Systemic sclerosis: new hope for an unyielding disease

Helen J Englert and Nicholas Manolios

There is still no cure, but what advances have been made in managing this disabling condition?

In its more aggravated forms diffuse scleroderma is one of the most terrible of all human ills. Like Tithonus [a Greek mythological hero who was granted immortality but not eternal youth] to “wither slowly” and like him to be “beaten down and marred and wasted” until one is literally a mummy, encased in an evershrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern.

Scleroderma encompasses the name of a disease and a clinical sign (thickened skin) that have eluded any unifying mechanism of causation. While we still await a cure, new and significant pharmacological agents are now available that can assist in the symptomatic treatment and disease modification of this condition.

The disease is uncommon, with Australian estimates of prevalence per 10,000 population ranging from 0.4–0.9 (Sydney, 1974–1988) to 1.47 (South Australia, 1993) to 2.4 (Tasmania, 2007). Scleroderma is classified into either localised (skin alone) disease or systemic (internal organ involvement ± skin) disease, which is known as systemic sclerosis. The principal subsets of systemic sclerosis are: diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis, systemic sclerosis sine scleroderma (systemic disease with no skin involvement), environmentally induced scleroderma, overlap syndromes and pre-scleroderma.

In limited disease, skin thickening is limited to the extremities distal to the elbows and knees, and the face. Diffuse disease, at its maximal extent, affects not only the skin of the distal extremities and face but also the skin over the proximal extremities and trunk. The disease has three pathological features: fibrosis with excessive collagen and other ground substance deposition; vasculopathy involving small and large vessels; and smooth muscle atrophy. In diffuse systemic sclerosis, inflammation and fibrosis predominate, whereas in limited disease, vascular changes predominate. While skin involvement (dermal inflammation and fibrosis) is associated with variable morbidity, it is the systemic manifestations, especially pulmonary and cardiac, and occasionally renal and gastrointestinal, that are responsible for much of the disease-related premature mortality.

Therapy is classified as either “disease-modifying” or “symptomatic” and is tailored to the individual’s tolerance and need. Therapeutic decisions are determined by the pattern of organ involvement (vital or non-vital), underlying pathological features, and other comorbidities. General measures such as staying warm, using gloves and skin moisturisers, taking antireflux or bowel motility agents, modifying timing and volume of meals, brushing teeth regularly to prevent caries, using eye drops for sicca symptoms, and avoiding aggravating factors are important first steps in treating and managing the condition.

In the early onset of systemic sclerosis, an activated immune system (Box 1) may be important in the pathogenesis of subsequent fibrotic and vascular lesions, so early disease-modifying drug therapy is aimed at suppressing the immune response. Immunosuppressive drugs such as methotrexate, cyclophosphamide and mycophenolate, often in conjunction with judicious use of corticosteroids (there is some controversy surrounding the causal association between high-dose corticosteroids and scleroderma renal crisis), intravenous gammaglobulin, and minocycline, have been used with varying measures of success. The levels of evidence for therapeutic intervention strategies are outlined in Box 2.

“Heavier” immunosuppression, with or without haemopoietic stem cell rescue, is contemplated in patients with early inflammatory vital organ involvement of the lung or myocardium. Two large multicentre Phase III studies — the ASTIS (Autologous Stem cell Transplantation International Scleroderma) Trial in Europe, and the SCOT (Scleroderma: Cyclophosphamide Or Transplantation) study in the United States — to determine the relative efficacy of haemopoietic stem cell transplantation compared with less rigorous immunosuppression are well underway.

In Australia, we have performed autologous stem cell transplantation in seven patients with systemic sclerosis who had progressive vital organ involvement and in whom conventional immunosuppression had failed, and noted a dramatic, sustained, long-term remission in four of them that featured marked skin softening, stabilisation of interstitial lung disease and a three- to fourfold fall in antinuclear antibody titre (HJE, personal communication). These findings support the use of autologous stem cell transplantation as a disease-modifying modality. The use of mesenchymal stem cells (MSCs) in the treatment of arthritic disease is novel, and this approach has shown great potential because of the ease of isolation, rapid growth and extensive culture expansion of MSCs suitable for therapeutic use. In diseases such as scleroderma where there is excessive mesenchymal overactivity, MSCs are an ideal candidate cell type for tissue regeneration and repair of damaged structures. Trials of therapeutic uses of MSCs are currently in progress.
Pulmonary arterial hypertension is a relatively common complication of systemic sclerosis and is caused by pulmonary arterial narrowing and thickening leading to increased pulmonary vascular resistance and arterial pressures (>25 mmHg). As early diagnosis and treatment can have a profound effect on outcome, it is extremely important to screen patients for this condition. The gold-standard screening procedure is right heart catheterisation. There is level I evidence of efficacy of three categories of medications for pulmonary arterial hypertension: endothelin receptor antagonists, prostanoids, and phosphodiesterase inhibitors. These may be used as a single agent or in combination, with combined epoprostenol and sildenafil being more efficacious than combined bosentan and sildenafil.

The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been found to favourably modify the outcome of the vascular pathological features of scleroderma renal crisis. Symptomatic therapies for microvascular hyperreactivity, upper and lower gastrointestinal dysmotility, and musculoskeletal symptoms are outlined in Box 2.

Promising new approaches include the use of a protein tyrosine kinase inhibitor, imatinib mesylate (Glivec, Novartis), that interferes with the signalling of platelet-derived growth factor and transforming growth factor-β, two pivotal mediators of the fibrotic process of systemic sclerosis. However, no biological agent has shown definitive evidence of efficacy thus far. Overall, despite the obvious absence of a cure, progress is being made in the understanding and management of this chronic and disabling rheumatic condition.

**Competing interests**

We have both received financial research support from Actelion (manufacturer of bosentan) in the past.

**Author details**

Helen J Englert, MB BS, PhD, FRACP, Rheumatologist and Head of Scleroderma Research, Centre for Research and Management of Systemic Sclerosis

Nicholas Manolios, MB BS, PhD, FRACP, Rheumatologist and Director Department of Rheumatology, Westmead Hospital, Sydney, NSW. 

**Correspondence:** nick_manolios@wmi.usyd.edu.au

**References**


Therapies directed toward modification of established fibrosis have been uniformly disappointing. D-penicillamine, previously the gold standard of scleroderma therapy, has fallen into disrepute after a US multicentre study showed no outcome difference between very low dose and usual dose D-penicillamine therapy. However, occasionally patients will exhibit resolution of skin fibrosis with little or no therapeutic intervention.