CHAPTER 17

Systemic Sclerosis
C. Treatment and Assessment

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- Systemic sclerosis (SSc; scleroderma) targets several aspects of disease pathophysiology: vascular features that are currently highly treatable; inflammatory features that are currently partly amenable to therapy; fibrotic features for which therapies of modest efficacy (at best) exist; and atrophic, end organ damage for which only supportive therapy is available.
- The extent of skin involvement is neither a robust primary outcome measure for clinical trials nor a reliable guide to the therapy of individual patients.
- Regular pulmonary function testing is a cornerstone of assessment.
- Continuous intravenous epoprostenol, subcutaneous or intravenous treprostinil, and bosentan all have important roles in selected patients with pulmonary arterial hypertension.
- Early recognition of scleroderma renal crisis (SRC) and prompt treatment with angiotensin-converting enzyme (ACE) inhibitors has improved outcomes in SRC dramatically.
- Cyclophosphamide is a cornerstone of interstitial lung disease treatment in SSc, but the therapeutic gains from this agent are relatively small.
- Long-term proton-pump inhibition is highly effective in treating the gastroesophageal reflux. High doses, sometimes two to three times the normal therapeutic dose, are required to alleviate symptoms.

Systemic sclerosis (SSc, scleroderma) has one of the highest mortality rates among all connective tissue disorders. To date, no effective therapy that addresses the underlying disease process exists. Significant strides have been made in improving survival, however, largely through therapies directed at the treatment of specific organ complications. State-of-the-art management entails organ-based therapy with particular attention to lung and renal involvement, the major causes of morbidity and mortality. This strategy emphasizes the role of early detection of internal organ involvement, and the timely implementation of treatment. In simple terms, SSc includes vascular features that are eminently treatable; inflammatory features that are at least partly amenable to therapy, as well; fibrotic features for which therapies of modest efficacy (at best) exist; and atrophic, end organ damage for which only supportive therapy is available.

ASSESSMENT OF DISEASE

The extent of skin involvement is the basis for SSc subset classification and a major indicator of risk for certain internal organ complications. Unfortunately, skin involvement is neither a robust primary outcome measure for clinical trials nor a reliable guide to the therapy of individual patients. Monitoring for lung involvement with regular pulmonary function testing is a cornerstone of assessment, particularly in patients with early diffuse scleroderma. Reduction in forced vital capacity suggests the presence of interstitial lung disease, which is usually confirmed then by the demonstration of reticular or alveolar parenchymal disease on high resolution computed tomography (CT) of the chest.

Isolated or disproportionate reduction in diffusing capacity suggests pulmonary vascular pathology; namely, pulmonary arterial hypertension (PAH).

Doppler echocardiography can provide estimates of pulmonary artery pressures and is useful in serial follow-up, but right heart catheterization remains the gold standard for confirmation of that diagnosis (1).

Measures of renal function and blood pressure serve as prime indicators of scleroderma renal crisis in early diffuse disease. Creatinine phosphokinase and aldolase levels are sensitive indicators of myositis/myopathy. Specific serologies, including antitopoisomerase and anti-U1RNP antibodies, predict diffuse disease. In contrast, anticentromere antibodies predict limited SSc. Not all patients with scleroderma are positive for one of these autoantibodies (see Chapter 17A).

TREATMENT

When treating individual complications, a core set of principles applies, regardless of patients' subset and stage. Certain targeted treatment approaches may also address individual organ system components of disease. Disease subset and stage, however, are key in guiding initial treatment. Progression of skin changes in early, diffuse SSc signals the need for aggressive management to limit internal organ damage. The precise choice of therapy depends upon the specific organ system manifestations.

The natural tendency for skin involvement to improve by the second to third year complicates the assessment of treatment efficacies. Therapeutic strategies have evolved rapidly in recent years, but still permit relatively few evidence-based approaches (see Figure 17C-1). The next sections focus in turn on treatments of the vascular, inflammatory, and fibrotic components of scleroderma.

Vascular Therapy

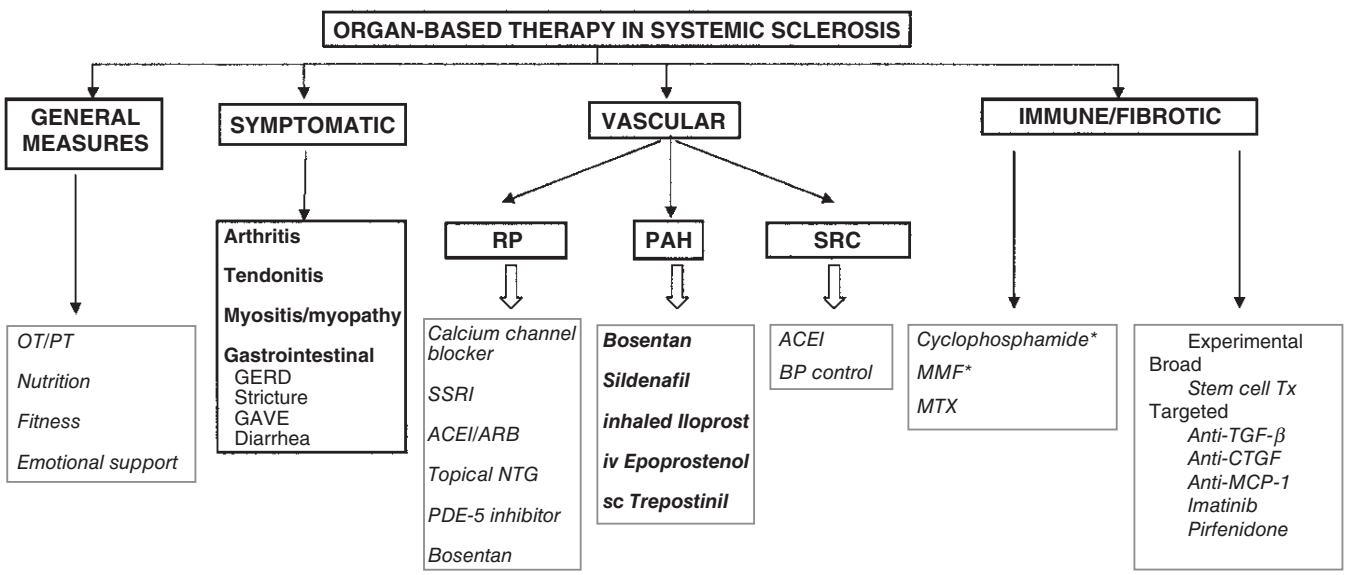
Complications of scleroderma that result clearly from vascular dysfunction include PAH, scleroderma renal crisis (SRC), and Raynaud's phenomenon (RP). Treatment approaches to these disease manifestations are evolving rapidly (2).

Pulmonary Arterial Hypertension

The endothelial dysfunction of PAH leads to increased endothelin and reduced nitric oxide and prostacyclin. Continuous intravenous epoprostenol (Flolan) and subcutaneous or intravenous treprostinil (Remodulin), both US Food and Drug Administration (FDA)–approved therapies, are consensus first-line treatments for PAH patients with World Health Organization (WHO) class IV disease. The delivery systems (indwelling catheters), associated risks (line infection), and

FIGURE 17C-1

A summary of organ-directed treatment in limited and diffuse scleroderma. Treatments in bold: FDA-approved. Cyclophosphamide*: Confirmed efficacy over placebo in a randomized, double-blind study in patients with interstitial lung disease. MMF×: No controlled studies. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CTGF, connective tissue growth factor; GAVE, gastric antral venous ectasia; GERD, gastroesophageal reflux disease; MCP-1, macrophage chemoattractant protein 1; MMF, mycophenylate mofetil; MTX, methotrexate; NTG, nitroglycerin; OT/PT, occupational therapy/physical therapy; PAH, pulmonary arterial hypertension; PDE-5, type 5 phosphodiesterase; RP, Raynaud's phenomenon; SRC, scleroderma renal crisis; SSRI, specific serotonin receptor uptake inhibitor; Stem cell Tx, stem cell transplantation; TGF-β, transforming growth factor beta.



other side effects (infusion site pain) have forced a search for alternative therapies.

The selectivity of prostacyclin's effects on pulmonary vasculature provided the rationale behind the development of inhaled therapy for PAH, which have the added potential advantage of avoiding some systemic side effects. Repeated inhalation of iloprost (Ventavis) has been shown to improve function and hemodynamics, and to slow the rate of clinical decline. The role of endothelin 1 in idiopathic PAH and SSc-PAH pathophysiology has led to the development of endothelin receptor antagonists (ERA). Bosentan (Tracleer), an oral, nonselective ERA, is considered a first-line therapy in WHO class III patients. Regular monitoring is required for possible abnormal liver function.

Other ERA therapies are under investigation. Type V phosphodiesterase (PDE-5) metabolizes cyclic guanine monophosphate (cGMP). Inhibition of cGMP metabolism with the PDE-5 inhibitor sildenafil (Viagra) enhances pulmonary vasodilation. Side effects include axial muscle cramps. To date, long-term studies examining mortality as the primary outcome are not available for any agent. Combination therapies using agents from each of the different classes are under active investigation.

Scleroderma Renal Crisis

Development of accelerated to malignant hypertension with microangiopathic hemolytic anemia is the definition of SRC. Until the availability of angiotensin-converting enzyme (ACE) inhibitors, the treatment of SRC was extraordinarily difficult despite the use of other antihypertensive approaches, and the onset of SRC nearly always signaled a terminal phase of the illness.

Early recognition of SRC and the prompt institution of ACE inhibition (at the maximum tolerable dose) has improved outcomes in SRC dramatically. Deaths from SRC are now decidedly rare, and fewer than 50% of patients in SRC progress to end-stage renal disease (ESRD) (3). If patients do progress to ESRD, ACE inhibition should be continued into the phase of dialysis; some patients demonstrate renal recovery even after several months of dialysis.

For patients with diffuse scleroderma—the subset at highest risk for SRC—prophylactic treatment with an ACE inhibitor is advisable. Although not yet tested in a rigorous fashion, angiotensin receptor blockade (ARB) therapies are also probably efficacious in SRC.

Raynaud's Phenomenon

A growing number of treatments are now available for RP. A cornerstone of the therapy of this complication, however, is the maintenance of a warm core body temperature. In addition to gloves, handwarmers, and other approaches to warming the extremities, patients are strongly advised to several layers of clothing over their entire bodies, particularly during cold months.

Calcium-channel blockers, such as amlodipine, nifedipine, or felodipine, are the initial medical treatment for RP. Low dose selective serotonin reuptake inhibitors (SSRIs) are also used because of their allegedly salubrious effects on platelet aggregation and activation. Among the SSRIs, fluoxetine (Prozac; Symbyax; Sarafem) is the best studied. Despite their striking effectiveness in SRC, ACE inhibitors and ARBs are not particularly effective for RP.

Digital ischemia and ulceration are often managed with intermittent intravenous iloprost, particularly during the winter months. In addition, therapies introduced originally for the management of PAH now are being applied to the treatment of recalcitrant RP. Two large, multicenter, controlled trials of bosentan confirmed a reduction in the development of new digital ulcers compared to placebo (4). Case series and reports have suggested improved RP control with the use of sildenafil. Despite the improved options for the treatment of RP now, therapy is expensive, access often limited, and the responses (albeit dramatic in some patients) frequently inconsistent.

Anti-Inflammatory Treatments

In addition to the vascular nature of some scleroderma-related problems, other manifestations of this disease, for example, interstitial lung disease and myositis, have clear inflammatory components. At the present time, anti-inflammatory therapies for scleroderma are less targeted than are those for vascular problems. An approach involving the use of nonspecific, broadly immunosuppressive agents assumes that immunological activation influences both the fibrotic and vascular components.

Cyclophosphamide

Cyclophosphamide (CYC) has been used as the primary therapeutic agent for interstitial lung disease in scleroderma. In a recent controlled trial (5), cyclophosphamide improved forced vital capacity (FVC) by only 2.9% compared to placebo. Although the demonstration of a modest benefit of CYC supports its continued use, the small effect suggests the need for a more targeted approach.

Autologous Stem Cell Transplantation

Immunoablation with immune reconstitution using autologous peripheral stem cells has been considered for severe diffuse scleroderma. Pilot studies have suggested robust effects on skin and patient function and neutral effects on internal involvement (6). Ongoing studies comparing stem cell transplantation with CYC treatments will determine the appropriateness of this strategy.

Methotrexate

A randomized, controlled trial evaluating efficacy of methotrexate in early diffuse scleroderma suggested greater disease stability compared with placebo (7). The precise advantages conferred in clinical practice remain uncertain. Methotrexate use is reserved generally for early diffuse cases with features limited to skin and musculoskeletal systems, including myositis.

Mycophenolate Mofetil

Mycophenolate mofetil has not been studied in any controlled trials. Current anecdotal evidence suggests it may be effective in early diffuse disease, including cases complicated by interstitial lung disease (8).

Antifibrotic Therapy

Despite the fact that fibrosis is a central component to the pathophysiology of scleroderma, no agent designed to prevent fibrosis has been proven effective to date. Nonspecific agents, including D-penicillamine (9) and recombinant human relaxin, have failed in clinical trials. The importance of transforming growth factor beta (TGF-beta) expression in the pathogenesis of scleroderma has prompted the evaluation of agents that either trap or block TGF-beta. Although the use of an anti–TGF-beta antibody has been suggested in early studies to be safe, clinical benefit remains to be observed. Other anticytokine therapies, all of which remain unvalidated in scleroderma, are included in Figure 17C-1.

Other Organ-Specific Therapies

Aside from therapies directed against disorders of the lung, kidneys, and peripheral vasculature in scleroderma, the gastrointestinal tract is a common focus for organ-specific therapy. Long-term proton-pump inhibition is highly effective in treating gastroesophageal reflux, often a chronic problem leading to significant complications in scleroderma. High doses, sometimes two to three times the normal therapeutic dose, are required to alleviate symptoms. Dilatation of esophageal strictures is undertaken where indicated. Watermelon stomach, also known as gastric antral venous ectasia (GAVE), is now considered the most common cause of gastrointestinal bleeding in scleroderma. GAVE is diagnosed and treated with endoscopy and laser photocoagulation.

With regard to gut function, smooth muscle atrophy results in gastroparesis and small bowel hypomotility. Prokinetic agents, including metoclopramide and domperidone (the latter not available in the United States), are used with variable effects. Intestinal pseudo-obstruction may be managed cautiously with subcutaneous octreotide, a somastatin analogue. Abdominal bloating and/or diarrhea suggest small bowel bacterial overgrowth. This is treated with antibiotics, often rotating courses, to circumvent antibiotic resistance. One- to two-week courses of metronidazole (250 mg t.i.d.) or ciprofloxacin (500 mg q.d.) are usually prescribed. Advanced scleroderma involvement of the gastrointestinal tract may be dominated by fecal incontinence and constipation. Antidiarrheal agents and behavioral therapy in the form of biofeedback is undertaken to manage incontinence. Stool bulking and softening agents are the mainstay of treatment in addressing constipation.

CONCLUSION

Modern management of scleroderma is characterized most appropriately as organ-based therapy. Specific gains in the treatment of scleroderma renal crisis and pulmonary hypertension have unequivocally improved overall outcome and survival. Continued progress in our understanding of the disease will lead to more targeted, effective treatments.

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