My Approach to the Treatment of Scleroderma

Ami A. Shah, MD, MHS, and Fredrick M. Wigley, MD

Abstract

Systemic sclerosis (scleroderma) is unique among the rheumatic diseases because it presents the challenge of managing a chronic multisystem autoimmune disease with a widespread obliterative vasculopathy of small arteries that is associated with varying degrees of tissue fibrosis. The hallmark of scleroderma is clinical heterogeneity with subsets that vary in the degree of disease expression, organ involvement, and ultimate prognosis. Thus, the term *scleroderma* is used to describe patients who have common manifestations that link them together, whereas a highly variable clinical course exists that spans from mild and subtle findings to aggressive, life-threatening multisystem disease. The physician needs to carefully characterize each patient to understand the specific manifestations and level of disease activity to decide appropriate treatment. This is particularly important in treating a patient with scleroderma because there is no treatment that has been proven to modify the overall disease course, although therapy that targets specific organ involvement early before irreversible damage occurs improves both quality of life and survival. This review describes our approach as defined by evidence, expert opinion, and our experience treating patients. Scleroderma is a multisystem disease with variable expression; thus, any treatment plan must be holistic, yet at the same time focus on the dominant organ disease. The goal of therapy is to improve quality of life by minimizing specific organ involvement and subsequent life-threatening disease. At the same time the many factors that alter daily function need to be addressed, including nutrition, pain, deconditioning, musculoskeletal disuse, comorbid conditions, and the emotional aspects of the disease, such as fear, depression, and the social withdrawal caused by disfigurement.

 ■ Mayo Clin Proc. 2013;88(4):377-393

Scleroderma is considered a rare disease, with an estimated prevalence in the United States of 276 to 300 cases per million[1-3] and an incidence of approximately 20 cases per million per year.[2] Females are more commonly affected than males (4.6 to 1),[2] and it tends to be more severe among African Americans and Native Americans than white people.[4,5] It is rare in children, with a peak age at onset of approximately 45 to 60 years, and has a worse prognosis in older individuals; for example, an increased risk for developing pulmonary hypertension (PH) exists with late-age disease onset (>65 years).[6,7] Scleroderma is a complex polygenetic disease. A recent genome-wide association study confirmed a strong association with the major histocompatibility complex and autoimmunity.[8] Multicase families are uncommon but occur with a relative risk among first-degree relatives of 13 (95% CI, 2.9-48.6; $P<.001$), with a recurrence rate of 1.6% within families vs 0.026% in the general population.[9] A study of twin pairs reported an overall concordance rate of disease in only 4.7%, a rate that is the same for both monozygotic and dizygotic pairs.[10] Only circumstantial evidence has implicated certain environmental triggers, including silica[11] and solvents.[12] An immune response to cancer is likely another trigger for the disease in a subset of patients.[13]

Scleroderma causes significant physical distress, is disfiguring, and can decrease normal life expectancy. The 10-year survival has reportedly improved from the 1970s (54%-60%) to the 1990s (66%-78%).[14,15] This improvement is likely due to earlier disease detection and better management of specific organ disease, especially the successful treatment of scleroderma renal crisis (SRC) with angiotensin-converting enzyme (ACE) inhibitors. Risk factors for increased mortality include African American race, later age at disease onset, the presence of interstitial lung disease (ILD) or PH, and higher levels of modified Rodnan skin score or rapid progression of skin disease.[2,14,16,17] Scleroderma often causes significant disability and general poor quality of life (QOL).[18-20] Dissatisfaction with appearance and social discomfort

From the Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD.

due to distress from body image are common and often not properly managed.[21,22]

MAKING A DIAGNOSIS

Early detection of scleroderma provides the opportunity to manage the disease process before damage and fibrosis lead to organ failure and poor outcomes. The most common first sign of scleroderma is Raynaud phenomenon (RP), a clinical problem of cold- and stress-induced vasospasm of the digital arteries and cutaneous arterioles involved in body thermoregulation. Raynaud phenomenon occurs for a variety of reasons in approximately 3% to 5% of the general population.[23] Most cases are due to primary RP, a benign disorder without systemic disease. Primary RP usually develops in younger individuals (in their 20s-30s) compared with scleroderma-associated RP. Raynaud phenomenon associated with scleroderma is also distinguished from primary RP by its positive serologic status, nailfold capillary abnormalities, and severity of the events in frequency, duration, and patient-related morbidity; it also is often accompanied by finger swelling (Figure, D) and stiffness and/or the presence digital ischemic ulcers or digital tip pitting (Figure, B). After the onset of RP, patients may be otherwise asymptomatic for years, or they may rapidly develop other early symptoms and signs of disease activity, such as fatigue, weight loss, musculoskeletal pain, gastrointestinal reflux disease, nailfold capillary changes (Figure, A), and edema in the extremities or obvious skin thickening.

Skin thickening is the most obvious physical finding that leads to a diagnosis of scleroderma, but the pattern and degree of skin involvement vary a great deal among patients. In 1980, a multicenter, cooperative study defined a diagnosis of scleroderma by 1 major criterion of skin thickening proximal to the metacarpophalangeal joints or any 2 of 3 minor criteria of digital pitting scars, sclerodactyly, or bibasilar pulmonary fibrosis on chest radiograph.[24] Through tradition, the presence of at least 3 of 5 features of the CREST syndrome (calcinosis [Figure, F], RP, esophageal dysmotility, sclerodactyly, telangiectasia) has also been used as diagnostic criteria. It is now appreciated that these criteria fail to identify patients with early disease, those with limited skin findings, or patients with no skin disease (systemic sclerosis sine scleroderma). It is argued that patients with definite RP, typical nailfold capillary changes, and the presence of a scleroderma specific antibody (Table 1)[25-28] can be diagnosed as having scleroderma because these findings indicate a very high probability (80%) of developing definite manifestations of scleroderma within a short follow-up period.[29] New American College of Rheumatology and the European League Against Rheumatism (EULAR) classification criteria for scleroderma are also being developed by an expert panel to aid in earlier diagnosis of scleroderma. Thus, the physician confronted with a patient with new-onset definite RP, particularly in older individuals, should consider scleroderma as a cause and perform a careful review of systems and specific examination, including a magnified view of the nailfold capillaries and a search for telangiectasia (Figure, C) and skin changes. In this setting, it is appropriate to order scleroderma-related autoantibodies (Table 1).[25-28] Early detection of disease sets the scene for further investigation and definition of interventions.

MANAGEMENT PRINCIPLES

Define the Clinical Phenotype

Once a diagnosis of scleroderma is suspected, the specific phenotype or disease subtype should be defined by careful clinical examination and appropriate laboratory testing. Each clinical subtype has unique features and different risks for organ complications (Table 2). In 1988, an international panel of experts classified patients into 2 major subtypes by the extent of skin sclerosis on physical examination: limited (hands, forearms, feet, legs, and face) and diffuse (proximal and distal limb or truncal involvement).[30] The rationale was that these 2 subsets were distinguished from each other clinically and serologically and that further subsetting added little to management decisions. Others now disagree and believe that a more refined phenotyping both clinically and serologically can provide important guidelines to treatment and predictors of disease expression. For example, the CREST syndrome falls into the traditional limited subtype, yet evidence suggests that survival is better in those with the CREST syndrome than an intermediate group of patients in the limited group who have skin changes extending onto the forearms.[31] Likewise, this intermediate group fares better when compared with those with diffuse skin disease.[15] Although the skin disease is often the most notable clinical

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

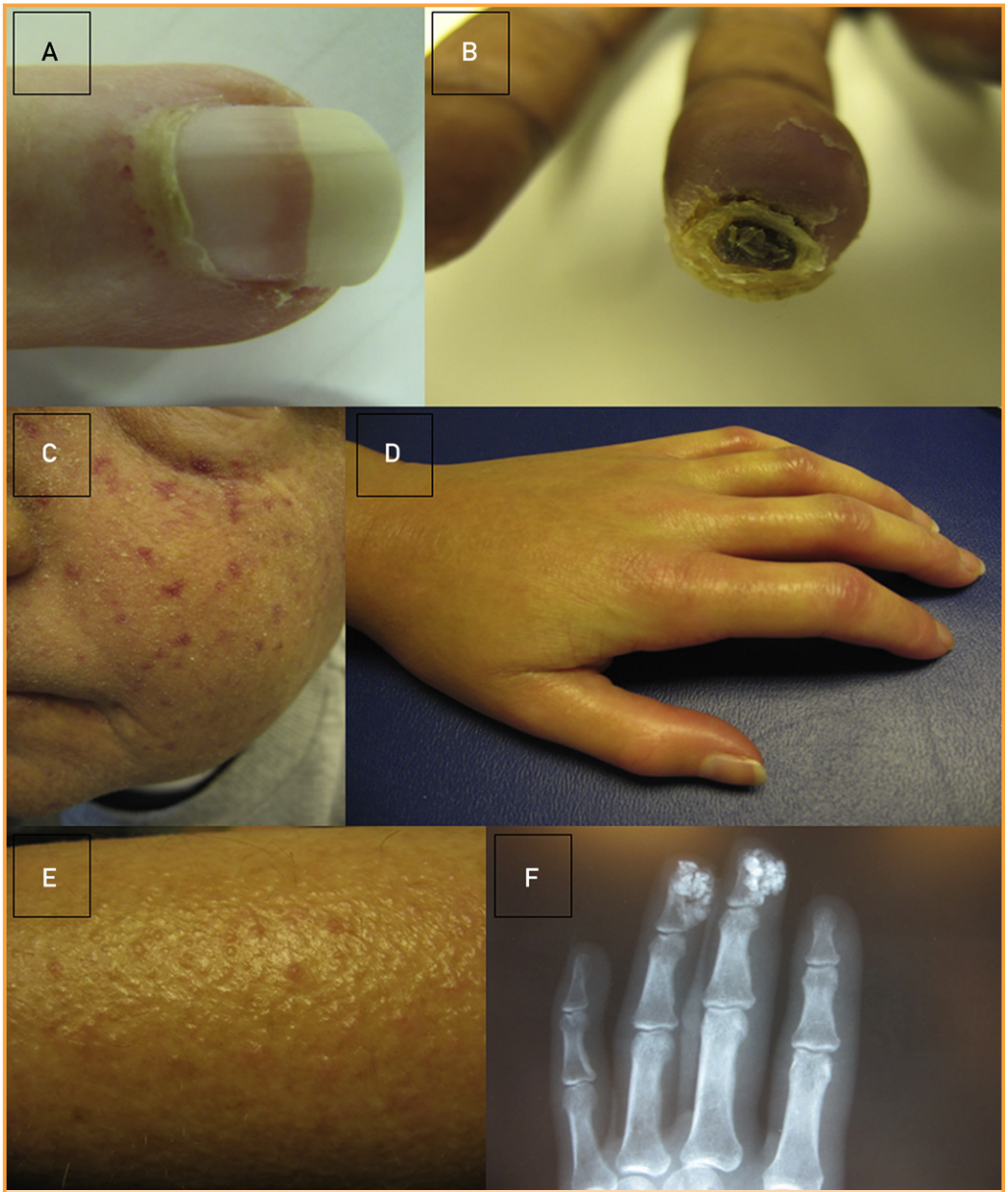

FIGURE. Clinical features in systemic sclerosis. A, Grossly dilated nailfold capillaries; B, ischemic digital ulcer; C, matted telangiectasia; D, sclerodactyly and hand scleroderma with finger flexion contractures; E, forearm scleroderma with papules due to fibrosis of dermis with lymphedema; and F, subcutaneous calcinosis.

feature, the disease process is more than skin deep. The other major target organs that can be involved include the peripheral circulation, gastrointestinal tract, kidneys, lung, heart, and musculoskeletal system. Therefore, most experts use the traditional classification for publication but for practical day-to-day management use a system that defines "fine phenotyping" with stratification of patients considering skin pattern, status of disease activity, and associated organ involvement supported by laboratory features. It is notable that when there is a rapid rate of skin thickening and widespread skin changes, there is increased risk of more severe internal organ disease and worse overall prognosis.[17,32] The physician should carefully determine not only

TABLE 1. Phenotypic Characteristics and Their Autoantibody Associations in Scleroderma[a,25-28]

Autoantibody	Phenotype
Centromere proteins B, C	Limited cutaneous disease/CREST (calcinosis, RP, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome
	Ischemic digital loss
	PAH
	Overlap syndromes: Sjögren syndrome, Hashimoto syndrome, primary biliary cirrhosis
Topoisomerase I (Scl-70)	Diffuse > limited cutaneous disease
	ILD
	African Americans
RNA polymerase III	Rapidly progressive diffuse cutaneous disease, contractures
	Contemporaneous cancer with disease onset
	Renal crisis (25%-33%)
	Myopathy and cardiac disease
	GAVE
U1-RNP	Limited > diffuse cutaneous disease
	SLE overlap
	Inflammatory arthritis
	Myositis overlap
	PAH
	ILD
	African Americans
U3-RNP (fibrillarin)[b]	Diffuse > limited cutaneous disease
	PAH
	ILD
	Cardiac and skeletal muscle disease
	Small bowel involvement
	African Americans
B23[b]	PAH
PM/Scl	Limited > diffuse cutaneous disease
	Myositis overlap
	Acro-osteolysis
	ILD
Th/To[b]	Limited cutaneous disease
	ILD
	PAH
	Small bowel involvement
U11/U12 RNP[b]	ILD
Ku[b]	Limited cutaneous disease
	Myositis

[a]GAVE = gastric antral vascular ectasia; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; SLE = systemic lupus erythematosus.
[b]These antibodies are not easily available or commercially available at present.

the pattern of skin disease but also the tempo of skin changes both historically and with prospective serial skin examinations. A reliable and reproducible method used is the traditional modified Rodnan skin score[33] performed by pinching 17 body areas and scoring each from 0 (normal) to 3 (very thick). The skin assessment coupled with serologic markers can subtype patients and help predict future disease course (Table 2).

Define the Clinical Stage of the Disease

The biology of scleroderma is complex and dynamic with features of inflammation, autoimmunity, tissue injury, and fibrosis. The traditional modified Rodnan skin score provides insight into the extent and severity of the disease, but without serial measures it does not measure the quality or activity of the skin process. It is essential that the physician assess the biological stage of disease by distinguishing disease *activity* from *severity* and irreversible *damage*. For example, in the subtype of patients with diffuse skin disease there is a natural course of skin changes that moves from an edematous inflammatory phase to a noninflammatory fibrotic phase. Both make the skin on examination feel thick, but the texture and quality of the skin differ in each phase. In the edematous phase the patient experiences diffuse soft tissue discomfort and itching; the skin appears erythematous, with nonpitting edema. During the active phase the involved areas show hair and subcutaneous fat loss, skin pigment changes, and small papules over areas of trauma (Figure, E). Deeper fibrosis may result in tendon friction rubs, causing joint discomfort, stiffness, and restricted range of motion. In most patients with early diffuse skin disease, the skin continues to worsen and then typically peaks at approximately 12 to 18 months, after which the skin begins to slowly evolve and potentially soften, eventually leaving residual abnormally pigmented fibrotic or atrophic areas.

During the active skin phase there is an increased risk of the onset of internal organ involvement. This increased risk suggests that active systemic disease and organ injury may be clinically silent but biologically under way during the early clinically obvious progressive skin disease. In diffuse scleroderma, most new organ involvement (gastrointestinal, lung, heart, and kidney) occurs within the first 3 years of disease onset.[34] Clearly, there are many individual exceptions with either no internal organ disease or flares and the new onset of organ disease late in the disease course. However, the important principle of management is that organ disease occurs early and its detection offers an opportunity to prevent progression and minimize damage using

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

TABLE 2. Management Principles[a]

OVERARCHING PRINCIPLES

1. Define the clinical phenotype: The disease has a highly variable expression.
2. Evaluate for specific organ involvement: The disease is deeper than the skin.
3. Define the clinical stage and activity of the disease: The biology of the disease is dynamic and uniquely complex.
4. Customize and redesign therapy: Specific focused therapy can positively affect longevity and quality of life.

SPECIFIC STEPS[b]

Determine peripheral vascular disease severity: Raynaud phenomenon

- How frequently do attacks occur?
- Does this affect the patient's ADLs and ability to work?
- Are there digital ulcers, pits (signs of prior damage), or signs of active and ongoing ischemia (fixed pallor or violaceous discoloration)?

➢ Therapeutic principle: Dihydropyridine calcium channel blocker therapy is the mainstay first-line treatment for Raynaud phenomenon. For more severe disease (ulcers or active ischemia), PDE5 inhibitors, endothelin receptor antagonists, prostacyclin analogs, and antiplatelet therapy could be added. Sympathectomy or amputation should be a last resort.

Assess extent of cutaneous/dermal sclerosis and its activity

Limited: fingers, hands, forearms, lower legs, face

Diffuse: also involving proximal extremities (upper arms, thighs), chest, abdomen

- Is the skin itching?
- Are new body areas involved?
- Is there increasing tightness in already involved body areas?
- What is the pace of change?
- Are there tendon friction rubs on examination?

➢ Therapeutic principle: Traditional cytotoxic Immunosuppressive therapies (eg, methotrexate, mycophenolate, and cyclophosphamide) or novel treatments through participation in clinical trials should be considered in the patient with evidence of active, diffuse cutaneous disease.

Monitor for cardiopulmonary complications: ILD and PAH

- Is FVC decreasing on serial PFTs?
- Is the RVSP ≥40 mm Hg OR is the RVSP increasing on serial echocardiograms OR is there an isolated decline in D_{LCO} (without a decrease in FVC)?
- Is there new-onset, unexplained dyspnea?

➢ Evaluation strategies and therapeutic principle: HRCT should be performed in the patient with decreasing FVC to evaluate for ILD. Evidence of ground glass changes with fibrosis may warrant immunosuppressive therapy. In the patient with high or increasing RVSP, or declining D_{LCO}, assessment with exercise testing and right-sided heart catheterization for PAH is necessary.

Identify dominant gastrointestinal symptoms that are attributable to scleroderma: GERD, dysphagia, abnormal gastric emptying, constipation, diarrhea, and fecal incontinence

- Are there symptoms of indigestion or heartburn?
- Is xerostomia a contributing factor to dysphagia?
- Is there difficulty with oropharyngeal bolus transfer to suggest pharyngeal weakness?
- Are there episodes of choking to suggest aspiration?
- Is there difficulty swallowing to suggest lower esophageal dysfunction?
- Does the patient have early satiety or regurgitation hours after eating?
- Are there prolonged bouts of constipation, diarrhea, or both?
- Does the patient have episodes of fecal urgency and soilage?

➢ Evaluation strategies and therapeutic principle: For GERD, a trial of proton pump inhibitor therapy should be instituted, dosed 30 minutes before meals. Elevation of the head of the bed and avoiding oral intake for at least 2 hours before bedtime are recommended. Oral dryness should be treated. A cine esophagram should be considered to evaluate for pharyngeal muscle weakness, especially if there is a concomitant myositis. Esophageal manometry, solid- and liquid-phase gastric emptying study, and upper endoscopy is recommended if the patient is not responding to therapy. Titration to twice daily dosing, addition of nighttime histamine$_2$-blocker and/or the addition of a prokinetic drug (metoclopramide or domperidone) may be necessary. Therapy should be directed at the underlying cause. For lower gastrointestinal tract symptoms, a bowel regimen (eg, polyethylene glycol) for constipation and a trial of antibiotics for diarrhea may improve quality of life, and IBS medications may be helpful. Fecal incontinence can be evaluated with anorectal manometry to see if biofeedback therapy is warranted.

[a]ADLs = activities of daily living; D_{LCO} = diffusing lung capacity for carbon monoxide; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; IBS = irritable bowel syndrome; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase 5; PFT = pulmonary function test; RVSP = right ventricular systolic pressure.

[b]Details for these areas and for musculoskeletal, renal, cardiac, dental, sexual, and endocrine manifestations may be found in the text and accompanying references.

currently available agents. This concept is also supported by the idea that inflammation or an active immune process is thought to drive downstream tissue injury and fibrosis. Once fibrosis is established it can progress independently by a self-perpetuating biological pathway that may no longer be solely driven or amplified by an immune-mediated process. Thus, immunosuppression or anti-inflammatory drug intervention is less effective once the disease moves into the fibrotic phase. Likewise, the failure to reverse or modify scleroderma may be explained by the lack of early intervention or the lack of available effective antifibrotic agents. The use of immunosuppression alone in cases that have advanced into a late fibrotic phase is generally disappointing. In addition, it is not appropriate to treat end-stage inactive disease or advanced fibrosis with potent immunosuppressive agents. However, supportive care (eg, pain control and physical therapy) and management of specific organ disease improve QOL in later stages of disease.

Customize and Redesign Therapy

The disease process and its associated complications often change with time. Frequently, systemic disease is subclinical before expressing physical distress. Therefore, it is recommended that all patients with scleroderma have periodic reevaluation, including an office visit and specific special testing to detect emerging organ disease. Late complications are often related to progressive cardiopulmonary disease, peripheral vascular disease, or complex gastrointestinal dysmotility issues. For example, symptomatic cardiac disease is often a late manifestation, but sensitive testing, such as echocardiography (especially tissue Doppler imaging), can often detect systolic or diastolic dysfunction in the asymptomatic patient.[35,36] It is recommended that the clinically stable patient have basic blood cell counts, pulmonary function testing, and an echocardiographic study yearly. These data will define early changes that may need treatment.

TREATMENT APPROACH

Although the pathogenesis of the disease is incompletely understood, it is clear that the physician must consider 3 biological processes when treating a patient: autoimmunity, a vasculopathy of peripheral arteries causing ischemia-reperfusion injury, and progressive tissue fibrosis. There is no single agent that has been proven to modify the disease course in scleroderma, but there is evidence to support treatment and management of specific organ manifestations. The European League Against Rheumatism and the EULAR Scleroderma Trials and Research group have published 14 evidence-based and consensus-derived treatment recommendations.[37] These guidelines were not intended to replace the judgment of the physician but to present expert opinion with flexibility in actual decision making. They also attempt to define directions for future clinical research. The Canadian Scleroderma Research Group found that 25% to 40% of patients who qualify actually receive the treatment recommended in the guidelines.[38]

Raynaud Phenomenon

Raynaud phenomenon is commonly the first symptom of scleroderma, often preceding other manifestations of the disease by years. It is present in all subsets of the disease and is the visible expression of a systemic vascular disease that is fundamental to the pathogenesis of scleroderma. The severity of RP is variable, and the patient's view of the severity can be measured by a simple Raynaud condition score. The patient is asked to score the distress caused by RP, taking into account the frequency, duration, pain, numbness, and the daily effect of the attacks.[39] Patients typically fall into 3 characteristic groups: RP alone without ischemic ulcerations, RP with ischemic digital ulcers (DUs), and RP with macrovascular disease and associated loss of digits.[40] The presence of limited skin disease and anticentromere antibodies increases the risk of major events with loss of digits,[41] whereas young age at disease onset, diffuse skin disease, and presence of antitopoisomerase antibody is associated with DUs.[42] Studies also suggest that the lack of use of vasodilator therapy increases the risk of DUs,[42,43] suggesting that all patients should be treated to prevent digital ischemic events.

Three biological processes need to be addressed in patients with scleroderma and RP: cold- and stress-triggered vasospasm, an occlusive vasculopathy, and ischemic tissue injury. There is no more potent treatment for RP than cold avoidance and stress management. Vasodilator therapy is recommended for every patient because of the high risk of

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

digital ischemic injury and the potential systemic benefit of treating the underlying vascular disease. Among the many vasodilators tested, the extended-release dihydropyridine-type calcium channel blockers continue to be the preferred first-line therapy. Our approach is to treat patients with a calcium channel blocker alone, adjusting the dose guided by clinical measures of effective control and signs of adverse reactions (Table 2).[25-28] If full doses do not benefit or if DUs emerges while the patient is taking a calcium channel blocker, then a second vasodilator is added (topical nitroglycerin, phosphodiesterase inhibitor, or intermittent infusion of prostacyclin). Digital sympathectomy or repair of occlusive macrovascular disease is considered in selective cases. Patients with recurrent DUs are administered either an endothelin receptor antagonist[44] or an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[45] These decisions are based on the rationale that vasoprotective agents may help prevent new DUs as suggested by clinical trials[44-46]; however, we recognize that the current data to support this approach are limited. Antiplatelet and antioxidant agents (eg, *N*-acetylcysteine) are used, but solid evidence for their benefit is lacking. Long-term anticoagulation is not recommended in the absence of a hypercoagulable state. Acute digital ischemia can suddenly threaten a deep tissue infarction and loss of an entire digit. This condition should be considered a medical emergency that requires rapid intervention, such as infusion of a prostacyclin analog[47] (Table 2).

Skin

No one agent has proven effective in the treatment of scleroderma skin disease. When the patient has mild skin disease limited to the face and fingers, there is no indication to use systemic therapy. Although there is strong evidence that immunosuppressive drugs effectively treat distinct clinical manifestations that can occur in scleroderma, such as inflammatory arthritis and myositis, the benefit of these agents for progressive skin disease is still unproven. Focusing intervention with immunosuppressive therapy on subtypes of disease with early, active inflammatory disease could be beneficial; by contrast, later fibrotic disease might not respond to immunosuppressive therapy alone. One survey found that immunosuppressive therapy was adopted in 35.8% of all patients with scleroderma but more frequently in those with the diffuse form (46.4%) or overlap syndrome (60%) than in those with other systemic sclerosis subtypes.[48] Our approach is that patients with active diffuse skin disease *without* major organ disease have 3 treatment options: (1) follow with serial observations to define the severity and course of the disease in that in many the skin disease is mild and largely reversible; (2) institute traditional low-dose antimetabolite/immunosuppressive therapy (eg, methotrexate, mycophenolate, or cyclophosphamide); or (3) move to novel innovative therapy, including research trials with new biological agents or immunoablation with or without stem cell rescue. The choice among these options is a clinical one based on stratification and phenotyping the patient via careful physical examination of the skin, assessment of internal organ disease, tabulation of known predictive risk factors, and patient preference.

In patients presenting with mild skin disease alone, an observation period alone will usually define the disease course within 3 to 6 months, but long-term observation for systemic disease is key. The evidence that low-dose immunosuppressive therapy or a new investigational agent works is mostly from anecdotal reports, cases series, and a few relatively short-term controlled trials. Several agents (D-penicillamine, relaxin, colchicine, minocycline, para-aminobenzoic acid, interferons, photopheresis, and cyclosporin) are no longer used because of an unfavorable experience, undue toxic effects, or lack of evidence-based efficacy. Methotrexate for skin disease is recommended by the EULAR expert panel based on several small studies[49]; however, in our experience methotrexate is most helpful for muscle and joint disease and disappointing for active skin disease unless used in combination with mycophenolate mofetil. Uncontrolled experience with mycophenolate is encouraging and at present is our preferred first-line agent for active skin disease.[50,51] We consider a positive response to mycophenolate when the patient notes or the examination findings demonstrate no progression of skin disease; this usually occurs within 9 to 12 weeks of beginning full-dose (3-g) therapy. Some use antithymocyte globulin (ATG) with mycophenolate.[52] For patients who do not respond, we then move to

intravenous gammaglobulin[53] with or without mycophenolate or add low-dose methotrexate. Low-dose cyclophosphamide (monthly intravenously or usually 2 mg/kg orally daily) is used if skin disease progression is severe. We recognize that the skin disease is highly variable and can spontaneously improve, remain unchanged for long periods, or very slowly progress. Thus, controlled studies are needed to define a drug's efficacy. In fact, a retrospective survey reported that the overall outcome in mycophenolate mofetil–treated cases was not significantly different when scoring rate of skin score change from other treatment groups (including cyclophosphamide, ATG followed by mycophenolate mofetil, or no disease-modifying treatment).[54]

Several other treatment approaches are being used or are under study. A recent survey reported that 577 of 1396 patients with scleroderma (41.3%) received corticosteroids.[48] They were prescribed frequently in patients with diffuse skin involvement or overlap clinical features (approximately 49% and 63.5%, respectively) and in approximately 31% of those with limited skin involvement. The use of corticosteroids to treat active scleroderma skin disease is questionable and potentially dangerous, given the recognized association with serious complications, such as SRC.[55] Our practice is to limit corticosteroid use to low doses (<15 mg) in patients in inflammatory disease in other systems, such as musculoskeletal disease. We have been disappointed in tyrosine kinase inhibitors because of lack of response and toxic effects but recognize some report a positive experience.[56] Biological agents (rituximab), anticytokines (tocilizumab and anti–transforming growth factor β), proteasome inhibitors (bortezomib), agents that may alter integrin binding, and agents that block lysophosphatidic acid are being studied, but their efficacy and safety are still unknown. Use of these agents is limited by availability, and when used these agents should be given at specialty centers or in the setting of an organized clinical trial.

Immunoablation therapy with hematopoietic stem cell transplantation (HSCT) can be considered in severe cases of rapidly progressive skin disease, particularly with significant associated internal organ disease. Hematopoietic stem cell transplantation has been compared with intravenous cyclophosphamide therapy in preliminary trials in the United States and Europe. A large European trial was reported in abstract form.[57] Patients with early progressive diffuse scleroderma with or without major organ involvement were eligible. Seventy-nine patients randomized to a transplantation arm underwent mobilization with cyclophosphamide (2 g/m^2 2 times) and granulocyte colony-stimulating factor (10 μg/kg/d), conditioning with cyclophosphamide (200 mg/kg), rabbit ATG (7.5 mg/kg), and reinfusion of CD34$^+$ autologous HSCT. Seventy-seven randomized to the control arm were treated with 12 monthly intravenous pulse doses of cyclophosphamide (750 mg/m).[57] The trial reported fewer deaths in the transplantation arm (n=16/79) compared with the cyclophosphamide arm (n=24/77); a higher treatment related mortality (n=8/79 [10%]) was seen in the HSCT group. No deaths occurred from treatment-related causes in the control arm.[57] One similarly designed but smaller US study reports improvement in skin and lung function during 12-month follow-up in all 10 patients in the HSCT group and none of the 9 patients in the cyclophosphamide group.[58] Another US trial is comparing the safety and efficacy of cyclophosphamide, total body irradiation, and ATG autologous transplantation vs monthly intravenous cyclophosphamide. The results of this trial are still pending. An uncontrolled trial demonstrated that immunoablation (cyclophosphamide, 50 mg/kg/d for 4 days) followed by granulocyte colony-stimulatory factor (5 μg/kg/d) without stem rescue also led to rapid control of progressive skin disease in 5 of 6 patients; one treatment-related death occurred.[59] These studies suggest that intense immunoablation can be considered in a select group of patients with severe disease. However, this approach needs more study to define better the treatment regimen and to understand the long-term outcome and consequences.[60]

Musculoskeletal

Musculoskeletal involvement is often the most distressing feature of scleroderma and a major contributing factor to disability.[18] A deep process can entrap joints and tendons, causing pain, contractures, deep tendon friction rubs, and weakness. An inflammatory arthritis is frequently superimposed on an intense fibrotic

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

process. A skeletal myopathy defined by weakness and elevated creatine kinase concentration, abnormal electromyography, and/or muscle biopsy may also be present and was detected in 17% of 1095 patients in one study.[61]

The inflammatory component responds to traditional therapy for synovitis or myositis, whereas the treatment for the fibrotic process is not ideal and follows the same approach as outlined for the overlying skin disease. A nonsteroidal anti-inflammatory agent, low-dose (<10 mg) corticosteroids, and pain control will improve the QOL. Weekly methotrexate is the recommended first-line disease-modifying therapy for musculoskeletal disease. Tumor necrosis factor inhibitors are reported to be effective for active polyarthritis.[62] Intravenous gammaglobulin is used in patients with muscle and joint disease, particularly those with an inflammatory myopathy.[63]

It is most important to begin physical and occupational intervention early in the disease to improve function and maintain activities of daily living. Evidence supports the idea that physical activity and active motion of involved tissues improve long-term outcomes.

Lung

Lung disease is now the leading cause of death in patients with scleroderma.[16] Involvement often is detected before there are clinical signs or symptoms, and it is common in all subtypes of disease. There are 2 major pathological processes present to some degree in the lungs of most patients: (1) fibrosing alveolitis that can lead to restrictive lung disease and (2) obliterative vasculopathy of medium and small pulmonary vessels that in some cases causes pulmonary arterial hypertension (PAH).

Interstitial Lung Disease

Interstitial lung disease is reported in approximately 50% of patients with diffuse skin disease and 35% of patients with limited disease.[64] The risk factors for developing severe ILD include African American ethnicity, the presence of antitopoisomerase antibodies, the presence of abnormal lung function test at presentation, and more extensive findings on high-resolution computed tomography (HRCT), especially fibrosis.[2,4,65-67] Because lung disease can begin in early and late disease, we perform pulmonary function testing at least annually in all patients and often at 4- to 6-month intervals in high-risk patients.

Treatment for lung disease is still not fully defined. We define active ILD when there is depression of forced vital capacity (FVC) at presentation and either declining FVC on serial studies (confirmed >10% decrease usually in 4-6 months) or abnormal findings of ground glass changes with some fibrosis on HRCT. Bronchoalveolar lavage or lung biopsy is not recommended because these studies do not predict clinical course or alter treatment decision.[68] The outcome of untreated alveolitis is progressive pulmonary fibrosis, a restrictive ventilatory defect with ineffective gas exchange that becomes life-threatening in approximately 15% to 20% of patients.[34] If active alveolitis is present, treatment with immunosuppressive drugs is indicated as supported by a placebo-controlled clinical trial that demonstrated that daily oral cyclophosphamide (2 mg/kg) prevented progressive decline in lung function and improved QOL measures.[69,70] It is important to remember that in this trial the active treatment phase was for 1 year. The 2-year posttreatment follow-up found no difference between the cyclophosphamide and placebo arms, suggesting either no long-term benefit or the need for prolonged immunosuppression.[70] Others have used monthly intravenous cyclophosphamide.[71,72] Although the 1-year oral exposure to cyclophosphamide had a tolerable toxicity profile,[73] most experts will now move from cyclophosphamide to another maintenance immunosuppressive drug (eg, mycophenolate or azathioprine) for long-term disease control. Several uncontrolled studies suggest that mycophenolate alone can control active ILD.[74] Currently, a US multicenter, blinded study is under way comparing cyclophosphamide to mycophenolate in the treatment of scleroderma ILD. We now use mycophenolate in cases of early disease when the FVC is modestly reduced or in a young patient and daily oral cyclophosphamide for 6 to 12 months in severe disease followed by mycophenolate maintenance for 3 to 5 years or until disease inactivity is defined. Although some advocate the use of corticosteroids, the evidence from our viewpoint does not support its use. In addition, corticosteroid therapy confers additional risk of SRC. For refractory cases, other immunosuppressive/antifibrotic agents

are being used but have been ineffective (eg, endothelin-1 blocker)[75] or need controlled trials (eg, rituximab and imatinib).[76]

Pulmonary Vascular Disease

Isolated PAH is more common in patients with limited skin disease and is seen in approximately 8% to 12% of all patients.[34,77,78] The presence of numerous cutaneous telangiectasias,[79] a decreasing diffusing capacity on pulmonary function,[80] an increasing estimated right ventricular systolic pressure as estimated by serial echocardiography,[81] late age at disease onset,[6] elevated N-terminal pro—brain natriuretic peptide,[82] and the presence of anticentromere antibody are associated with an increased risk of developing PH. Annual screening with pulmonary function testing and echocardiography is recommended.

Pulmonary vascular disease in scleroderma can be caused by isolated PAH, PH secondary to left heart disease, PH due to severe ILD and/or chronic hypoxia, and, rarely, pulmonary veno-occlusive disease. Therefore, a right-sided heart catheterization is required to confirm the diagnosis, exclude elevated left heart filling pressure, and assess right ventricular function, a critical determinant of outcome.[83] Early diagnosis and treatment before right heart disease is advanced may improve the clinical course; this concept supports the screening of all patients with scleroderma.[84] Noninvasive testing using both echocardiographic and pulmonary function studies are being used to better detect early disease and select appropriate high-risk patients for right-sided heart catheterization.[85] Exercise-induced PH may represent an early phase of cardiopulmonary disease that can be detected by exercise echocardiography or an exercise challenge during right-sided heart catheterization.[86] Although more studies are needed to confirm whether this approach is effective, exercise studies are being performed at specialty centers to discover early emerging PAH or PH in patients suspected of having early pulmonary vascular disease (unexplained breathlessness, isolated low diffusing lung capacity for carbon monoxide, or borderline high estimated right ventricular systolic pressure by echocardiography).[87]

Although current therapy for PAH in scleroderma is reported to improve survival,[88] it has not resulted in a notable long-term improvement,[89] especially when started in the setting of an advanced World Health Organization (WHO) functional class or when there is associated severe ILD.[90-92] Goal-directed therapy is now used define treatment. For example, for patients diagnosed as having WHO functional class III PAH, the treatment goal is to improve to WHO functional class II. Oral therapy is recommended for moderate to severe WHO class II to III PAH, whereas continuous infusion of a prostacyclin analogue (epoprostenol, treprostinil, or iloprost) via a centrally placed intravenous catheter or subcutaneous route is used for severe cases or those in whom oral therapy fails. Oral agents include endothelin receptor antagonists (bosentan and ambrisentan) and phosphodiesterase type 5 inhibitors (sildenafil and taldalafil). Aerosolized prostaglandins (iloprost and treprostinil) are also now available for severe PAH. Monotherapy maintenance in patients with WHO functional class II PAH and systemic sclerosis often fails, and sequential goal-directed combination therapy is now becoming an accepted treatment strategy. Disease-modifying drugs rather than vasodilator drugs alone (eg, immunosuppression: rituximab or antifibrotic agents such as imatinib) are now being tested to determine whether this approach can prevent disease progression. Lung transplantation is a viable option for selected scleroderma patients with progressive and severe life-threatening disease.

Gastrointestinal

Gastrointestinal disease is a major contributor to a poor QOL,[93] and therefore every scleroderma patient needs to be fully evaluated for its presence. A 34-item patient reported questionnaire can be used to measure and assess gastrointestinal symptoms and their effect on QOL.[94] Patients with facial skin disease have a decreased oral aperture and difficulty with both chewing and routine dental care. Loss of normal amounts of saliva, gum recession, and periodontal disease can lead to loosening or loss of teeth.[95] It is important to have frequent sessions of dental care and to consider using a cholinergic agonist to improve saliva production. Upper pharyngeal function is usually normal but can be involved in a subset of patients secondary to striated muscle involvement (fibrotic or inflammatory), creating a risk for both malnutrition and aspiration. The most common problem (90% of cases)

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

in all subtypes of scleroderma is esophageal dysfunction, leading to heartburn, regurgitation, or dysphagia caused by atrophy and loss of normal smooth muscle function of the lower two-thirds of the esophagus.[96,97] If untreated, gastrointestinal reflux may lead to esophagitis, bleeding, esophageal strictures, and/or Barrett esophagus. The severity of patient-reported symptoms may not accurately reflect the seriousness of the esophageal disease; therefore, we tend to treat aggressively patients with mild symptoms.

Special studies (esophagogastroduodenoscopy, barium esophagram, cine-esophagram, and esophageal manometry) are reserved for patients who do not respond as expected to an aggressive antireflux program, and endoscopy is often the most informative study. Education about standard nondrug measures is critical, including eating several smaller meals rather than the traditional 3 large meals, avoiding food or liquid intake at least 2 hours before bedtime, elevating the head and upper trunk at night, and eliminating foods that aggravate symptoms. Treatment of esophageal reflux by suppression of gastric acid with histamine$_2$-blockers is generally not as effective as proton pump inhibitors (eg, omeprazole or esomeprazole). If patients do not respond to a 4-week trial of a proton pump inhibitor or if there are signs of gastrointestinal bleeding, then an endoscopy procedure is recommended.

Delayed gastric emptying often causes early satiety, aggravation of gastroesophageal reflux disease, anorexia, or the sensation of bloating. A prokinetic drug (eg, metoclopramide, domperidone, or erythromycin) is recommended when gastroparesis is present and/or when symptoms of dysphagia and reflux continue despite the use of effective acid suppression. These prokinetic drugs are more effective in early disease and less likely to help when there is advanced esophageal dysfunction. Among the current prokinetic drugs, we prefer domperidone for long-term management if there are no contraindications, such as prolonged cardiac conduction intervals.[98] A subset (5%-15%) of patients with either limited or diffuse skin disease develops gastric antral vascular ectasia with significant asymptomatic bleeding.[99] Argon plasma coagulation therapy is effective in controlling the bleeding in most of these cases, and cryotherapy can be considered in resistant cases.

Recurrent bouts of pseudo-obstruction, a manifestation of profound loss of bowel smooth muscle function that causes regions of dysmotility of the small and large bowel, are one of the most serious bowel problems in scleroderma. More common are minor bouts of bloating, abdominal distention, diarrhea, and/or constipation. Serious diarrhea secondary to bacterial overgrowth and malabsorption is seen in a small subset of patients, usually late in the disease. Incontinence of stool is not uncommon, resulting from bowel noncompliance and dysfunction of rectal sphincters. The mainstay of management of lower bowel disease is a strategy to avoid a constipation-diarrhea cycle (eg, fiber diet, stool softener, periodic polyethylene glycol, and probiotics) and the use of cyclic antibiotics. Octreotide is reported to be helpful in patients with recurrent pseudo-obstruction despite other measures.[100] Total parenteral nutrition may be necessary for patients who have severe scleroderma-related bowel disease without response to other medical therapy.

Kidney

The most important manifestation of scleroderma renal disease is an SRC defined as accelerated arterial hypertension and/or rapidly progressive oliguric renal failure. An SRC occurs in approximately 10% of all patients and 20% to 25% of patients with anti-RNA polymerase III antibodies, with 75% of cases occurring within the first 4 years of disease onset.[101] However, other causes of renal disease always need to be considered, especially in patients with limited scleroderma who present with abnormal sediment on urinalysis or significant proteinuria. For example, cases of scleroderma with lupus nephritis or antineutrophil cytoplasmic antibody–related crescentic glomerulonephritis are reported that can mimic an SRC.[102] Therefore, we recommend that a comprehensive workup, including a renal biopsy, is performed in patients who present with renal failure to exclude other treatable causes of disease.

In SRC, early detection and rapid use of an ACE inhibitor has resulted in a good outcome 60% of the time with prevention of death or end-stage renal disease.[103] Therefore, being aware of high-risk patients and educating patients and caregivers to frequently monitor

blood pressure and renal function is most important. Using an ACE inhibitor in a stable patient to prevent an SRC is not recommended.[103] Any hypertension (blood pressure >140/90 mm Hg) in a scleroderma patient should be urgently evaluated because patients who present later with a creatinine concentration greater than 3.0 mg/dL (to convert to μmol/L, multiply by 88.4) have a poor prognosis. High-risk patients are those with new-onset diffuse skin disease, especially with rapid skin progression, the presence of antibody to RNA polymerase III, new onset of unexplained anemia, new cardiac disease, and previous use of high-dose corticosteroids. An SRC mimics malignant hypertension, with rapidly progressive renal failure secondary to microvascular disease, vasospasm, and tissue ischemia. A microangiopathic hemolytic anemia and thrombocytopenia can accompany SRC, mimicking thrombotic thrombocytopenic purpura. In these cases plasma exchange has been used but benefit is not proven.

Once SRC is discovered, aggressive therapy and hospitalization are needed. The use of a short-acting ACE inhibitor is the first intervention recommended, maximizing the dose to control the blood pressure in 24 to 72 hours is possible. If blood pressure remains elevated on maximum dosing of an ACE inhibitor, other antihypertensive agents can be added (eg, calcium channel blocker, diuretics, hydralazine, and clonidine). Recent literature suggests that combination ACE-1 and angiotensin receptor blocker therapy may have significant risks in the general population, but further study is required in scleroderma.[104-107] An endothelin receptor antagonist can be tried if needed.[108]

Some patients continue to have progressive renal failure despite control of blood pressure. Patients with SRC who progress to renal failure and dialysis can recover renal function after months of therapy. Successful renal transplantation has been performed in scleroderma patients with an approximately 60% rate of graft survival at 3 years and an overall definite survival benefit.[109]

Heart

The heart is a major target in scleroderma, but the presence of cardiac involvement is often clinically silent and not appreciated until failure occurs. When heart disease is symptomatic, it is associated with a poor prognosis.[36] Objective testing (eg, electrocardiography, echocardiography, nuclear imaging, and magnetic resonance imaging) will frequently discover clinically silent pericardial effusions, left ventricular diastolic dysfunction, conduction abnormalities, arrhythmias, or right ventricular malfunction thought to be a consequence of immune-mediated inflammation (myocarditis), microvascular disease, and/or myocardial fibrosis. Reversible vasospasm of small coronary arteries and arterioles can occur that potentially cause ischemia reperfusion injury.[110] Although still controversial, there is epidemiologic evidence of an increased risk of atherosclerotic coronary artery disease similar to that found in other rheumatic diseases.[111-113] Patients with all subtypes of scleroderma are at risk for significant heart disease, but patients with rapidly evolving diffuse skin disease,[114] those with underlying skeletal muscle disease,[61,115] and those with anti-U3RNP are prone to develop a severe cardiomyopathy.

Management of heart disease begins with awareness and early detection of disease with specific therapy directed at the defined problem. Natriuretic peptides (pro—brain natriuretic peptide), electrocardiography, and Doppler echocardiography are the most useful screening tests to detect cardiac dysfunction and should be performed at first presentation and then at least yearly. There is evidence that early intervention with vasodilators, particularly the calcium channel blockers, improve cardiac perfusion and ventricular function.[116-118] Therefore, we use a calcium channel blocker early in the disease process not only for peripheral vascular disease but also with the hope that they can preserve cardiac function. These agents must be monitored closely because they can have a negative inotropic effect, cause a reflex tachycardia, aggravate gastrointestinal disease, and cause peripheral edema, and they must be used with caution in patients with severe PAH. Patients with severe cardiomyopathy or complex arrhythmias are treated in the conventional manner with the use of Holter monitoring and implantation of a pacemaker or defibrillator, if needed. In theory, the use of immunosuppressive therapy to prevent disease progression makes sense, but there is a lack of studies to guide this approach. We limit the use of anti-inflammatory or immunosuppressive therapy for heart disease in cases of proven myocarditis or severe pericarditis. An

Mayo Clin Proc. ■ April 2013;88(4):377-393 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.018
www.mayoclinicproceedings.org

asymptomatic small pericardial effusion can be watched cautiously. Current antifibrotic agents have not been studied for heart disease, and some may cause cardiac toxic effects (eg, imatinib mesylate).

Other

Several common problems are often overlooked, including microstomia, xerostomia, Sjögren syndrome, periodontal disease, audiovestibular disease, primary biliary cirrhosis, autoimmune hepatitis, bladder dysfunction, erectile dysfunction, thyroid disease, and neuropathy.[119] At baseline a comprehensive evaluation should be performed to seek evidence for these complications, including pulmonary function testing, echocardiography, a complete blood cell count, liver function testing, muscle enzyme measurement, thyroid function testing, and urinalysis. Baseline and follow-up ophthalmology and dental evaluation are recommended. Depression, anxiety, poor self-image, and fear are almost universal when a patient is confronting the various manifestations of scleroderma.[120,121] The emotional effect of the disease is best managed by providing emotional support and counseling with the use of appropriate medication to control pain and improve mood. Patients' psychosocial well-being is often affected more by disfigurement caused by facial changes (eg, telangiectasias, loss of vermillion border of the lip, and pronounced vertical perioral lines) and hand contractures than occult visceral disease.[122] Patients with disfiguring lesions can have appropriate cosmetic intervention. For example, laser therapy can be used to remove facial telangiectasia, and surgical removal of problematic calcinosis may alleviate pain. Low self-esteem alters social interactions and intimate relationships, particularly in younger patients, who are more prone to discomfort in social settings.[21] Problems with intimate relationships should be addressed with open discussion and appropriate consultation. Men with erectile dysfunction may respond to phosphodiesterase 5 inhibitors, and surgical options can be considered. Women may be helped with gentle musculoskeletal exercises, lubricants, and gynecology consultation. Management must be directed at both the underlying disease process and the effect that the physical and psychological factors have on an individual's QOL.[120,123]

MONITORING

Many tools used to measure scleroderma disease severity and activity are useful clinically and in research. At first encounter, performing a pulmonary function test with diffusing lung capacity for carbon monoxide is recommended. We repeat pulmonary function testing annually and perform an HRCT if pulmonary function is decreasing or the patient has developed new-onset dyspnea. Establishing a baseline modified Rodnan skin score and repeating this at each visit provide a reproducible measure of skin severity. This coupled with a patient assessment of skin activity can define level of disease activity. Patients (especially those with early-onset diffuse disease) should be instructed to monitor their blood pressure periodically at home. Measuring a panel (Table 1)[25-28] of autoantibodies at baseline helps identify the patient at risk for specific organ disease. Repeated measures of autoantibodies are not helpful. However, periodic measures of standard laboratory parameters to monitor complete blood cell count, metabolic state, and renal function are important. Yearly pulmonary function with careful attention to the FVC and diffusing lung capacity for carbon monoxide and an echocardiography to monitor the estimated right ventricular systolic pressure should be performed.[124] Age-appropriate malignancy screening should be performed given the increased risk of malignant tumors in patients with scleroderma. Visits to reexamine and discuss overall emotional and physical status are defined by the individual situation, but we recommend at least a 6-month bedside reevaluation in every patient. A European Scleroderma Study Group has proposed a composite index, including clinical examination, laboratory measures, patient assessment, and lung function, to determine scleroderma disease activity in clinical practice.[125,126] Special measures are helpful in the research setting, including Health Assessment Questionnaire-Disability Index modified for scleroderma,[127] Medical Outcomes Study 36-Item Short Form Health Survey, Medsger Severity Index,[128] the United Kingdom Function Score,[129] and various organ specific measures.[94]

RECOMMENDATIONS

The main message of this review is that although there is no curative treatment for scleroderma, many treatment options are available to improve

both QOL and survival. Early detection of disease and immediate intervention appear to make a difference. It is important to appreciate that scleroderma is a heterogeneous disease with both clinical and laboratory predictors available to define expected disease course. Refined clinical phenotyping and careful early evaluation for active occult organ disease are the keys to deciding appropriate treatment options. The physician community needs to collaborate with specialized centers and organized networks that are studying scleroderma to help define ideal diagnostic and therapeutic options and to perform well-designed clinical trials attempting to discover better therapy.

ACKNOWLEDGMENTS

We thank Pamela Hill for assistance with the manuscript.

Abbreviations and Acronyms: **ACE** = angiotensin-converting enzyme inhibitor; **ATG** = antithymocyte globulin; **DU** = digital ulcer; **FVC** = forced vital capacity; **HRCT** = high-resolution computed tomography; **HSCT** = hematopoietic stem cell transplantation; **ILD** = interstitial lung disease; **PAH** = pulmonary arterial hypertension; **PH** = pulmonary hypertension; **QOL** = quality of life; **RP** = Raynaud phenomenon; **SRC** = scleroderma renal crisis; **WHO** = World Health Organization

Grant Support: Dr Wigley's work was supported by the Scleroderma Research Foundation and the Catherine Keilty Memorial Fund for Scleroderma Research. Dr Shah's work was supported by grant K23 AR061439 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

Correspondence: Address to Ami A. Shah, MD, MHS, Department of Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, JHAAC, Room 1B.32, Baltimore, MD (Ami.Shah@jhmi.edu).

REFERENCES

1. Maricq HR, Weinrich MC, Keil JE, et al. Prevalence of scleroderma spectrum disorders in the general population of South Carolina. *Arthritis Rheum*. 1989;32(8):998-1006.
2. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum*. 2003;48(8):2246-2255.
3. Robinson D Jr, Eisenberg D, Nietert PJ, et al. Systemic sclerosis prevalence and comorbidities in the US, 2001-2002. *Curr Med Res Opin*. 2008;24(4):1157-1166.
4. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. *Arthritis Rheum*. 2012;64(9):2986-2994.
5. Arnett FC, Reveille JD, Goldstein R, et al. Autoantibodies to fibrillarin in systemic sclerosis (scleroderma): an immunogenetic, serologic, and clinical analysis. *Arthritis Rheum*. 1996;39(7):1151-1160.
6. Manno RL, Wigley FM, Gelber AC, Hummers LK. Late-age onset systemic sclerosis. *J Rheumatol*. 2011;38(7):1317-1325.
7. Schachna L, Wigley FM, Chang B, White B, Wise RA, Gelber AC. Age and risk of pulmonary arterial hypertension in scleroderma. *Chest*. 2003;124(6):2098-2104.
8. Zhou X, Lee JE, Arnett FC, et al. HLA-DPB1 and DPB2 are genetic loci for systemic sclerosis: A genome-wide association study in Koreans with replication in North Americans. *Arthritis Rheum*. 2009;60(12):3807-3814.
9. 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(6):1359-1362.
10. Feghali-Bostwick C, Medsger TA Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. *Arthritis Rheum*. 2003;48(7):1956-1963.
11. McCormic ZD, Khuder SS, Aryal BK, Ames AL, Khuder SA. Occupational silica exposure as a risk factor for scleroderma: a meta-analysis. *Int Arch Occup Environ Health*. 2010;83(7):763-769.
12. Kettaneh A, Al Moufti O, Tiev KP, et al. Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case-control studies. *J Rheumatol*. 2007;34(1):97-103.
13. Shah AA, Rosen A, Hummers L, Wigley F, Casciola-Rosen L. Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. *Arthritis Rheum*. 2010;62(9):2787-2795.
14. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007;66(7):940-944.
15. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: Demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)*. 2002;81(2):139-153.
16. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR scleroderma trials and research (EUSTAR) database. *Ann Rheum Dis*. 2010;69(10):1809-1815.
17. Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger TA Jr. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. *Ann Rheum Dis*. 2011;70(1):104-109.
18. Poole JL, Steen VD. The use of the health assessment questionnaire (HAQ) to determine physical disability in systemic sclerosis. *Arthritis Care Res*. 1991;4(1):27-31.
19. Rannou F, Poiraudeau S, Berezne A, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. *Arthritis Rheum*. 2007;57(1):94-102.
20. Hudson M, Steele R, Taillefer S, Baron M, Canadian Scleroderma Research. Quality of life in systemic sclerosis: psychometric properties of the world health organization disability assessment schedule II. *Arthritis Rheum*. 2008;59(2):270-278.
21. Jewett LR, Hudson M, Malcarne VL, Baron M, Thombs BD, Canadian Scleroderma Research Group. Sociodemographic and disease correlates of body image distress among patients with systemic sclerosis. *PLoS One*. 2012;7(3):e33281.
22. Thombs BD, van Lankveld W, Bassel M, et al. Psychological health and well-being in systemic sclerosis: State of the science and consensus research agenda. *Arthritis Care Res (Hoboken)*. 2010;62(8):1181-1189.
23. Wigley FM. Clinical practice: Raynaud's phenomenon. *N Engl J Med*. 2002;347(13):1001-1008.
24. 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(5):581-590.
25. Harris ML, Rosen A. Autoimmunity in scleroderma: the origin, pathogenetic role, and clinical significance of autoantibodies. *Curr Opin Rheumatol*. 2003;15(6):778-784.
26. Steen VD. The many faces of scleroderma. *Rheum Dis Clin North Am*. 2008;34(1):1-15.
27. Graf SW, Hakendorf P, Lester S, et al. South Australian Scleroderma Register: autoantibodies as predictive biomarkers of phenotype and outcome. *Int J Rheum Dis*. 2012;15(1):102-109.
28. Fertig N, Domsic RT, Rodriguez-Reyna T, et al. Anti-U11/U12 RNP antibodies in systemic sclerosis: a new serologic marker associated with pulmonary fibrosis. *Arthritis Rheum*. 2009;61(7):958-965.
29. Koenig M, Joyal F, Fritzler MJ, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis Rheum*. 2008;58(12):3902-3912.
30. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15(2):202-205.
31. Cottrell TR, Wigley FM, Wise R, Boin F. The degree of skin involvement predicts distinct interstitial lung disease outcomes in systemic sclerosis. *Arthritis Rheum*. 2010;62(10):S249-S250.
32. Clements PJ, Hurwitz EL, Wong WK, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. *Arthritis Rheum*. 2000;43(11):2445-2454.
33. Brennan P, Silman A, Black C, et al; UK Scleroderma Study Group. Validity and reliability of three methods used in the diagnosis of Raynaud's phenomenon. *Br J Rheumatol*. 1993;32(5):357-361.
34. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum*. 2000;43(11):2437-2444.
35. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-Doppler echocardiography during routine care: a controlled study of 100 consecutive patients. *Arthritis Rheum*. 2008;58(6):1803-1809.
36. Meune C, Vignaux O, Kahan A, Allanore Y. Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. *Arch Cardiovasc Dis*. 2010;103(1):46-52.
37. Kowal-Bielecka O, Landewe R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR scleroderma trials and research group (EUSTAR). *Ann Rheum Dis*. 2009;68(5):620-628.
38. Pope J, Harding S, Khimdas S, Bonner A, Canadian Scleroderma Research Group, Baron M. Agreement with guidelines from a large database for management of systemic sclerosis: results from the Canadian Scleroderma Research Group. *J Rheumatol*. 2012;39(3):524-531.
39. Merkel PA, Herlyn K, Martin RW, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum*. 2002;46(9):2410-2420.
40. Hummers LK, Wigley FM. Management of Raynaud's phenomenon and digital ischemic lesions in scleroderma. *Rheum Dis Clin North Am*. 2003;29(2):293-313.
41. Wigley FM, Wise RA, Miller R, Needleman BW, Spence RJ. Anticentromere antibody as a predictor of digital ischemic loss in patients with systemic sclerosis. *Arthritis Rheum*. 1992;35(6):688-693.
42. Denton CP, Krieg T, Guillevin L, et al. Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO registry. *Ann Rheum Dis*. 2012;71(5):718-721.
43. Hachulla E, Clerson P, Launay D, et al. Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. *J Rheumatol*. 2007;34(12):2423-2430.
44. Matucci-Cerinic M, Denton CP, Furst DE, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2011;70(1):32-38.
45. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J Rheumatol*. 2008;35(9):1801-1808.
46. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum*. 2004;50(12):3985-3993.
47. McMahan ZH WF. Raynaud's phenomenon and digital ischemia: a practical approach to risk stratification, diagnosis and management. *Int J Clin Rheumatol*. 2010;5(3):355-370.
48. Hunzelmann N, Moinzadeh P, Genth E, et al. High frequency of corticosteroid and immunosuppressive therapy in patients with systemic sclerosis despite limited evidence for efficacy. *Arthritis Res Ther*. 2009;11(2):R30.
49. Kowal-Bielecka O, Distler O. Use of methotrexate in patients with scleroderma and mixed connective tissue disease. *Clin Exp Rheumatol*. 2010;28(5 suppl 61):S160-S163.
50. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. *Ann Rheum Dis*. 2011;70(6):1104-1107.
51. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. *J Rheumatol*. 2012;39(6):1241-1247.
52. Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis: a retrospective analysis. *Rheumatology (Oxford)*. 2007;46(3):442-445.
53. Levy Y, Amital H, Langevitz P, et al. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study. *Arthritis Rheum*. 2004;50(3):1005-1007.
54. Herrick AL, Lunt M, Whidby N, et al. Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis. *J Rheumatol*. 2010;37(1):116-124.
55. Trang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatol Int*. 2012;32(3):645-653.
56. Spiera RF, Gordon JK, Mersten JN, et al. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. *Ann Rheum Dis*. 2011;70(6):1003-1009.
57. van Laar JM, Farge D, Sont JK, et al; EBMT/EULAR Scleroderma Study Group. The ASTIS trial: autologous stem cell transplantation versus IV pulse cyclophosphamide in poor prognosis systemic sclerosis, first results. *Ann Rheum Dis*. 2012;71(suppl 3):151.
58. Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet*. 2011;378(9790):498-506.
59. Tehlirian CV, Hummers LK, White B, Brodsky RA, Wigley FM. High-dose cyclophosphamide without stem cell rescue in scleroderma. *Ann Rheum Dis*. 2008;67(6):775-781.
60. Sullivan KM, Wigley FM, Denton CP, van Laar JM, Furst DE. Haemopoietic stem-cell transplantation for systemic sclerosis. *Lancet*. 2012;379(9812):219.
61. Follansbee WP, Zerbe TR, Medsger TA Jr. Cardiac and skeletal muscle disease in systemic sclerosis (scleroderma): a high risk association. *Am Heart J*. 1993;125(1):194-203.

62. Lam GK, Hummers LK, Woods A, Wigley FM. Efficacy and safety of etanercept in the treatment of scleroderma-associated joint disease. *J Rheumatol*. 2007;34(7):1636-1637.
63. Nacci F, Righi A, Conforti ML, et al. Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study. *Ann Rheum Dis*. 2007;66(7):977-979.
64. Walker UA, Tyndall A, Czirjak L, 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(6):754-763.
65. Plastiras SC, Karadimitrakis SP, Ziakas PD, Vlachoyiannopoulos PG, Moutsopoulos HM, Tzelepis GE. Scleroderma lung: initial forced vital capacity as predictor of pulmonary function decline. *Arthritis Rheum*. 2006;55(4):598-602.
66. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177(11):1248-1254.
67. Roth MD, Tseng CH, Clements PJ, et al. Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease. *Arthritis Rheum*. 2011;63(9):2797-2808.
68. Mittoo S, Wigley FM, Wise R, Xiao H, Hummers L. Persistence of abnormal bronchoalveolar lavage findings after cyclophosphamide treatment in scleroderma patients with interstitial lung disease. *Arthritis Rheum*. 2007;56(12):4195-4202.
69. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655-2666.
70. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med*. 2007;176(10):1026-1034.
71. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006;54(12):3962-3970.
72. Tochimoto A, Kawaguchi Y, Hara M, et al. Efficacy and safety of intravenous cyclophosphamide pulse therapy with oral prednisolone in the treatment of interstitial lung disease with systemic sclerosis: 4-year follow-up. *Mod Rheumatol*. 2011;21(3):296-301.
73. Furst DE, Tseng CH, Clements PJ, et al. Adverse events during the scleroderma lung study. *Am J Med*. 2011;124(5):459-467.
74. Tzouvelekis A, Galanopoulos N, Bouros E, et al. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: a meta-analysis. *Pulm Med*. 2012;2012:143637.
75. Seibold JR, Denton CP, Furst DE, et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. *Arthritis Rheum*. 2010;62(7):2101-2108.
76. Haroon M, McLaughlin P, Henry M, Harney S. Cyclophosphamide-refractory scleroderma-associated interstitial lung disease: remarkable clinical and radiological response to a single course of rituximab combined with high-dose corticosteroids. *Ther Adv Respir Dis*. 2011;5(5):299-304.
77. Avouac J, Airo P, Meune C, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol*. 2010;37(11):2290-2298.
78. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum*. 2005;52(12):3792-3800.
79. Shah AA, Wigley FM, Hummers LK. Telangiectases in scleroderma: a potential clinical marker of pulmonary arterial hypertension. *J Rheumatol*. 2010;37(1):98-104.
80. Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum*. 2003;48(2):516-522.
81. Shah AA, Chung SE, Wigley FM, Wise RA, Hummers LK. Changes in estimated right ventricular systolic pressure predict mortality and pulmonary hypertension in a cohort of scleroderma patients [published online ahead of print August 11, 2012]. *Ann Rheum Dis*.
82. Mathai SC, Bueso M, Hummers LK, et al. Disproportionate elevation of N-terminal pro-brain natriuretic peptide in scleroderma-related pulmonary hypertension. *Eur Respir J*. 2010;35(1):95-104.
83. Campo A, Mathai SC, Le Pavec J, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;182(2):252-260.
84. Hachulla E, Denton CP. Early intervention in pulmonary arterial hypertension associated with systemic sclerosis: an essential component of disease management. *Eur Respir Rev*. 2010;19(118):314-320.
85. Schreiber BE, Valerio CJ, Keir GJ, et al. Improving the detection of pulmonary hypertension in systemic sclerosis using pulmonary function tests. *Arthritis Rheum*. 2011;63(11):3531-3539.
86. Saggar R, Khanna D, Furst DE, et al. Exercise-induced pulmonary hypertension associated with systemic sclerosis: four distinct entities. *Arthritis Rheum*. 2010;62(12):3741-3750.
87. Shah AA, Mayer S, Girgis R, Mudd J, Hummers LK, Wigley FM. Correlation between exercise echocardiography and right heart catheterization in scleroderma patients at risk for pulmonary hypertension. *Arthritis Rheum*. 2011;63(suppl 10):S269.
88. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: Improved survival in the current era. *Heart*. 2006;92(7):926-932.
89. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum*. 2006;54(9):3043-3050.
90. Denton CP, Hachulla E. Risk factors associated with pulmonary arterial hypertension in patients with systemic sclerosis and implications for screening. *Eur Respir Rev*. 2011;20(122):270-276.
91. Hesselstrand R, Wildt M, Ekmehag B, Wuttge DM, Scheja A. Survival in patients with pulmonary arterial hypertension associated with systemic sclerosis from a Swedish single centre: prognosis still poor and prediction difficult. *Scand J Rheumatol*. 2011;40(2):127-132.
92. Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. *Arthritis Rheum*. 2011;63(8):2456-2464.
93. Bodukam V, Hays RD, Maranian P, et al. Association of gastrointestinal involvement and depressive symptoms in patients with systemic sclerosis. *Rheumatology (Oxford)*. 2011;50(2):330-334.
94. Khanna D, Hays RD, Maranian P, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum*. 2009;61(suppl 9):1257-1263.
95. Wood RE, Lee P. Analysis of the oral manifestations of systemic sclerosis (scleroderma). *Oral Surg Oral Med Oral Pathol*. 1988;65(2):172-178.
96. Thoua NM, Bunce C, Brough G, Forbes A, Emmanuel AV, Denton CP. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. *Rheumatology (Oxford)*. 2010;49(9):1770-1775.
97. Roberts CG, Hummers LK, Ravich WJ, Wigley FM, Hutchins GM. A case-control study of the pathology of oesophageal disease in systemic sclerosis (scleroderma). *Gut*. 2006;55(12):1697-1703.
98. Parkman HP, Jacobs MR, Mishra A, et al. Domperidone treatment for gastroparesis: demographic and pharmacogenetic characterization of clinical efficacy and side-effects. *Dig Dis Sci*. 2011;56(1):115-124.
99. Ingraham KM, O'Brien MS, Shenin M, Derk CT, Steen VD. Gastric antral vascular ectasia in systemic sclerosis: demographics and disease predictors. *J Rheumatol*. 2010;37(3):603-607.

100. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *N Engl J Med*. 1991;325(21):1461-1467.
101. Denton CP, Lapadula G, Mouthon L, Muller-Ladner U. Renal complications and scleroderma renal crisis. *Rheumatology (Oxford)*. 2009;48(suppl 3):iii32-iii35.
102. Kamen DL, Wigley FM, Brown AN. Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis in scleroderma: a different kind of renal crisis. *J Rheumatol*. 2006;33(9):1886-1888.
103. Penn H, Howie AJ, Kingdon EJ, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. *QJM*. 2007;100(8):485-494.
104. Chan KE, Ikizler TA, Gamboa JL, Yu C, Hakim RM, Brown NJ. Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients. *Kidney Int*. 2011;80(9):978-985.
105. Kurnik D, Vesterman-Landes J, Bialik M, et al. Hyperkalemia and renal function during monotherapy and dual renin-angiotensin blockade in the community setting. *Clin Ther*. 2011;33(4):456-464.
106. Holdiness A, Monahan K, Minor D, de Shazo RD. Renin angiotensin aldosterone system blockade: little to no rationale for ACE inhibitor and ARB combinations. *Am J Med*. 2011;124(1):15-19.
107. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547-553.
108. Dhaun N, MacIntyre IM, Bellamy CO, Kluth DC. Endothelin receptor antagonism and renin inhibition as treatment options for scleroderma kidney. *Am J Kidney Dis*. 2009;54(4):726-731.
109. Chang YJ, Spiera H. Renal transplantation in scleroderma. *Medicine (Baltimore)*. 1999;78(6):382-385.
110. Alexander EL, Firestein GS, Weiss JL, et al. Reversible cold-induced abnormalities in myocardial perfusion and function in systemic sclerosis. *Ann Intern Med*. 1986;105(5):661-668.
111. Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, Van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. *Ann Rheum Dis*. 2012;71(12):1980-1983.
112. Au K, Singh MK, Bodukam V, et al. Atherosclerosis in systemic sclerosis: a systematic review and meta-analysis. *Arthritis Rheum*. 2011;63(7):2078-2090.
113. Turiel M, Gianturco L, Ricci C, et al. Silent cardiovascular involvement in patients with diffuse systemic sclerosis: a controlled cross-sectional study. *Arthritis Care Res (Hoboken)*. 2012;65(2):274-280.
114. Perera A, Fertig N, Lucas M, et al. Clinical subsets, skin thickness progression rate, and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. *Arthritis Rheum*. 2007;56(8):2740-2746.
115. Allanore Y, Meune C, Vonk MC, et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR scleroderma trial and research group (EUSTAR) database of patients with systemic sclerosis. *Ann Rheum Dis*. 2010;69(1):218-221.
116. Kahan A, Devaux JY, Amor B, et al. Pharmacodynamic effect of nicardipine on left ventricular function in systemic sclerosis. *J Cardiovasc Pharmacol*. 1990;15(2):249-253.
117. Kahan A, Devaux JY, Amor B, et al. Nifedipine and thallium-201 myocardial perfusion in progressive systemic sclerosis. *N Engl J Med*. 1986;314(22):1397-1402.
118. Meune C, Allanore Y, Devaux JY, et al. High prevalence of right ventricular systolic dysfunction in early systemic sclerosis. *J Rheumatol*. 2004;31(10):1941-1945.
119. Shah AA, Wigley FM. Often forgotten manifestations of systemic sclerosis. *Rheum Dis Clin North Am*. 2008;34(1):221-238.
120. Benrud-Larson LM, Heinberg LJ, Boling C, et al. Body image dissatisfaction among women with scleroderma: extent and relationship to psychosocial function. *Health Psychol*. 2003;22(2):130-139.
121. Roca RP, Wigley FM, White B. Depressive symptoms associated with scleroderma. *Arthritis Rheum*. 1996;39(6):1035-1040.
122. Amin K, Clarke A, Sivakumar B, et al. The psychological impact of facial changes in scleroderma. *Psychol Health Med*. 2011;16(3):304-312.
123. Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. *Rheum Dis Clin North Am*. 2003;29(2):427-439.
124. Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. *Best Pract Res Clin Rheumatol*. 2010;24(3):387-400.
125. Valentini G, Della Rossa A, Bombardieri 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(6):592-598.
126. Valentini G, D'Angelo S, Della Rossa A, Bencivelli W, Bombardieri S. European scleroderma study group to define disease activity criteria for systemic sclerosis, IV: assessment of skin thickening by modified Rodnan skin score. *Ann Rheum Dis*. 2003;62(9):904-905.
127. Steen VD, Medsger TA Jr. The value of the health assessment questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum*. 1997;40(11):1984-1991.
128. Medsger TA Jr, Silman AJ, Steen VD, et al. A disease severity scale for systemic sclerosis: development and testing. *J Rheumatol*. 1999;26(10):2159-2167.
129. Silman A, Akesson A, Newman J, et al. Assessment of functional ability in patients with scleroderma: a proposed new disability assessment instrument. *J Rheumatol*. 1998;25(1):79-83.