Systemic sclerosis: hypothesis-driven treatment strategies

Christina Charles, Philip Clements, Daniel E Furst

We review data from controlled trials and randomised controlled trials to examine the hypothesis for the pathogenesis of systemic sclerosis. Strategies used to treat the vascular complications in systemic sclerosis have so far shown the biggest successes, especially in the management of renal crisis and pulmonary arterial hypertension. Because these drugs have improved function and quality of life and have increased survival rates, they can truly be classified as disease-modifying compounds. Immunosuppressive therapy with cyclophosphamide in particular has also shown evidence of efficacy, and randomised controlled trials of autologous stem-cell transplantation are underway. So far, strategies to reduce or control fibrosis directly (bosentan, interferon gamma, and relaxin) have been disappointing but new strategies against fibrosis based on advanced understanding of the molecular biology of systemic sclerosis hold promise. Treatments against several cardinal features of the disorder simultaneously have not yet been examined but are being considered for future trials.

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Department of Medicine, Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA (C Charles MD, Prof P Clements MD, Prof D E Furst MD)

Correspondence to:
Prof Daniel E Furst, David Geffen School of Medicine at UCLA, 1000 Veteran Ave, Los Angeles, CA 90095-1670, USA
defurst@mednet.ucla.edu

Scleroderma is a rare but potentially devastating disease that occurs in 65–265 people per million.[1] The name scleroderma is derived from the Greek word skleros, which means hard, and derma, which means skin, hence the term "hard skin". This name describes the physical characteristic of skin hardening and thickening that includes a somewhat heterogenous group of disorders.[2,3] Scleroderma is divided into two forms: localised and systemic. Localised scleroderma is restricted to the skin and subcutaneous tissues. It includes disorders such as morphea, linear scleroderma, and other related syndromes. Systemic scleroderma, more appropriately referred to as systemic sclerosis, affects not only the skin but also internal organs.[4,5] In this Seminar, we focus on systemic sclerosis; we describe recent advances in the understanding of the pathogenesis of the disease and therapies that target three central areas of this pathogenic process. We also present data from controlled trials and randomised controlled trials to validate or invalidate pathophysiological aspects that are integral to the pathogenic hypothesis of systemic sclerosis. Since the trials have investigated the relations and interactions between the three cardinal features of the disorder (figure 1)[6] and not the environmental and genetic factors, we will also focus on these three cardinal features.

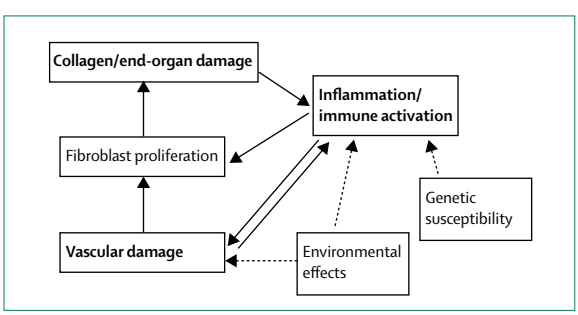

Figure 1: **Hypothesis for the pathogenesis of systemic sclerosis**

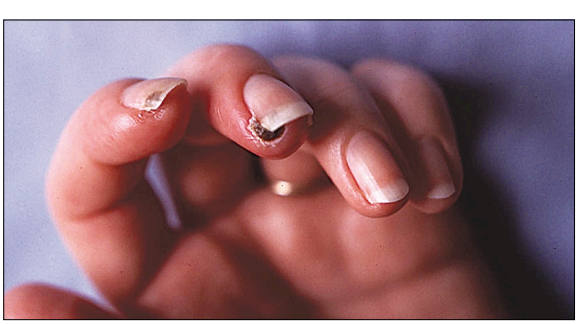

Figure 2: **Digital ulcers in the second and third digits of a patient with limited scleroderma**

Systemic sclerosis is divided into two major categories defined by the extent of skin affected.[4,5,7] Limited cutaneous scleroderma (or limited cutaneous systemic sclerosis; figure 2) is defined by skin thickening in areas solely distal to the elbows and knees, with or without facial effects. CREST syndrome, with its cardinal features of calcinosis, Raynaud's disease, oesophageal dysmotility, sclerodactyly, and telengiectasias, is an outdated term for what is now referred to as limited cutaneous systemic sclerosis. Diffuse cutaneous scleroderma (or diffuse cutaneous systemic sclerosis; figure 3) is defined by the presence of skin thickening that is proximal, as well as distal, to the elbows and knees, with or without facial or truncal effects.

The initial symptoms of systemic sclerosis (whether limited or diffuse) are typically non-specific and often include Raynaud's disease, fatigue, musculoskeletal complaints, and hand swelling. Oesophageal dysfunction, manifested as gastroesophageal reflux or dysphagia, is also an early manifestation of systemic sclerosis. The most reliable clinical sign to the diagnosis of systemic sclerosis is skin thickening, which typically begins as swelling or puffiness of the skin, usually on the fingers and hands. The clinical course can vary substantially, depending on whether the patient develops limited or diffuse cutaneous systemic sclerosis. The diffuse disorder is typically the

Search strategy and selection criteria

We searched PubMed using the key word "scleroderma" with the relevant topics—eg, "pathogenesis", "CREST", "genetic predisposition", "transforming growth factor beta", "autoimmunity", "vascular damage". Fields were restricted to publications in English. We also searched the citations from obtained papers. References were chosen based on the best evidence from clinical or laboratory studies. Review articles of scleroderma published in the past 5 years were also examined to ensure minimum overlap with this Seminar.

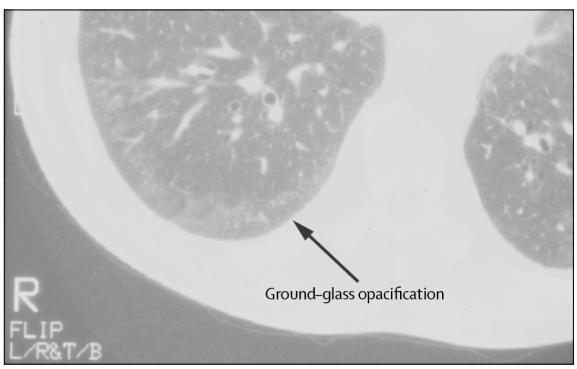

Figure 3: **High-resolution CT of the chest showing ground-glass opacities in a patient with diffuse scleroderma**

more severe form, causing aggressive widespread skin thickening and internal organ damage.[4,8,9]

Limited cutaneous scleroderma

Calcinosis and telangiectases, seen in the classic CREST variant, could take years or even decades to develop into limited cutaneous systemic sclerosis.[7] Patients with the limited disorder generally have more favourable outcomes than patients with the diffuse form, and the 5-year survival rate has been reported to be as high as 86%.[10] However, substantial morbidity and mortality can occur from occlusive digital vascular disease, gastrointestinal effects, interstitial lung fibrosis, and pulmonary hypertension. Patients who are anti-centromere-antibody-positive seem to have more severe recurrent digital ulcerations and digit loss than patients who are not.[11] Pulmonary hypertension is the leading cause of mortality in patients with limited disease and can occur in the absence of interstitial lung disease.[8,10]

Diffuse cutaneous scleroderma

Patients with diffuse cutaneous systemic sclerosis typically have a much more aggressive early disease course than those with the limited form.[5,7] Raynaud's phenomenon might not be present initially and could, in fact, follow the onset of skin swelling. Initial presentation can include diffusely swollen, oedematous, pruritic skin; fatigue; and non-specific joint and muscle pain. Skin thickening is typically rapid, extending proximally on the arms and legs, with or without truncal effects, within several months.[5,7] Visceral organ involvement can also be rapid and severe, often occurring in the first 3 years of disease. In a closely followed Pittsburgh cohort of 953 patients with diffuse cutaneous systemic sclerosis seen in 1972–95, severe skin and kidney effects occurred during the first 3 years in 70% of those who developed renal effects. Severe heart, lung, and gastrointestinal tract effects developed during the first 3 years in 45–55% of these patients.[12] Patients who showed early rapid progression of their skin thickening with development of anaemia, pericardial effusion, or congestive heart failure were at especially high risk for scleroderma renal crisis (figure 4).[13] Pulmonary interstitial changes are also common early in the disease, especially in patients with anti-topoisomerase antibodies.[14] Visceral organ involvement affects mortality greatly, with the 9-year cumulative survival rate of patients in the Pittsburgh cohort with severe organ effects reported as 38%, compared with a rate as high as 72% in patients without such involvement ($p<0\cdot0001$).[12]

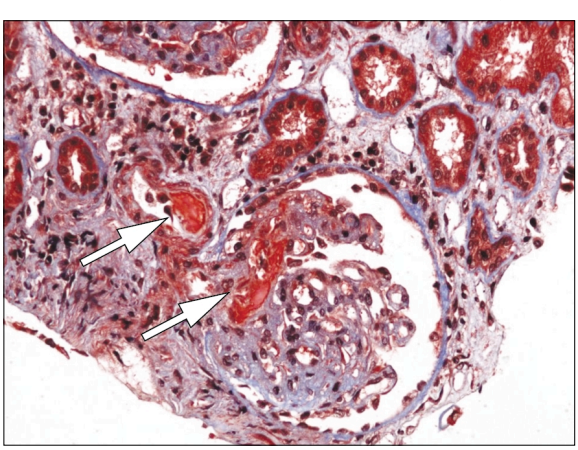

Figure 4: **Kidney biopsy sample from a patient with scleroderma renal crisis showing thrombus (arrows) in both the afferent arteriole and glomerular tuft**
Sample stained with Masson trichrome; original magnification ×200.

Pathogenesis

The clinical presentation of systemic sclerosis is typified by three cardinal features: excessive collagen production and deposition, vascular damage, and inflammation or autoimmunity (figure 1).[6,13] Although the causes of the disorder are not yet understood, a plausible hypothesis has been forwarded to explain the inter-relations and interactions among these three features (figure 1). The three major clinical features and their interactions can be seen as a pathophysiological triangle of systemic sclerosis. Environmental triggers and genetic effects interact with the three features in the triangle at several entry points. Improved understanding of these interactions should provide clues for the development of treatments that can interrupt the abnormal interactions and lead to amelioration of the disease.

Genetic predisposition

Although studies of twins have failed to show an important genetic component,[15] recent results indicate a genetic predisposition, with offspring of patients with systemic sclerosis at a small but definite risk of developing the disorder themselves[16] and Choctaw American Indians having a high prevalence of the disorder (469 cases per million *vs* about 100 cases per million in the rest of the USA).[17,18] The increased frequency of certain HLA haplotypes in various ethnic populations with systemic sclerosis[18] and polymorphisms in specific relevant genes related to the disease[19,20] lend further support to an indirect genetic predisposition.

Environmental factors

The occurrence of a scleroderma-like form of graft-versus-host disease (GVHD) after allogeneic bone-marrow transplantation supports the notion that the frequently occurring microchimerism that follows normal pregnancy could provide an environmental stimulus to the development of systemic sclerosis.[21,22] Changes similar to systemic sclerosis have been recorded in multiparous mice (but not in nulliparous mice) exposed to vinyl chloride, which further supports the hypothesis that an appropriate stimulus, not yet known in human beings, in an individual who harbours naturally occurring microchimera could be enough to trigger systemic sclerosis.[23] However, identification of microchimeric cells both in the organs affected by non-autoimmune conditions and in the peripheral blood of healthy people has raised some questions as to whether microchimeric cells are responsible for the pathological events in systemic sclerosis or are merely remnants of a pregnancy remote in time.[24] Selva-O'Callaghan and colleagues[25] also reported no increase in the presence of microchimerism in peripheral blood cells from a cohort of 47 patients with scleroderma compared with 40 healthy controls.

Other support for an environmental stimulus is seen in the pronounced scleroderma-like appearance of arterial vessels in interferon-γ knockout mice after they have been irradiated and infected with cytomegalovirus.[26] The increased prevalence of human parvovirus B19 DNA in sclerodermic skin and bone marrow suggests another possible viral trigger.[27] Notable epidemiological associations between certain pesticides and exposure to benzene derivatives in patients have been made[6] and exposure to silica has also been linked to the development of scleroderma in coal, gold, and uranium miners[28] and in stonemasons. Some studies have shown the ability of silica dust in vitro to activate microvascular endothelial cells, peripheral blood mononuclear cells, and dermal fibroblasts in a way similar to pathophysiological events in systemic sclerosis.[29]

Immune activation/inflammation

The presence of antinuclear antibodies, inflammatory lesions in the skin and lung, and increased amounts of profibrotic chemokines in the blood and tissues typify the inflammatory and immune activation aspects of systemic sclerosis. The role of transforming growth factor β (TGFβ) and connective tissue growth factor (CTGF) in the dysregulation of collagen production has become better understood.[30] TGFβ, which is produced by stimulated immune cells, seems to be very important in the pathogenesis of fibrosis. TGFβ stimulates cell growth, apoptosis, and differentiation; promotes collagen and matrix protein production; inhibits the synthesis of collagen-degrading metalloproteinases; and stimulates fibroblasts to maintain an activated state. Additionally, fibroblasts in systemic sclerosis express increased concentrations of TGFβ receptors, which could account for enhanced TGFβ-induced signalling that promotes collagen production.[30,31] TGFβ cannot stimulate its own synthesis and is thus unable to sustain profibrotic effects in its absence.

CTGF, another potentially important growth factor, can trigger angiogenesis, apoptosis, chemotaxis, extracellular matrix formation, and the structural organisation of connective tissues.[30] TGFβ is a potent stimulator of CTGF synthesis in fibroblasts, vascular smooth muscles, and endothelial cells. CTGF could, in fact, be a downstream mediator for TGFβ. Since CTGF can stimulate its own production and collagen production,[30,32] it might be a downstream stimulus that, once activated, could chronically perpetuate collagen overproduction in systemic sclerosis.

Non-TGFβ-related pathways could also have a role in abnormal fibrosis. These non-TGFβ activities include those of p38 kinase, Cδ kinase and phosphatidylcholine phospholipase C kinase.[33] Recent evidence also suggests that in-vivo activation of T cells, as well as the presence of increased profibrotic cytokines (such as interleukin 4) have roles in stimulating abnormal fibrosis.[34] Tsuji-Yamada and colleagues found a significantly higher frequency of interleukin-4-producing CD4 and CD8 T cells in blood from patients with systemic sclerosis than in controls.[35] A subset of scleroderma patients at increased risk for progressive lung disease were shown to have activated, long-lived, CD8 T cells in their lungs that could promote fibrosis directly through production of profibrotic cytokines such as interleukin 4, or indirectly through activation of TGFβ.[36]

Vascular damage

Clinical manifestations of vascular damage include Raynaud's disease, digital ulcers, renal crisis (acute renal failure, usually accompanied by accelerated hypertension), pulmonary hypertension, and abnormal nailfold capillaries. The typical vascular lesion in systemic sclerosis includes proliferation of the vascular intima, which can lead to narrowing of the vessel lumen and reduced blood flow. Notably, vascular smooth muscle cells, and possibly circulating monocytes, become activated when the endothelium is damaged and migrate into the intimal layer of the blood vessel where they differentiate into myofibroblasts. The build-up of the intima by myofibroblasts can lead to thickening of the intimal layer and narrowing of the vessel lumen. Speculation is that substances such as endothelin and platelet-derived growth factor (PDGF) could change the phenotype of smooth muscle cells to that of myofibroblasts. Endothelial damage and vascular dysfunction could be one of the earliest alterations in systemic sclerosis.[37]

Endothelial damage, whether caused by immunological stimuli, ischaemia-reperfusion injury, or other pathways, results in the increased production of endothelin 1 and impaired prostacyclin release, as can be seen in pulmonary hypertension.[37] Whether initiated by immune activation or enhanced immune dysregulation, the vascular endothelium

is clearly important in the pathogenesis of systemic sclerosis. New evidence suggests that activated lymphocytes secrete cytokines, such as TGFβ, which cause endothelial cell injury and expression of MHC and intercellular adhesion molecule 1 (ICAM1), upregulate CTGF to increase production of the extracellular matrix, and upregulate PDGF. Increased PDGF expression promotes endothelial cell proliferation and downregulates vascular endothelial growth factor (VEGF), which usually promotes neovascularisation.[38] Because of a deficiency of vasodilators and a large increase in endothelin (a potent vasoconstrictor),[39,40] vasodilatation is impaired in patients with systemic sclerosis. Such an imbalance can lead to ischaemia-reperfusion injury, endothelial damage, and subsequent increased collagen gene expression.

Collagen deposition

Fibrosis represents the phenotypic expression (typified by skin thickening and interstitial lung fibrosis) of systemic sclerosis. Patients with the disease have an increase in collagen types 1 and 3, with type 1 being the most abundant. Type 1 collagen is encoded by the *COL1A1* and *COL1A2* genes, which are at least partly controlled by the transcription factor SP1.[41] Increased SP1 binding activity has been recorded in sclerodermic fibroblasts and its activity has shown to be associated with increased gene expression of type 1 collagen in patients with systemic sclerosis.[42] Gene expression of type 1 collagen is also affected by TGFβ, which indicates a possible synergistic profibrotic interaction between SP1 and the TGFβ pathway via the SMAD3/4 complexes.[43] SP1, in turn, is modulated by proteins called the TATA-associated factors, one of which is TAF110.[44] Another regulator of the collagen gene, a protein called the CCAAT-binding factor, also interacts with TAF110.[45] Thus, SP1 transcription factors and CCAAT-binding factors are implicated in the initiation of *COL1A1* gene activity. Inhibitory factors also exist. C-KROX mediates the inhibition of *COL1A1* gene expression in mice and its human homologue represses *COL1A1* gene transcription in people.[46] Reduced amounts of SMAD7 (an inhibitor of collagen gene expression) have also been reported in systemic sclerosis, which suggests that the loss of this inhibitory effect allows TGFβ to stimulate unfettered, excessive accumulation of extracellular matrix.[47]

Treatment

Evolution of trial design, study conduct, and outcome measures

Although drugs such as methotrexate, sulfasalazine, gold, and even cyclophosphamide have existed for decades to treat rheumatoid arthritis, the recent introduction of four new disease-modifying anti-rheumatic drugs (DMARDs; eg, leflunomide, etaneracept, inflixamab, and adalimamab) has given physicians and patients new alternatives to treat the symptoms of rheumatoid arthritis and to decrease the rate of joint destruction, deformity, and disability. These recent advances were made possible by improved quantification of the extent and the activity of the disease and by reliable measurement of the changes in disease activity and severity in response to therapies. The development of both the rheumatoid arthritis core set (to measure disease activity) and the ACR 20% response variable (to measure the response to therapy) are examples.[48,49] These measures have led to the development and approval of new and more effective therapies by the US Federal Drug Administration (FDA).

Attempts to systematically assess whether therapies could modify systemic sclerosis began in the 1960s and 1970s.[50–53] Although these trials failed to prove that any therapy for the disorder was efficacious, it became apparent that these early studies had many similar methodological flaws. The absence of accurate information about the natural history of the disease was a major factor underlying these early failures. For example, most of the trials did not account for the duration of the disease at entry, the extent and distribution of skin thickening (ie, diffuse *vs* limited cutaneous systemic sclerosis); the naturally occurring changes in the skin over time; the timing of new onset of myocardial, interstitial pulmonary, or acute sclerosis-related renal disease; the courses of these visceral effects over time; and the timing of onset of pulmonary hypertension and its course. Another major failing was the absence of standardised, validated outcome measures; therefore, the sample size needed to show a significant change in any one variable could not be calculated. As a result, these early trials were very underpowered.

In the early 1970s, Steen and Medsger developed a longitudinal database that now contains demographic, clinical, and laboratory information on all patients with systemic sclerosis who were investigated at Pittsburgh.[11,54,55] After their initial assessment, all patients are queried every 1–2 years about the course of their disease, visceral effects, treatments, outcomes, and functional abilities. This database continues to enter new patients after nearly 30 years and contains initial and follow-up information on more than 2500 patients. Follow-up has been about 93% so far.[54,55] The analyses derived from this database have provided, and continue to provide, preliminary data for the generation of treatment hypotheses, which can then be tested in controlled trials.

In the 1980s and 1990s, controlled trials and randomised controlled trials of systemic sclerosis became longer in duration (1 to 3 years), with increasing attention paid to the selection of patients, trial design, and careful analysis.[50,56–63] These details include: the duration of systemic sclerosis, comparison between subsets of diffuse and limited disease, primary or secondary Raynaud's disease, presence of active alveolitis associated with declining lung function, early detection of renal failure with or without hypertension (renal crisis), and the semi-quantitative estimation of the degree and extent of skin thickening (by skin scoring).

The late 1990s and early 2000s have been associated with an appreciation that trials should be multicentred, outcome measures should be standardised by careful training of

investigators, the design should account for what is known about the natural history of the scleroderma subset being studied, trials should be controlled, sample sizes should be appropriately large, functional ability and quality of life are important outcomes, and patients should be encouraged to complete their final visits (even if they have previously stopped taking study treatment), among other factors.[64–73] In 1995, White and colleagues[74] published the American College of Rheumatology guidelines for the conduct of trials investigating disease-modifying interventions in systemic sclerosis. These guidelines, which were derived by consensus, iterated and summarised recommendations on how DMARD trials in systemic sclerosis should be designed, undertaken, and analysed. In 2003, a committee reviewed published work on possible outcome variables that could or should be included in such trials. In conclusion, the committee presented a list of variables that were regarded to be validated for use in clinical trials (table).[75]

Treatments targeting vascular complications

As discussed previously, we now better understand of the potential role of cells, cytokines, paracrine signalling, and hormones at the cellular and molecular level in systemic sclerosis. The greatest advances have been in the management of vascular complications. Although no randomised controlled trial has proven the efficacy of angiotension-converting-enzyme (ACE) inhibitors in renal crisis, the rheumatological community has accepted these drugs as the preferred choice in the management of this once rapidly fatal complication of systemic sclerosis. Their mechanism of action has been well known (even in the late 1970s) and thought to be especially appropriate to treat a hypertensive state that was associated with, and driven by, raised amounts of renin (and thus angiotensin and aldosterone). A review by Steen and colleagues,[76] based on the Pittsburgh longitudinal database, records that 1-year survival is better than 70% in renal crisis patients treated with ACE inhibitors, but less than 20% in those not treated with ACE inhibitors.

Five drugs have now been approved by the FDA for scleroderma-related pulmonary arterial hypertension (PAH), based on improved knowledge of molecular biology. Epoprostenol, treprostinil, and iloprost can supply prostacyclin that the pulmonary vascular endothelium itself no longer supplies in adequate quantities; sildenafil can raise amounts of nitric oxide (itself a vasodilator) in tissues; and bosentan can inhibit endothelin, which is frequently increased in the serum of patients with PAH.[69–71,77,78] All these compounds have been shown to improve the distance walked in 6 min (6-MWD), which is associated with mortality in other forms of PAH, as well as

	Response measures that could be useful but are not fully validated	Validated response measure
Cardiopulmonary effects	Chest radiograph High-resolution CT of the chest (HRCT) Bronchoalevolar lavage (BAL) Diffusing capacity for carbon monoxide (DLCO) Electrocardiogram Echocardiography	Right heart catheterisation Vital capacity
Health-related quality of life/function	Short form-36 Systemic sclerosis questionnaire (SySQ) Functional questionnaire Scleroderma functional index Scleroderma-modified health assessment questionnaire	Health assessment questionnaire disability index (HAQ-DI)
Raynaud's disease	Patients' diaries Cold provocation tests Plethysmography Thermography	Raynaud's condition score (RCS) Physician global for Raynaud's disease Patient-derived visual analogue scale (VAS) for digital ulcer
Renal effects	Blood pressure Proteinuria Serum renin	Serum creatinine Complete blood count
Skin effects	Percentage of surface area affected UCLA skin score Kahaleh skin score Diameter of skin ulcers Hand spread, oral aperture	Modified Rodnan skin score
Musculoskeletal effects	Tender joint count Swollen joint count	None
Gastrointestinal effects	Oesophageal measures (motility, ultrasonography, scintigraphy) Gastric emptying time Endoscopies Hydrogen breath tests Body-mass index	None

Clinical trials include those validated and those used but not yet validated. UCLA=University of California, Los Angeles.

Table: **Outcome and response measures in clinical trials of systemic sclerosis**

with improvement of quality of life. Increasing evidence suggests that the two treatments that have been approved the longest (epoprostenol and bosentan) could improve survival in PAH overall; recent work also suggests a potential survival benefit in patients with systemic sclerosis after treatment with bosentan as first-line therapy.[79,80] Several other treatments with good molecular-based rationale are being investigated: inhaled treprostinil (a prostacyclin-like compound), inhaled nitric oxide, and other endothelin inhibitors such as sitaxsentan.[81,82]

Raynaud's disease and digital ischaemia are also manifestations of the vasculopathy of systemic sclerosis. Randomised controlled trials have shown that calcium-channel blockers (especially nifedipine), intravenous iloprost and epoprostenol, and nitroglycerin paste (ointment) are effective in lessening Raynaud's disease attacks and, to a lesser extent, in healing digital ulcers.[83–87] Sildenafil has also shown some effectiveness in a small placebo-controlled trial of patients with secondary Raynaud's disease resistant to multiple therapies.[88]

Two randomised placebo-controlled studies (RAPIDS-1 and 2),[89,90] have shown that bosentan, an oral endothelin-receptor antagonist approved for scleroderma-related PAH, prevents occurrence of new digital ulcers in patients with systemic sclerosis, but does not speed healing of present digital ulcers.

Our recommendations for the management of the vascular complications of systemic sclerosis include: the use of calcium-channel blockers for moderate to severe Raynaud's disease that is not responsive to non-pharmacological therapies, undertaking of trials to investigate the benefit of nitroglycerin ointment applied locally to areas proximal to digital ulcers, and consideration of parental prostacyclins (eg, epoprostenol, treprostinil) or other novel therapies (eg, bosentan, sildenafil) if conventional drugs cannot control tissue-threatening ischaemia. All patients with systemic sclerosis should be monitored closely for evidence of pulmonary hypertension and assessed for treatment when appropriate.

Treatments targeting immune activation and inflammation

Skin score and pulmonary function testing have been used as surrogates of skin fibrosis and lung fibrosis. The effects of immunosuppressive therapies on these two outcome measures have been examined in several studies. In 1990, the effect of fluorouracil on skin score and other variables was reported in a placebo-controlled trial of 46 patients with systemic sclerosis.[62] Although skin score, hand extension, and patients' global assessment were improved significantly in the group treated with fluorouracil ($p<0·05$), visceral outcomes were not affected by the treatment. The drug is not currently in widespread use for management of scleroderma.

Two small, randomised placebo-controlled trials of methotrexate have shown promising results. Trends favoured the use of methotrexate in reducing skin score ($p=0·06$) and improving patients' global assessment ($p=0·19$) at the final 6-month visit in a Netherland study (n=29).[65] In a Canadian-US study (n=71), the methotrexate group showed significant improvement in the Rodnan skin score ($p=0·009$) and the physician global assessment ($p=0·039$) at the 1-year final visit.[66]

No randomised controlled trial of ciclosporin has been reported, although one controlled trial (not randomised) has been published.[91] In this trial, oral ciclosporin was started at 1 mg/kg per day and gradually increased to 5 mg/kg per day in patients with early diffuse cutaneous systemic sclerosis. At 48 weeks, the mean UCLA skin tethering score had improved by 36% in ciclosporin-treated patients but was unchanged in matched controls. Eight of ten ciclosporin-treated patients had more than a 30% rise in serum creatinine amounts or had the onset of hypertension, which severely restricted use of the drug in this study. The researchers thought that the toxic effects outweighed the benefits of the drug. However, the improvement seen in skin score suggests that inhibition of interleukin 2 by a less toxic drug would be worth further investigation.

An open controlled study (not randomised)[92] showed that the 30 patients with systemic sclerosis as well as alveolitis (by bronchoalveolar lavage criteria) who refused cyclophosphamide treatment lost 7% forced vital capacity (FVC) and 9% diffusing capacity for carbon monoxide (DLCO) during a median follow-up of 13 months. By contrast, the 39 patients with alveolitis who received cyclophosphamide had stable FVC and DLCO for 16 months, similar to the 34 controls who did not have alveolitis as defined by bronchoalveolar lavage criteria and were therefore not treated with cyclophosphamide.

Researchers have completed two randomised placebo-controlled trials of cyclophosphamide treatment for pulmonary alveolitis or interstitial lung disease (or both) in systemic sclerosis.[73,93,94] The Scleroderma Lung Study compared oral cyclophosphamide with placebo in 163 patients with systemic sclerosis and alveolitis. The drug had a statistically significant (but clinically mild) effect on the primary outcome of FVC (measured as the percentage predicted) after 1 year, and a statistically and clinically significant effect on the extent of dyspnoea as measured by the transition dyspnoea index (TDI). Furthermore, the disability index of the patients' health assessment questionnaire (HAQ-DI) and the vitality and health transition components of the medical outcomes short form-36 (SF-36) were significantly better in the cyclophosphamide group than in the placebo group. Skin scores also fell moderately in the cyclophosphamide group compared with placebo, especially in patients with diffuse disease ($p=0·03$).[73,93] Another randomised placebo-controlled trial in the UK confirmed the favourable effects of cyclophosphamide on FVC. 45 patients with scleroderma-related pulmonary fibrosis were randomly assigned to placebo or to intravenous pulse cyclophosphamide given monthly for 6 months with prednisolone 20 mg every

other day, followed by oral placebo or azathioprine (2·5 mg/kg) for 6 months. Patients treated with the cyclophosphamide-azathioprine therapy showed a substantial improvement or stabilisation of FVC at 1 year compared with the placebo group. Furthermore, use of intravenous cyclophosphamide seemed to reduce the occurrence of toxic effects (haematuria, cytopenias) that were seen at an increased frequency in the oral cyclophosphamide trial.[94]

Despite the potential of autologous stem-cell transplantation as treatment, no randomised controlled trials have been completed. Uncontrolled experiences suggest possible effectiveness for autologous stem-cell transplantation but its transplant-related mortality and morbidity remain worrisome.[95,96] However, the multicentre European ASTIS (Autologous Stem-cell Transplantation International Scleroderma) trial and the multicentre US SCOT (Scleroderma Cyclophosphamide Or Transplant) trials are in progress and should address the effectiveness and toxic effects of transplantation of stem cells in early, diffuse, cutaneous systemic sclerosis.

In summary, progress has been made in immunosuppressive therapies for aggressive systemic sclerosis, especially in scleroderma-related lung disease, and patients should be referred to physicians or academic centres experienced in dealing with systemic sclerosis for appropriate investigation and treatment.

Treatments targeting fibrosis

The BUILD-1 and BUILD-2 (Bosentan Use In Interstitial Lung Disease) studies were designed to prove whether inhibition of the A and B receptors of endothelin 1 would prevent or ameliorate lung fibrosis in idiopathic pulmonary fibrosis (BUILD-1) and lung fibrosis associated with systemic sclerosis (BUILD-2), with the 6-MWD as the primary endpoint. Neither study showed an effect on the primary endpoint, although BUILD-1 showed positive, non-significant trends for secondary endpoints such as combined incidence of death or treatment failure at 12 months (defined as worsening in pulmonary function tests) or acute decompensation of idiopathic pulmonary fibrosis (36·1% placebo *vs* 22·5% bosentan; p=0·076).[97]

A positive effect of interferon gamma on total lung capacity and blood oxygen tension at rest and with exercise (as surrogates for lung fibrosis) was reported in a randomised controlled trial of 18 patients with idiopathic pulmonary fibrosis.[98] Another trial of 330 patients with idiopathic pulmonary fibrosis (but not with systemic sclerosis) failed to meet its endpoints, but unexpectedly showed fewer deaths in the interferon-gamma-treated group than in the placebo group.[99] A follow-up trial of more than 800 patients is underway, with death as the primary endpoint.

A randomised controlled trial of interferon gamma (controls were randomised but no placebo was used) was undertaken in 44 patients with systemic sclerosis (27 received the drug).[67] The trial did not show a significant benefit of interferon gamma in improving skin thickness score compared with controls. Although a phase II, randomised controlled trial of recombinant-relaxin showed that the drug at 25 ug/kg per day was more effective in reducing skin score than placebo,[72] a follow-up phase III trial found no significant differences in the 6-month course of skin score (or any of the secondary outcome variables) in the placebo, the 10 ug/kg per day dose group, or the 25 ug/kg per day dose group.[97] Reduced blood pressure and haemoglobin in the relaxin groups showed that relaxin was physiologically active.

Treatments targeting profibrotic cytokines

Since TGFβ and CTGF are two probable cytokines implicated in abnormal fibrosis, they are natural treatment targets. At least four pharmaceutical firms have monoclonal antibodies or trapping strategies that could inactivate or reduce the effect of these two naturally occurring profibrotic cytokines. At least one of these compounds has undergone an early study in patients with systemic sclerosis.[100] Although toxic effects were at a minimum, no efficacy was shown. Hopefully, more effective inhibitors of prefibrotic cytokines will become available to test against systemic sclerosis.

Conflict of interest statement

P Clements is a consultant to Actelion, Genzyme, and Encysive. D E Furst is a consultant on study design to Actelion, Encysive, Bristol-Meyers-Squib (BMS), Mellenium, and the National Institute of Health (NIH). We have received no payment for the writing of this Seminar.

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