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My Approach to the Treatment of Scleroderma

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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 that have common manifestations that link them together, while a highly variable clinical course exists that spans from mild and subtle findings to aggressive life-threatening multisystem disease. The clinician needs to carefully characterize each patient to understand the specific manifestations and level of disease activity in order to decide appropriate treatment. This is particularly important in managing a patient with scleroderma because there is no treatment that has been proven to modify the overall disease course; while therapy that targets specific organ involvement early before irreversible damage occurs does improve 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 both 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, co- morbid conditions and the emotional aspects of the disease such as fear, depression and the social withdrawal caused by disfigurement.

Introduction

Scleroderma is considered a rare disease with an estimated prevalence in the United States of 276–300 cases per million [1–3] and an incidence of about 20 cases per million per year [2]. Females are more commonly affected (4.6 to 1) [2] and it tends to be more severe among African and Native Americans than Caucasians[4,5]. It is rare in children with a peak age of onset about 45–60 years and has a worse prognosis in older individuals; for example, an increased risk for developing pulmonary hypertension exists with late-age disease onset (>65 years) [6,7]. Scleroderma is a complex polygenetic disease. A recent Genome Wide Association Study (GWAS) confirmed a strong association with the Major Histocompatibility Complex (MHC) and autoimmunity[8]. Multicase families are uncommon

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but do occur with a relative risk among first degree relatives of 13 (95% CI 2.9–48.6, $p < 0.001$) with a recurrence rate of 1.6% within families versus 0.026% in the general population[9]. A study of twin pairs showed 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 1970's (54–60%) to the 1990's (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 with ACE inhibitors. Risk factors for increased mortality include African American race, later age of disease onset, the presence of interstitial lung disease (ILD) or pulmonary hypertension (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 due to distress from body image is 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 leads to organ failure and poor outcomes. The most common first sign of scleroderma is Raynaud's phenomenon, a clinical problem of cold and stress induced vasospasm of the digital arteries and cutaneous arterioles involved in body thermoregulation. Raynaud's occurs for a variety of reasons in about 3–5% of the general population[23]. Most cases are due to primary Raynaud's phenomenon, a benign disorder without systemic disease. Primary Raynaud's phenomenon usually develops in younger individuals (20s–30s) as compared to scleroderma-associated Raynaud's phenomenon. Raynaud's phenomenon associated with scleroderma is also distinguished from primary Raynaud's phenomenon 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 1D) and stiffness and/or the presence digital ischemic ulcers or digital tip pitting (Figure 1B). After the onset of Raynaud's phenomenon, 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 (GERD), nailfold capillary changes (Figure 1A), edema in the extremities or obvious skin thickening.

Skin thickening is the most obvious physical finding to make a diagnosis of scleroderma, but the pattern and degree of skin involvement varies a great deal among patients. In 1980, a multicenter cooperative study defined a diagnosis of scleroderma by one major criterion of skin thickening proximal to the metacarpophalangeal joints or any two of three minor criteria: digital pitting scars, sclerodactyly or bibasilar pulmonary fibrosis on chest radiograph[24]. Through tradition, the presence of at least 3 out of 5 features of the CREST syndrome (Calcinosis (Figure 1F), Raynaud's phenomenon, 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 Raynaud's phenomenon, 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 ACR/

EULAR classification criteria for scleroderma are also being developed by an expert panel to aid in earlier diagnosis of scleroderma. Thus, the clinician confronted with a patient with new onset definite Raynaud's, particularly if it begins 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, a search for telangiectasia (Figure 1C) 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 (Table 2)

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 two 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 two subsets were distinguished from each other clinically and serologically and that further subsetting added little to management decisions. Others now disagree and feel 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 (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangeictasias) 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 does better when compared to those with diffuse skin disease[15]. While the skin disease is often the most dramatic clinical 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 (see below) 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 clinician should carefully determine not only 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 serological markers can subtype patients and help predict future disease course (see 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 clinician 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 non-inflammatory fibrotic phase. Both make the skin on examination feel thick but the texture and quality of the skin differs in each phase. In the edematous phase the patient

complains of diffuse soft tissue discomfort and itching; the skin appears erythematous with non-pitting 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 1E). Deeper fibrosis may result in tendon friction rubs causing joint discomfort, stiffness, and restricted range of motion. In the majority of patients with early diffuse skin disease, the skin continues to worsen and then typically peaks at about 12–18 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 suggests that active systemic disease and organ injury may be clinically silent but biologically underway 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 currently available agents. This concept is also supported by the idea that inflammation or an active immune process is thought to drive down stream 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 anti-fibrotic agents. The use of immunosuppression alone in cases that have advanced into a late fibrotic phase is generally disappointing. Also it is not appropriate to treat end-stage inactive disease or advanced fibrosis with potent immunosuppressive agents. However, supportive care (e.g. pain control, physical therapy) and management of specific organ disease (see below) improves 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 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 counts, pulmonary function testing and an echocardiographic study yearly. These data will define early changes that may need treatment.

Treatment Approach

While the pathogenesis of the disease is incompletely understood, it is clear that the clinician must consider three biological processes when managing 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 (EULAR) and the EULAR Scleroderma Trials and Research (EUSTAR) group have published 14 evidence-based and

consensus-derived treatment recommendations[37]. These guidelines were not intended to replace the judgment of the clinician 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 (CSRG) found that 25–40% of patients who qualify actually receive the treatment recommended in the guidelines[38].

Raynaud's phenomenon

Raynaud's phenomenon (RP) 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's Condition Score". The patient is asked to score the distress caused by RP taking into account the frequency, duration, pain, numbness and the daily impact of the attacks[39]. Patients typically fall into three characteristic groups: Raynaud's phenomenon alone without ischemic ulcerations, RP with ischemic digital ulcers (DU), and those with macrovascular disease and associated loss of digits[40]. The presence of limited skin disease and anti-centromere antibodies increases the risk for major events with loss of digits[41], while young age of disease onset, diffuse skin disease and presence of anti-topoisomerase antibody is associated with DU[42]. Studies also suggest that the lack of use of vasodilator therapy increases the risk to develop DU[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 for 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 (CCB) continue to be the preferred first line therapy. Our approach is to treat patients with a CCB alone, adjusting the dose guided by clinical measures of effective control and signs of adverse reactions (Table 1) [25–28]. If full doses do not benefit or if DU emerges while on CCB, 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 DU are started on either an endothelin receptor antagonist[44] or inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMG-CoA) [45]. These decisions are based on the rationale that vasoprotective agents may help prevent new DU as suggested by clinical trials[44–46]; however, we recognize that the current data to support this approach are limited. Anti-platelet and anti-oxidant agents (e.g. N-acetycysteine) are used, but solid evidence for their benefit is lacking. Chronic 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 should be considered a medical emergency requiring 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 SSc subtypes[48]. Our approach is that patients with active diffuse skin disease **without** major organ disease have three 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 anti-metabolite/ immunosuppressive therapy (e.g. 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 cases presenting with mild skin disease alone, an observation period alone will usually define disease course within 3–6 months; but long-term observations 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, cyclosporine) are no longer used because of an unfavorable experience, undue toxicity 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 personal 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 exam demonstrates no progression of skin disease; this usually occurs within 9–12 weeks of beginning full dose (3 gm) therapy. Some use anti-thymocyte globulin (ATG) with mycophenolate[52]. For patients who do not respond, we then move to intravenous gammaglobulin (IVIG) [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 either 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 MMF-treated cases was not significantly different when scoring rate of skin score change from other treatment groups (including cyclophosphamide, anti-thymocyte globulin followed by MMF, or no disease-modifying treatment) [54].

Several other treatment approaches are being used or are under study. A recent survey reported that 577 of 1,396 (41.3%) patients with scleroderma received corticosteroids[48]. They were prescribed frequently in patients with diffuse skin involvement or with 'overlap' clinical features (about 49% and 63.5%, respectively) and in approximatley 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 scleroderma renal crisis[55]. Our practice is to limit corticosteroid use to low dose (<15 mg) in patients in inflammatory disease in other systems such as musculoskeletal disease. We have been disappointed in tyrosine kinase inhibitors due to lack of response and toxicity but recognize some report a positive experience[56]. Biological agents (rituximab), anti-cytokines (tocilizumab, anti-TGF-beta), proteasome inhibitors (bortezomib), agents that may alter integrin binding, and blocking lysophosphatidic acid are being studied, but their efficacy and safety is still unknown. Use

of these agents is limited by availability and when used should be done at specialty Centers or in the setting of an organized clinical trial.

Immunoablation therapy with hematopoietic stem cell transplant (HSCT) can be considered in severe cases of rapidly progressive skin disease, particularly with significant associated internal organ disease. HSCT has been compared to intravenous cyclophosphamide (CYC) therapy in preliminary trials both in the United States and Europe. A large European trial (ASTIS- trial) was reported in abstract[57]. Patients with early progressive diffuse scleroderma with or without major organ involvement were eligible. Seventy-nine patients randomized to a transplant arm underwent mobilization with cyclophosphamide 2×2 g/m^2 + G-CSF 10mcg/kg/d, conditioning with cyclophosphamide 200 mg/kg, rbATG 7.5 mg/kg, followed by reinfusion of CD34+ autologous HSCT. Seventy-seven randomized to the control arm were treated with 12 monthly intravenous pulse cyclophosphamide 750 mg/m^2[57]. The trial showed fewer deaths in the transplant arm (16/79) compared to cyclophosphamide (24/77); a higher treatment related mortality (8/79; 10%) was seen in the HSCT group. There were no deaths from treatment related causes in the control arm[57]. One similarly designed but smaller USA 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 USA trial (SCOT-trial) is comparing the safety and efficacy of CYC/total body irradiation (TBI)/ATG autologous transplant versus monthly IV cyclophosphamide. The results of this trial are still pending. An uncontrolled trial demonstrated that immunoablation (CYC 50 mg/kg/day X 4 days) followed by granulocyte colony stimulatory factor (5 microg/kg/day) 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 process. A skeletal myopathy defined by weakness and elevated CPK, abnormal electromyography and/or muscle biopsy may also be present and was detected in 17% of 1,095 patients in one study[61].

The inflammatory component responds to traditional therapy for synovitis or myositis, while the treatment for the fibrotic process is not ideal and follows the same approach as outlined for the overlying skin disease. A non-steroidal anti-inflammatory, low dose (<10mg) corticosteroids, and pain control will improve the QOL. Weekly methotrexate is the recommended first-line disease modifying therapy for musculoskeletal disease. TNF inhibitors are reported to be effective for active polyarthritis[62]. IVIG 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 course of disease to improve function and maintain activity of daily living. Evidence supports the idea that physical activity and active motion of involved tissues improves long-term outcomes.

Lung

Lung disease is now the leading cause of death in scleroderma[16]. Involvement often is detected before there are clinical signs or symptoms, and it is common in all subtypes of disease. There are two major pathological processes present to some degree in the lungs of

most patients: (1) fibrosing alveolitis that can lead to restrictive lung disease or (2) obliterative vasculopathy of medium and small pulmonary vessels that in some cases causes pulmonary arterial hypertension (PAH).

Interstitial Lung Disease—Interstitial lung disease (ILD) is reported in about 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 anti-topoisomerase 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 both early and late disease, we perform pulmonary function at least annually in all patients and often at 4–6 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% decline usually over 4–6 months) or abnormal findings of ground glass changes with some fibrosis on HRCT. Bronchoalveolar lavage (BAL) 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 about 15–20% 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 one year. The 2-year post treatment 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 IV cyclophosphamide[71,72]. Although the 1-year oral exposure to cyclophosphamide had a tolerable toxicity profile[73], most experts will now move from cyclophosphammide to another maintenance immunosuppressive drug (e.g. 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 underway comparing cyclophosphamide to mycophenolate in 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 6–12 months in severe disease followed by mycophenolate maintenance for 3–5 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 scleroderma renal crisis. For refractory cases, other immunosuppressive/anti-fibrotic agents are being used but have been either ineffective (e.g. endothelin-1 blocker) [75] or controlled trials are needed (e.g. rituximab, imatinib) [76].

Pulmonary vascular disease—Isolated PAH is more common in patients with limited skin disease and is seen in about 8–12% of all patients[34,77,78]. The presence of numerous cutaneous telangiectasias[79], a decreasing diffusing capacity on pulmonary function[80], a rising estimated right ventricular systolic pressure as estimated by serial echocardiography[81], late age of disease onset [6], elevated NT-proBNP[82] and presence of anti-centromere antibody are associated with an increased risk of developing pulmonary hypertension. It is recommended that annual screening with pulmonary function testing and echocardiography be performed.

Pulmonary vascular disease in scleroderma can be caused by isolated pulmonary arterial hypertension (PAH), pulmonary hypertension (PH) secondary to left heart disease, PH due

to severe ILD and/or chronic hypoxia and, rarely, due to pulmonary veno-occlusive disease (PVOD). 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]. Non-invasive testing using both echocardiographic and pulmonary function studies are being used to better detect early disease and select appropriate high risk patient for RHC[85]. Exercise-induced pulmonary hypertension may represent an early phase of cardio-pulmonary disease that can be detected by exercise echocardiography or an exercise challenge during right heart catheterization[86]. While more studies are needed to confirm if this approach, exercise studies are being done at specialty Centers to discover early emerging PAH or PH in patients suspected of having early pulmonary vascular disease (unexplained breathlessness, isolated low DLCO 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 dramatic long-term improvement[89]; especially when started in the setting of an advanced WHO functional class (FC) or when there is associated severe ILD[90–92]. Goal directed therapy is now used define treatment. For example, for PAH patients diagnosed in WHO FC III, the treatment goal is to improve to WHO FC II. Oral therapy is recommended for moderate to severe PAH with clinical status of WHO class II-III; while continuous infusion of a prostacyclin analogue (epoprostenol, treprostinil or iloprost) via a centrally placed intravenous line or subcutaneous route is used for severe cases or those failing oral therapy. Oral agents include endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase type 5 inhibitors (sildenafil, taldalafil). Aerosolized prostaglandins (iloprost, treprostinil) are also now available for severe PAH. Maintenance of PAH-SSc patients in WHO FC II with monotherapy often fails, and sequential goal-directed combination therapy is now becoming an accepted treatment strategy. Disease modifying drugs rather than vasodilator drugs alone (e.g. immunosuppression: rituximab or antifibrotic agents such as imatinib) are now being tested to determine if 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 impact 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) 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's esophagus. The severity of patient reported symptoms may not accurately reflect the seriousness of the esophageal disease, and therefore we tend to treat patients with mild symptoms aggressively.

Special studies (esophagogastroduodenoscopy, barium esophagram, cine-esophagram, esophageal manometry) are reserved for patients who do not respond as expected to an

aggressive anti-reflux program, and endoscopy is often the most informative study. Education about standard nondrug measures is critical including eating several smaller meals rather than traditional three 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 H2-blockers is generally not as effective as proton-pump inhibitors (e.g., omeprazole or esomeprozole). 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 GERD, anorexia, or the sensation of bloating. A prokinetic drug (e.g, metoclopramide, domperidone, 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 pro-kinetic 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 (GAVE) with significant asymptomatic bleeding[99]. Argon plasma coagulation therapy is effective in controlling the bleeding in the majority 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 causing 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 non-compliance and dysfunction of rectal sphincters. The mainstay of management of lower bowel disease is a strategy to avoid a constipation-diarrhea cycle (e.g, fiber diet, stool softener, periodic polyethylene glycol, probiotics) and the use of cyclic antibiotics. Octreotide is reported 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 a scleroderma renal crisis (SRC) defined as accelerated arterial hypertension and/or rapidly progressive oliguric renal failure. A SRC occurs in approximately 10% of all patients and 20–25% of patients with anti-RNA polymerase III antibodies, with 75% of cases occurring within the first four 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 ANCA-related crescentric glomerulonephritis are reported that can mimic a SRC[102]. Therefore, we recommend that a comprehensive work-up including a renal biopsy is done in patients presenting with renal failure to exclude other treatable causes of disease.

In SRC, early detection and rapid use of an of angiotensin-converting enzyme (ACE) inhibitors 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 a SRC is not recommended[103]. Any hypertension (>140/90) in a scleroderma patient should be urgently evaluated in that patients presenting later with a creatinine greater than 3.0 mg/dL 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. A 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 scleroderma renal crisis mimicking thrombotic thrombocytopenic purpura (TTP). In these cases plasma exchange has been used but benefit is not proven.

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

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

Heart

The heart is 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 associates with a poor prognosis[36]. Objective testing (e.g. electrocardiography, echocardiography, nuclear imaging, MRI) 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 causes ischemia reperfusion injury[110]. Although still controversial, there is epidemiological evidence for an increased risk of atherosclerotic coronary artery disease similar to that found in other rheumatic diseases[111–113]. 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 BNP), 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, 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 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 asymptomatic small pericardial effusion can be watched cautiously. Current anti-fibrotic agents have not been studied for heart disease and some may have cardiac toxicity (e.g. imatinib mesylate).

Other

Several common problems are often overlooked including microstomia, xerostomia, Sjogren's syndrome, periodontal disease, audiovestibular disease, primary biliary cirrhosis, autoimmune hepatitis, bladder dysfunction, erectile dysfunction, thyroid disease and neuropathy[119]. It is recommended that at baseline a comprehensive evaluation is done to seek evidence for these complications including specific tests: pulmonary function testing, echocardiography, a complete blood count, liver function, muscle enzymes, 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 impact 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 (e.g. telangiectasias, loss of vermillion border of the lip, 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 PDE5 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 impact that the physical and psychological factors have on an individual's QOL[120,123].

Monitoring

There are many tools used to measure scleroderma disease severity and activity that are useful both clinically and in research. At first encounter performing a pulmonary function test with diffusing capacity (DLCo) is recommended. We repeat PFTs annually, and obtain a HRCT if pulmonary function is declining or the patient has developed new onset dyspnea. Establishing a baseline modified Rodnan skin score and repeating this at each visit provides 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 count, metabolic state, and renal function are important. Yearly pulmonary function with careful attention to the FVC and DLCo and an echocardiography to monitor the estimated right ventricular systolic pressure should be done[124]. Age-appropriate malignancy screening should be performed given the increased risk of malignancy in patients with scleroderma. Visits to re-examine and discuss overall emotional and physical status is defined by the individual situation but we recommend at least a 6 month bedside re-evaluation 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], SF-36, Medsger severity index[128], the United Kingdom Function Score[129] and various organ specific measures[94].

Summary

The main message of this review is that while there is no curative treatment for scleroderma, there are many treatment options to improve both quality of life and survival. Early detection of disease and immediate intervention appears to make a difference. It is important to appreciate that scleroderma is a very 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.

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Abbreviations

ATG	Anti-thymocyte globulin
DU	Digital ulcers
FVC	Forced vital capacity
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
PH	Pulmonary hypertension
PAH	Pulmonary arterial hypertension
QOL	Quality of life
RP	Raynaud's phenomenon

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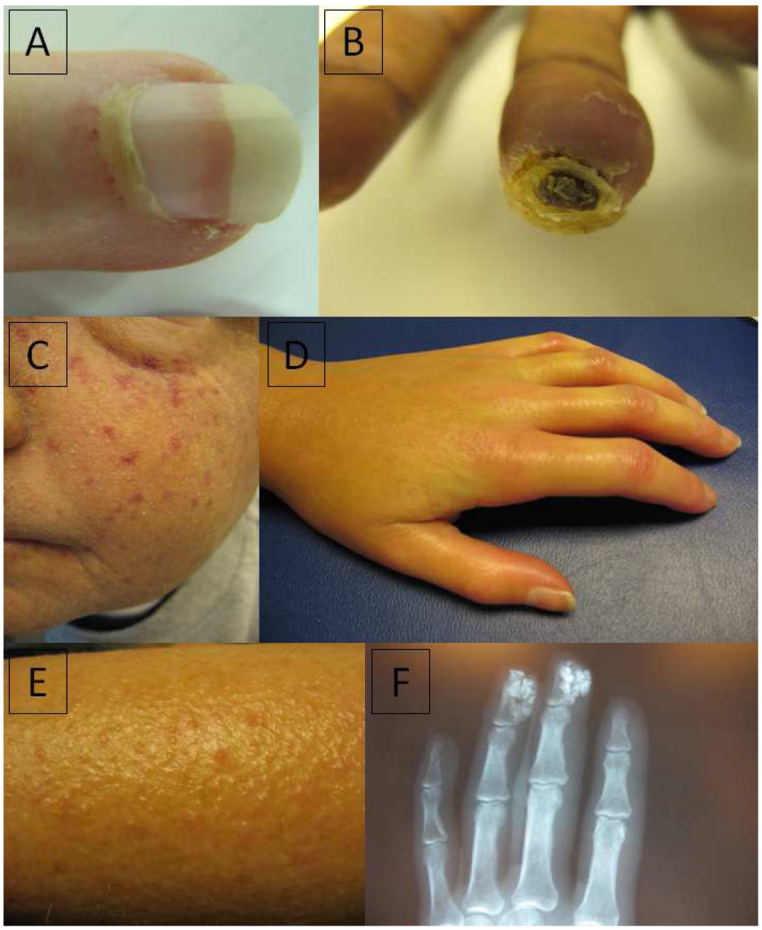

Figure 1. Clinical features in systemic sclerosis

(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, (F) Subcutaneous Calcinosis.

Table 1

Phenotypic characteristics and their autoantibody associations in scleroderma[125,126, 27,28]

Autoantibody	Phenotype
Centromere proteins B, C	Limited cutaneous disease/CREST syndrome
	Ischemic digital loss
	PAH
	Overlap syndromes: Sjogren's, Hashimoto's, 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) *	Diffuse > limited cutaneous disease
	PAH
	ILD
	Cardiac and skeletal muscle disease
	Small bowel involvement
	African-Americans
B23 *	PAH
PM/Scl	Limited > diffuse cutaneous disease
	Myositis overlap
	Acro-osteolysis
	ILD
Th/To *	Limited cutaneous disease
	ILD
	PAH
	Small bowel involvement
U11/U12 RNP *	ILD
Ku *	Limited cutaneous disease
	Myositis

GAVE: gastric antral vascular ectasia, PAH: pulmonary arterial hypertension, ILD: interstitial lung disease

*These antibodies are not easily available or commercially available at present.

Table 2

Management Principles

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 impact longevity and quality of life.**

SPECIFIC STEPS *

Determine peripheral vascular disease severity: Raynaud's phenomenon

- How frequently do attacks occur?
- Does this impact 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's 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 exam?

➢ Therapeutic principle: Traditional cytotoxic Immunosuppressive therapies (e.g. methotrexate, mycophenolate, 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 declining on serial PFTs?
- Is the RVSP ≥ 40 mmHg OR is the RVSP rising on serial echocardiograms OR is there an isolated decline in DLCO (without decline in FVC)?
- Is there new onset, unexplained dyspnea?

➢ Evaluation Strategies and Therapeutic Principle: HRCT should be performed in the patient with declining FVC to evaluate for ILD. Evidence of ground glass changes with fibrosis may warrant immunosuppressive therapy. In the patient with high or rising RVSP, or declining DLCO, assessment with exercise testing and right heart catheterization for PAH is necessary.

Identify dominant gastrointestinal symptomatology that is attributable to scleroderma: GERD, dysphagia, abnormal gastric emptying, constipation, diarrhea, fecal incontinence

- Are there symptoms of indigestion or heartburn?
- Is xerostomia a contributing factor to dysphagia?
- Is there difficulty with oropharygeal bolus transfer to suggest pharyngeal weakness?
- Are there episodes of choking or 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 is 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 not responding to therapy. Titration to twice daily dosing, addition of night-time H2-blocker and/or the addition of a prokinetic drug (metoclopramide, domperidone) may be necessary. Therapy should be directed at the underlying etiology. For lower GI symptoms, a bowel regimen (e.g. polyethylene glycol) for constipation and 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.

* Details for these areas as well as musculoskeletal, renal, cardiac, dental, sexual and endocrine manifestations may be found in the text and accompanying references.