Systemic sclerosis (scleroderma, SSc) is a serious multi-system disease of unknown etiology that affects approximately 100,000 individuals in the United States. SSc has a predilection for women, with a peak onset during childbearing years, but it also affects men, children, and the elderly. Although the etiology of SSc remains obscure, research over the past 30 years implicates an altered immune system that, in ways that are only now becoming clear, leads to vascular injury and fibroblast activation. The latter process culminates in excess collagen synthesis. Collagen deposition in the skin leads to the hallmark of the disease, scleroderma, and deposition in vessels and internal organs may lead to significant morbidity and mortality (Table 1).

The cost of SSc has been difficult to ascertain, largely because it is a relatively rare condition and reliable national databases are virtually nonexistent. Nevertheless, a recent study utilizing primary and secondary data sources and a prevalence-based, human capital approach estimated the annual direct and indirect costs of SSc in the United States to be $1.5 billion [1]. Morbidity represents the major cost burden, with costs of nearly $820 million (56% of total costs). Thus, like other relatively rare diseases, SSc has a low frequency but a high economic impact.

Systemic sclerosis is perceived as a serious and often life-threatening disease for which no treatment is available. The perception that “nothing can be done” may exist because the failure of therapies aimed at treating the skin manifestations of SSc has overshadowed advances in the treatment of internal organ complications. Although a disease-modifying treatment for SSc has remained elusive, the situation for an individual patient is far from hopeless.

Standardized instruments to measure clinically important changes in disease status have only recently been developed. The modified Rodnan skin score has been shown to have acceptable interobserver and intraobserver validity and is now used in clinical trials as a primary endpoint for effects of treatment on skin thickening [2,3]. A Scleroderma Health Assessment Questionnaire (SHAQ) has been developed and is being used in clinical trials as a measure of the impact of the disease on patients’ quality of life [4]. A preliminary disease severity scale that was recently developed and validated [5] should be useful for assessing disease severity status in individual patients and will assist in the design and conduct of clinical trials.

This article will review the therapeutic approaches used to manage the complications of SSc, with a focus on the impact of treatment on patient outcome.

Management of Clinical Manifestations

Skin Involvement

Although skin thickening is the hallmark of SSc, it is not a cause of mortality. However, there is certainly morbidity from cutaneous ulcerations and from diminished mobility of joints (particularly in the hands). Despite many attempts using various drugs and procedures, no systemic treatment has been shown to have an effect on skin thickening in properly controlled trials.

Many treatments have been proposed and tested in SSc. The scleroderma literature is marked by a recurrent finding: Treatments that appeared to be beneficial when applied in uncontrolled pilot trials have failed to have demonstrable efficacy when subjected to rigorously controlled trials. The natural history of SSc contributes to this pattern. In patients with diffuse SSc, the most rapid worsening of the skin often occurs within the first few years of illness, followed by a gradual decline in the thickness of skin, with the end result being an atrophic dermis. A treatment initiated at the time of maximal skin thickening creates an illusion of effectiveness, when in reality the improvement has resulted from the natural history of the disease process. Furthermore, no treatment is likely to be beneficial when employed in late-stage disease.

A number of proposed therapies have been investigated in controlled trials, with disappointing results [6–19] (Table 2). Pilot trials of various treatments have been reported as well, including cyclosporine [20], interferon [21], and, most recently, minocycline [22]. All of these trials reported improvement or stabilization of skin score, but a cautious skepticism must be reserved until controlled trials are undertaken. There has been recent interest in autologous stem cell transplantation for treatment of SSc, with reports of both success and failure.
of this very aggressive therapy [23,24]. For now, stem cell transplantation must be considered a possible but unproven therapy.

A placebo-controlled study of the protein hormone relaxin is currently underway. This substance is known to decrease collagen synthesis in vitro and to “relax” uterine and pelvic tissue during pregnancy. The results of a preliminary study were encouraging, but whether relaxin will be the first scientifically proven treatment for scleroderma remains to be seen.

Renal Disease
Improving survival of patients in renal crisis has been the single most dramatic change in the outcome of SSC. Renal crisis manifests as the abrupt onset of severe hypertension and a rapid deterioration of the glomerular filtration rate. This life-threatening event is more likely to occur in individuals with diffuse cutaneous SSC when their skin disease is rapidly worsening. The use of glucocorticoid medications and heart involvement have also been associated with the development of renal crisis. The pathogenesis of this renal disease involves narrowing of the lumen of the renal arterioles, leading to decreased blood flow. Elevated renin levels stimulate further vasoconstriction through increased angiotensin levels. Thus, a cycle is established that results in elevation of arterial pressure to malignant levels. Prior to the introduction of medications capable of interrupting this cycle, the result was rapid progression to end-stage renal disease, often with concomitant cerebrovascular accidents and/or heart failure.

The introduction of angiotensin-converting enzyme (ACE) inhibitors in the late 1970s dramatically altered the course of this feared complication (Figure). These medications have become the standard of treatment because of their ability to interrupt the renin-angiotensin system responsible for severe hypertension. The early administration of ACE inhibitors can not only control the hypertension but can also prevent deterioration of renal function. Even when renal failure occurs and patients progress to dialysis, the continued use of these potent drugs has allowed some patients to discontinue dialysis after 1 year.

Detection of SSC renal crisis in its earliest stages is critical. Patients should be counseled to purchase home blood pressure monitoring equipment and should be given systolic and diastolic parameters. Patients should be asked to call the physician if these parameters are exceeded so that appropriate treatment can be started. Because the outcome of renal crisis hinges to such a degree on initiation of early therapy, patients with acute onset hypertension with or without renal failure should be hospitalized to allow close monitoring of blood pressure and ACE inhibitor dose titration. Treatment should be initiated with an ACE inhibitor that has a short plasma half-life so that dose changes can be accomplished quickly. The first ACE inhibitor, captopril, has the shortest half-life and consequently is recommended in this circumstance. Dose escalation should occur.
every 6 to 12 hours as necessary to normalize the blood pressure. Other antihypertensive agents such as calcium channel blockers, α-adrenergic blockers, β blockers, or minoxidil should be added as necessary to control blood pressure in the normal range. Even if dialysis is required, the ACE inhibitor should be continued to allow the best chance of return of renal function. Once blood pressure control is achieved, a long-acting ACE inhibitor can be substituted for captopril. There are isolated reports of the newer angiotensin II–receptor blockers being used for control of SSc renal crisis, since they are also able to interrupt the renin-angiotensin system. Because these drugs have a long half-life, they should not be used for initial therapy but can be used for maintenance of blood pressure control.

Occasionally, renal failure occurs in SSc patients who have not become hypertensive (ie, normotensive renal failure). This complication appears to occur more often in patients who have had myositis and have been treated with glucocorticoids. Many of these individuals have thrombocytopenia and hemoptysis. In our experience, normotensive renal failure does not respond to ACE-inhibitor therapy and carries a high mortality.

Raynaud’s Phenomenon
Raynaud’s phenomenon (RP)—episodic blanching and/or cyanosis of the digits upon cold exposure—is a common symptom in the general population (3% to 10% in population-based studies). The term primary RP is applied to this benign form. Among SSc patients, however, the prevalence of RP is 90% to 95%, and RP is often the initial symptom of SSc. In patients with primary RP, the digital blood vessels are histologically normal yet display increased cold-induced vasoconstriction, whereas in SSc patients the digital blood vessels have intimal hyperplasia compromising the vessel lumen. The result is painful, cold-induced ischemia of the digits with development of digital tip ulcerations, gangrene, and, among some patients, autoamputation.

When evaluating RP in SSc patients, it is important to keep in mind that there may be proximal arterial disease as well as involvement of the digital arteries and arterioles. Radial or ulnar artery involvement should be sought by applying Allen’s test. Arteriography should then be used to test for blockage in 1 of these arteries. Bypass surgery to alleviate the blockage, in combination with microdissection and digital artery sympathectomy, has been demonstrated to improve blood flow and speed healing of ulcers in some cases [25]. Pharmacologic treatment of RP is based on vasodilating drugs to decrease the number and severity of RP attacks. Calcium channel blockers such as nifedipine have been shown to decrease attack rates and are generally well tolerated by patients. Some problems that may occur with the use of these drugs include headache, edema, postural hypotension, and worsening of gastroesophageal reflux. If calcium channel blockers fail or are poorly tolerated, α-adrenergic blockers such as prazosin may be substituted or added. Although there is no proof of its effectiveness, low-dose aspirin is usually given to inhibit platelet function. Topical nitroglycerin may be applied at the base of digits to dilate arteries.

When ischemic digital ulcerations become infected, treatment with topical or systemic antibiotics may be required. Healing times can be quite prolonged due to the ischemic nature of the ulcers.

Gastrointestinal Involvement
Nearly all SSc patients have involvement of the gastrointestinal tract, although the severity of symptoms varies widely. More than 90% of patients have esophageal symptoms. Diminished lower esophageal sphincter function with resultant gastroesophageal reflux results in pyrosis, bleeding, and/or stricture formation. Reduced effectiveness of peristalsis causes dysphagia and regurgitation.

No medication has been shown to alter the pathology seen in the esophageal musculature, but the secondary effects of esophageal involvement can be ameliorated. Medications to increase gastric pH can be effective in reducing the symptoms of reflux. Although histamine, receptor blockers are somewhat effective in this regard, proton pump inhibitors are much more effective and widely preferred by patients. Use of prokinetic drugs such as cisapride may increase esophageal motility. This medication increases peristalsis and is taken 30 minutes before meals and at bedtime. Physical measures to reduce acid reflux are also important and should include elevating the head of the bed 4" to
Heart Involvement
Cardiac involvement in SSc may include the myocardium (manifest as congestive heart failure and arrhythmias), the pericardium (pain and/or tamponade), or the conduction system (heart block). Such involvement is associated with a significantly reduced survival rate. The underlying pathology of the myocardial involvement is fibrosis, which may result from intramyocardial coronary artery involvement. Histologic examination may show contraction band necrosis indicative of ischemia. There has been some interest in using vasoactive drugs to treat the myocardial pathology seen in SSc. Defects in perfusion of the myocardium can be detected by thallium scanning and have been shown to be improved by vasodilators such as nifedipine, nicardipine, and captopril. However, whether this demonstrated improvement in myocardial blood flow has clinically important benefits is unknown.

Heart failure, heart block, and arrhythmias are treated as they would be in any other clinical situation. ACE inhibitors are useful, particularly when hypertension complicates the clinical picture. Treatment of pericarditis with nonsteroidal anti-inflammatory drugs or corticosteroids may be necessary. Tamponade may necessitate percutaneous or open surgical drainage. Heart block may require pacemaker insertion.

Pulmonary Involvement
Significant and life-threatening lung disease has become a more important clinical issue since the introduction of ACE inhibitors and the resultant improved survival from renal crisis. Life-threatening SSc lung disease generally takes 1 of 2 forms: severe interstitial fibrosis or severe pulmonary artery hypertension. In the former, the presence of increased numbers of activated alveolar macrophages, neutrophils, and eosinophils in bronchoalveolar lavage (BAL) fluid is a marker of alveolitis and is associated with greater pulmonary dysfunction and a higher propensity for decline in pulmonary function than in SSc patients whose BAL fluid has normal cellularity.

No drug has been shown to effectively alter the course of SSc lung disease in a controlled, prospective trial. Forced vital capacity (FVC) generally is not improved by treatment with D-penicillamine, para-aminobenzoic acid, colchicine, griseofulvin, or chlorambucil; however, in both a retrospective study and an uncontrolled prospective trial, cyclophosphamide increased FVC significantly. Based on these and similar studies, the National Institutes of Health recently funded a prospective, double-blind, placebo-controlled trial of daily oral cyclophosphamide for SSc patients whose pulmonary involvement includes the presence of active alveolitis.

Another potentially life-threatening pulmonary complication of SSc is pulmonary hypertension. Clinically significant pulmonary hypertension occurs in approximately 10% of patients with CREST syndrome (a form of SSc characterized by the presence of Calcinosis, Raynaud’s phenomenon, Esophageal dysfunction, Sclerodactyly, and Telangiectasia), usually many years after the onset of RP. Marked reduction in the diffusing capacity of lung for carbon monoxide (DLCO), particularly in the absence of radiographic or spirometric evidence of restrictive lung disease, should alert the clinician to the presence of pulmonary hypertension. Any SSc patients with complaints of dyspnea, chest pain, or syncope in whom the DLCO is reduced should undergo echocardiography with noninvasive Doppler estimation of pulmonary artery pressure.

Patients with CREST syndrome and pulmonary hypertension have a 2-year cumulative survival rate of only 40%, compared with 88% for patients with CREST syndrome without pulmonary hypertension. Calcium channel blockers such as nifedipine may lower pulmonary artery resistance. Nifedipine therapy (10 mg 3 times daily) may also be associated with a rise in the DLCO [26]. For SSc patients whose pulmonary hypertension fails to respond to conventional vasodilator therapy, continuous intravenous infusion of epoprostenol may provide significant benefits by lowering pulmonary vascular resistance, raising cardiac output, and improving quality of life. Such therapy is costly (up to $60,000 annually) and may be complicated by infections, bleeding, and/or clotting problems [27]. However, it can be life-saving for the SSc patient who fails conventional therapy and for whom heart-lung transplantation is rarely an option. Less costly and less invasive methods of drug delivery are currently under investigation.

Future Directions
Clearly, the capability of physicians to manage the outcome of SSc has improved in recent years. The future is even brighter, as we are on the cusp of new breakthroughs associated with the introduction of biologic response modifiers directed against cytokines and growth factors. The challenges of SSc remain early diagnosis and staging of disease, together with basic research on the mechanisms governing fibrosis.
Despite the obstacles of managed care and the turmoil in academic health centers, major advances are on the horizon and the outcome for many SSc patients will certainly improve.

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References