyclin analogs, endothelin receptor antagonists, and cyclophosphamide have been shown to improve hemodynamics, exercise capacity, and/or symptoms in patients with SSc lung disease³⁴⁻³⁷. However, there appears to be some variation within the rheumatology community regarding the utilization of diagnostic tests and therapeutic interventions. A recent survey found both bronchoalveolar lavage (for interstitial lung disease) and right heart catheterization (for PAH) are used significantly more often by rheumatologists with more than 10 patients with SSc under their care³⁸. The same held true for medication related to treatment of these 2 pulmonary components of SSc. In general, specialists who care for higher numbers of patients with SSc tend to make more frequent use of gold standard testing³⁸. Furthermore, in light of the complex care of such patients, it has been suggested that a multidisciplinary approach to scleroderma should be the new standard of care³⁹. Additional longitudinal research is needed to determine if earlier diagnosis and treatment in this patient group results in improved outcomes.

There are potential limitations to consider in the interpretation of our study results that may affect their internal and external validity. One potential threat to the internal validity of all patient surveys is the accuracy of the data the respondents describe. In our study the percentage of patients with a family history of RA and pulmonary hypertension was much higher than the percentage of patients with a family history of heart disease. Recall bias may have affected patients' responses to questions. The anonymity of questionnaire responses prevented us from verifying responses by other means. Another potential threat to the generalizability of these results is the response rate. Although our study had a respectable response rate compared to other patient surveys, selection bias among responders may skew results. Characteristics of the non-responders in this study are unknown. However, with a sample size of 813, this study is the largest scleroderma patient survey to our knowledge. Our results indicate a number of provocative findings and provide data for hypothesis generation for future research.

Our findings indicate that low percentages of scleroderma patients are receiving specialist care or investigations for systemic effects of scleroderma at baseline. Despite advances in the understanding of scleroderma and medical technology, time to diagnosis appears to have remained unchanged over the past 3 decades. Further research is needed to determine potential reasons for these findings including research evaluating determinants of access to care, at the patient, primary care physician, and specialist levels.

A number of actions can be taken as a consequence of these study results. Scleroderma patient advocacy groups should

consider strategies to target the varied demographic segments of the scleroderma population and consider further development of educational and support material for their members. At the level of the primary care physician and specialist, policy implications may include improvement of primary care training and continuing medical education strategies, and expand access to specialist care. Only through further research in these areas can the complete care of patients with scleroderma be optimized and improved.

REFERENCES

1. Mayes MD. Scleroderma epidemiology. *Rheum Dis Clin North Am* 2003;29:239-54.
2. Arnett FC, Cho M, Chatterjee S, Aguilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. *Arthritis Rheum* 2001;44:1359-62.
3. Young MA, Rose S, Reynolds JC. Gastrointestinal manifestations of scleroderma. *Rheum Dis Clin North Am* 1996;22:797-823.
4. Scussel-Lonzetti L, Joyal F, Raynauld JP, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine Baltimore* 2002;81:154-67.
5. Traub YM, Shapiro AP, Rodnan GP, et al. Hypertension and renal failure (scleroderma renal crisis) in progressive systemic sclerosis. Review of a 25-year experience with 68 cases. *Medicine Baltimore* 1983;62:335-52.
6. Livi R, Teghini L, Pignone A, Generini S, Matucci-Cerinic M, Cagnoni M. Renal functional reserve is impaired in patients with systemic sclerosis without clinical signs of kidney involvement. *Ann Rheum Dis* 2002;61:682-6.
7. Janosik DL, Osborn TG, Moore TL, Shah DG, Kenney RG, Zuckner J. Heart disease in systemic sclerosis. *Semin Arthritis Rheum* 1989;19:191-200.
8. Hong P, Pope JE, Ouimet JM, Rullan E, Seibold JR. Erectile dysfunction associated with scleroderma: a case-control study of men with scleroderma and rheumatoid arthritis. *J Rheumatol* 2004;31:508-13.
9. Johnson SR, Dewar C. Erectile dysfunction and scleroderma. *J Rheumatol* 2004;31:2091-2.
10. Denton CP, Black CM. Scleroderma—clinical and pathological advances. *Best Pract Res Clin Rheumatol* 2004;18:271-90.
11. Denton CP. Overview of the treatment and prognosis of scleroderma adults. In: Rose BD, editor. *UpToDate*. Wellesley, MA: UpToDate, 2005.
12. Silver RM, Clements PJ. Interstitial lung disease in systemic sclerosis: Optimizing evaluation and management. *Scleroderma Care Res* 2003;1:3-11.
13. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000;43:2437-44.
14. Askew LJ, Beckett VL, An KN, Chao EY. Objective evaluation of hand function in scleroderma patients to assess effectiveness of physical therapy. *Br J Rheumatol* 1983;22:224-32.
15. Krizek C, Roberts C, Ragan R, Ferrara JJ, Lord B. Gender and cancer support group participation. *Cancer Pract* 1999;7:86-92.
16. Lasker JN, Sogolow ED, Sharim RR. The role of an online community for people with a rare disease: content analysis of messages posted on a primary biliary cirrhosis mailing list. *J Med Internet Res* 2005;7:e10.
17. Laing TJ, Gillespie BW, Toth MB, et al. Racial differences in scleroderma among women in Michigan. *Arthritis Rheum* 1997;40:734-42.
18. Englert H, Small-McMahon J, Chambers P, et al. Familial risk estimation in systemic sclerosis. *Aust N Z J Med* 1999;29:36-41.
19. Zhou X, Tan FK, Wang N, et al. Genome-wide association study for regions of systemic sclerosis susceptibility in a Choctaw Indian population with high disease prevalence. *Arthritis Rheum* 2003;48:2585-92.
20. Assassi S, Mayes MD. The genetics of scleroderma. What every rheumatologist should know. *Scleroderma Care Res* 2003;1:3-11.
21. Newman JH, Wheeler L, Lane KB, et al. Mutation in the gene for bone morphogenetic protein receptor II as a cause of primary pulmonary hypertension in a large kindred. *N Engl J Med* 2001;345:319-24.
22. McGoon M, Guterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:14S-34S.
23. Fahlman N. Scleroderma: Managing scleroderma. Scleroderma Society of Canada; 2004.
24. Edworthy S. Scleroderma: Medical tests. Scleroderma Society of Canada; 2004.
25. Claudepierre P, Flipo RM, Sibilia J, et al. Patient knowledge of their disease: a French multicenter study in ankylosing spondylitis. *Joint Bone Spine* 2004;71:550-6.
26. Goldenberg DL, Mason JH, De Horatius R, et al. Rheumatology education in United States medical school. *Arthritis Rheum* 1981;24:1561-6.
27. Renner BR, DeVellis BM, Ennett ST, et al. Clinical rheumatology training of primary care physicians: the resident perspective. *J Rheumatol* 1990;17:666-72.
28. Bolumar F, Ruiz MT, Hernandez I, Pascual E. Reliability of the diagnosis of rheumatic conditions at the primary health care level. *J Rheumatol* 1994;21:2344-8.
29. Stross JK, Bole GG. The impact of a new rheumatologist on the management of rheumatic disease patients in community hospitals. *Arthritis Rheum* 1983;26:1033-6.
30. Kidd BL, Cawley MI. Delay in diagnosis of spondylarthritis. *Br J Rheumatol* 1988;27:230-2.
31. Shipton D, Glazier RH, Guan J, Badley EM. Effects of use of specialty services on disease-modifying antirheumatic drug use in the treatment of rheumatoid arthritis in an insured elderly population. *Med Care* 2004;42:907-13.
32. Williams JI, Badley EM. The role of primary care physicians in treating arthritis. In: Williams JI, Badley EM, editors. *Patterns of health care in Ontario. Arthritis and related conditions. An ICES practice atlas*. Toronto: Institute for Clinical Evaluative Sciences, 1998:63-92.
33. Steen VD, Medsger TA, Jr. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000;133:600-3.
34. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
35. Badesch DB, Tapsos VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425-34.
36. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.
37. Clements P, Furst D, Silver R, et al. The scleroderma lung study shows the beneficial effects of cyclophosphamide over placebo in systemic sclerosis [abstract]. *Arthritis Rheum* 2005;52 Suppl:S257.
38. Khanna D, Clements PJ, Furst D, Park G, Merkel PA. Diagnostic and management preferences for lung disease in scleroderma: results of survey of rheumatologists. *Scleroderma Care Res* 2004;2:3-11.
39. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62:1088-93.