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REVIEWS

Diagnosis and treatment of systemic and localized scleroderma

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Scleroderma or progressive systemic sclerosis is diagnosed clinically by typical features of skin thickening, Raynaud's phenomenon and visceral organ involvement, and serologically by distinct autoantibody subsets. These differentiate the disease into the 'limited' and 'diffuse' variants. In addition, a distinct form of scleroderma, termed 'localized' scleroderma, is characterized by skin thickening in the absence of visceral involvement. Treatment of scleroderma in the past was largely symptomatic and with immunosuppressives, acting against the organ system involved and the aberrant immune system. Recently, with newer insights into disease pathogenesis, drug therapies targeting the pathogenetic mechanisms of fibrosis, vasculopathy and autoimmunity are being evolved. Some of these newer therapies are the endothelin receptor blockers, phosphodiesterase inhibitors, tyrosine kinase inhibitors and autologous stem cell transplant, while others are still evolving. They may hold the key to improved future outcome of this disease, which was once thought to be potentially incurable.

KEYWORDS: criteria • drugs • localized scleroderma • morphea • systemic sclerosis • therapy

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Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze the prognostic value of serum antibodies in scleroderma
- Evaluate treatment for the manifestations of scleroderma
- Distinguish the efficacy of immunomodulating drugs for scleroderma
- Describe the diagnosis and management of localized scleroderma (morphea)

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Scleroderma is a chronic multisystem connective tissue disorder characterized by a pathophysiological triad of vasculopathy, fibrosis due to excessive deposition of collagen and extracellular matrix components, and autoimmunity. This manifests clinically as Raynaud's phenomenon, skin thickening and involvement of visceral organs, including the gastrointestinal (GI) tract, lungs, heart and kidneys. The term scleroderma (sclera – hard, derma – skin) is used synonymously with systemic sclerosis, as the fibrotic process is not just confined to the skin but also extends to involve other organ systems.

Diagnosis of scleroderma

In practice, the diagnosis of scleroderma is clinical and is made by the presence of Raynaud's phenomenon, typical skin thickening and visceral involvement. Laboratory investigations are supportive. Serology for autoantibody profile helps in classifying the subtype of disease and excluding other scleroderma-mimicking conditions. Organ-specific investigations help to determine the extent and stage of visceral involvement due to the disease process.

Preliminary classification criteria have been developed by the American College of Rheumatology (ACR) for the purpose of uniformity in clinical studies [1]. The major criterion is the presence of sclerodermatous skin changes proximal to the metacarpophalangeal joint. Minor criteria are sclerodactyly, digital pitting scars or tissue loss of the volar pads of the finger tips and bibasilar pulmonary fibrosis. The diagnosis of scleroderma is based on the presence of the major criteria and two or more minor criteria. However, these criteria may not be applicable in clinical practice and not all patients may fulfill them.

Recently, it has been suggested that nailfold capillary microscopy changes and the presence of anticentromere antibodies (ACA) should be included in the minor criteria so as to more adequately incorporate patients with the limited subset of the disease [2].

In contrast to established disease, diagnosis of disease in the early stage may be difficult. Such patients may only present with Raynaud's phenomena and lack other clinical features at onset. In such cases, nailfold capillaroscopy changes (capillary loss and dilatation) and the determination of autoantibodies may serve as useful investigations for the prediction of evolution to full-blown disease [3]. Recently, a set of criteria have been identified, and are considered to be important in the early diagnosis of scleroderma

by the European League against Rheumatism (EULAR) scleroderma trials and research groups. They have been divided into three domains containing seven items each: skin domain (puffy fingers/puffy swollen digits turning into sclerodactyly); vascular domain (Raynaud's phenomenon, abnormal capillaroscopy with scleroderma pattern) and laboratory domain (antinuclear, anticentromere and antitopoisomerase-I antibodies). The validation of these items to establish diagnostic criteria is currently ongoing in a prospective observational cohort [4].

Two distinct subsets of scleroderma have been identified on the basis of the extent of skin thickening. The limited variant has symmetric skin thickening of the distal extremities (distal to elbows and knees) and face. The diffuse variant has skin thickening of proximal and distal extremities, face and trunk. The major differences between these two subsets are given in TABLE 1, but some amount of overlap exists. Either of these variants can exist with overlapping syndromes in which features of scleroderma are present with one or more connective tissue disorders, such as systemic lupus erythematosus (SLE) and polymyositis (PM). Another variant is 'scleroderma sine scleroderma' characterized by internal organ involvement and serological abnormalities but an absence of classical skin changes. Scleroderma can also occur in the localized form limited to skin and subcutaneous tissue without internal organ involvement, termed 'localized scleroderma' (discussed later).

Several conditions have scleroderma-like features and are termed 'scleroderma mimics'. These need to be excluded as treatment and outcome may differ. Scleredema adultorum of Buschke presents as painless edematous induration of face, trunk and proximal extremities usually secondary to previous streptococcal infection [5,6], and is sometimes associated with diabetes mellitus. It is usually self-limited. It is distinguished from scleroderma by the absence of Raynaud's and distal involvement, and histopathologically by the deposition of mucopolysaccharide material in the dermis. Scleromyxedema (papularmucinosis) is a rare disorder characterized by papular skin lesions associated with sclerosis and monoclonal gammopathy. The lesions occur on the face and arms and show dermal deposits of mucopolysaccharide and fibroblasts. There is an absence of Raynaud's phenomenon and distal involvement. Eosinophilic fasciitis, eosinophilia–myalgia syndrome and toxic oil syndrome are unified in presenting with fascial inflammation, fibrosis of dermis and subcutaneous tissue and eosinophilia. Despite similarities, they differ from each other in several aspects. They can

Table 1. Subsets of systemic sclerosis.

Disease characteristics	Limited scleroderma	Diffuse scleroderma
Skin involvement	Distal to elbows, knees, face	Distal and proximal extremities, face and trunk
Raynaud's phenomenon	May precede skin changes by many years	May occur simultaneously or a year or two prior to/after the onset of skin disease
Internal organ involvement	Gastrointestinal, pulmonary hypertension	Interstitial lung disease, renal, gastrointestinal, cardiac
Nailfold capillaries	Dilatation without dropouts	Dilatation with dropout
Antinuclear antibodies	Anticentromere	Antitopoisomerase I
Disease course and prognosis	Slowly progressive, better prognosis except in the subset developing pulmonary hypertension	Aggressive course in majority, with risk of visceral involvement early in the disease course

be distinguished from scleroderma by the absence of sclerodactyly, Raynaud's phenomenon, nailfold capillary abnormalities, antinuclear antibodies (ANA) and visceral involvement. Amyloidosis can involve skin-mimicking scleroderma, but spares the distal extremity. Some drugs can produce skin thickening resembling scleroderma, such as bleomycin, pentazocin and vinyl chloride.

Investigations in scleroderma

Nonspecific

Acute-phase reactants are generally not elevated. However, acute-phase response has been shown to be elevated in patients with synovitis, joint contracture and tendon friction rubs, as shown in a recent study with synovitis showing the highest strength of association [7]. Anemia may be seen, which may be attributed to either chronic disease, iron deficiency due to GI blood loss, B12/folic acid deficiency secondary to bacterial overgrowth due to intestinal hypomotility, or microangiopathic hemolytic anemia secondary to scleroderma renal crisis.

Specific for disease

Autoantibodies in scleroderma

Antinuclear antibodies are seen in 75–95% of patients with scleroderma. ANA specificities include distinct antibody subsets with different clinical associations (TABLE 2). It is controversial whether antibodies play a direct role in pathogenesis or whether they are an epiphenomenon of the disease process *per se*. The antibodies classically associated with scleroderma are ACA (limited variant) and antitopoisomerase I or anti-Scl-70 (diffuse variant). Less commonly occurring are the antinucleolar antibodies, which include anti-PML-Scl, antifibrillar/anti-U3 ribonucleoprotein, anti-Th/To and the anti-RNA polymerase family. In addition to disease-specific antibodies, other antibodies, such as anti-Ku, anti-Ro, antiphospholipid, anti-U1RNP and anti-Sm antibodies, are seen less frequently and are not specific for scleroderma *per se* [8].

Anticentromere antibody

Anticentromere antibody produces a speckled pattern of interphase cells and centromeric staining of the mitotic cells by immunofluorescence on Hep-2 cells. They react with six different centromere proteins, CENP-A–F. The frequency of ACA in patients with scleroderma ranges from 20 to 30%, and they are seen in as high as 50% of patients with the limited form, but in less than 5% of patients with the diffuse form of disease. When found in patients with Raynaud's phenomenon they predict the development of scleroderma. They are strongly associated with the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia). The presence of ACA carries a better prognosis than other scleroderma-associated autoantibodies.

Antitopoisomerase-I antibodies (anti-Scl-70 antibodies)

They are characterized by nuclear and nucleolar fine speckled staining pattern in interphase cells by immunofluorescence on Hep-2 cells. They are found in up to 40% of patients with diffuse scleroderma and less than 10% of patients with limited scleroderma.

When present in a patient with Raynaud's phenomenon, they predict the risk of developing scleroderma. ACA and anti-Scl 70 exist in isolation and are rarely found together. Anti-Scl-70 antibodies are associated with interstitial lung disease (ILD).

Antinucleolar antibodies

Antinucleolar antibodies show a nucleolar pattern on immunofluorescence. Anti-PM-Scl antibodies are found in approximately half of the patients with polymyositis/scleroderma overlap syndrome and as many as 80% of patients with these antibodies will have this disease. They are found in 2–3% of patients with scleroderma and 8% of patients with myositis. Anti-Th/To antibodies are directed against the ribonuclease mitochondrial RNA processing complex (MRP) and ribonuclease P complexes. They are present in 2–5% of patients with scleroderma and are more common in Japanese patients. They have also been seen in patients with SLE and PM. Similar to ACA, they indicate limited skin involvement. The anti-RNA polymerase group (I and III) is found in 20% of patients with scleroderma. They are associated with diffuse scleroderma and are correlated with higher mortality in scleroderma and right heart failure secondary to pulmonary arterial hypertension (PAH). Antifibrillar antibodies are found in 4% of patients with scleroderma. They are also associated with diffuse scleroderma and in this subset with myositis, PAH and renal disease.

Other autoantibodies

Anti-Ku antibodies are found in patients with overlap syndrome (involving features of scleroderma), SLE and scleroderma *per se*. Anti-Ro antibodies are identified in the sera of scleroderma patients with Sjögren syndrome. Anti-Sm antibodies are rarely seen in

Table 2. Antibodies in scleroderma.

Antibodies	Prevalence (%)	Clinical association
Anticentromere	20–30	Limited scleroderma, Crest syndrome, pulmonary hypertension
Antitopoisomerase (anti-Scl-70)	15–20	Diffuse scleroderma, interstitial lung disease
Anti-PM-Scl	2–3	Polymyositis/scleroderma overlap
Anti-To/Th	2–5	Limited scleroderma
Anti-RNA polymerase	20	Diffuse scleroderma
Antifibrillar	4	Diffuse scleroderma, myositis, pulmonary hypertension, renal disease
Anti-Ku, anti-Sm, anti-U1RNP	Rare	Overlap syndromes with features of scleroderma
Anticardiolipin antibodies	20–25	Limited/diffuse subsets, features of secondary antiphospholipid antibody syndrome rare

patients with scleroderma unless there are features of SLE overlap. When present, they predict a poor prognosis, with frequent renal involvement. Anti-U1-RNP antibodies are usually seen in association with CTD overlaps, specifically with Raynaud's phenomenon, joint involvement, myositis, limited scleroderma and a more favorable outcome. Anticardiolipin antibodies are seen in 20–25% of patients with scleroderma, although secondary antiphospholipid antibody syndrome is rare.

Skin biopsy

In most cases, skin biopsy is rarely indicated as the diagnosis is clinical, but it may be helpful in atypical presentations of disease and in differentiating from scleroderma mimics. In the early stages, mild inflammatory infiltrate consisting of lymphocytes, monocytes, histiocytes and plasma cells is seen around the blood vessels and ducts of the eccrine sweat glands and partly in the subcutaneous tissue. Abundant accumulation of connective tissue and matrix proteins is first seen in the vicinity of blood vessels in the reticular dermis and at the border of the dermis and subcutaneous tissue. In the later stages, infiltrates are reduced, the collagen bundles are thickened and there is intense dermal and subcutaneous fibrosis. The eccrine sweat glands and other dermal appendages are atrophic owing to surrounding fibrosis, and the epidermis is thinned out [9]. Apart from collagen deposition, fibroproliferative vasculopathy is present in the skin and affected organs. It is characterized by intimal proliferation and smooth muscle hypertrophy and fibrosis of the arterioles and small arteries. This leads to luminal narrowing and microthrombi formation in the damaged vessel wall.

Organ-specific investigations

The long-term prognosis of scleroderma depends on the organ system involved; hence, initial screening and subsequent monitoring for disease evolution is important, especially in the diffuse variant of scleroderma where organ involvement occurs early in the disease course.

The GI tract is frequently involved in scleroderma. The esophagus involvement may be in the form of hypomotility, reflux esophagitis, Barrett's metaplasia and fibrotic strictures. It is diagnosed by conventional radiography (barium swallow), which shows a stiff glass tube appearance, by manometric measurements [10] and by sensitive scintigraphic procedures that are quantitative and noninvasive [11]. Cardiac involvement is often present, but rarely clinically significant. Myocardial perfusion scintigraphy, ventriculography and echocardiography are the most sensitive techniques for diagnosis [12]. Electrocardiographic abnormalities seen are conduction system disturbances, signs of infarction and nonspecific ST and T-wave changes. Lung involvement ranks second to GI manifestations and needs early diagnosis to prevent subsequent morbidity and mortality [13,14]. All patients should have screening pulmonary function tests to measure forced vital capacity and diffusing capacity for carbon monoxide. In ILD, these two parameters tend to decline in parallel, whereas in isolated PAH, the diffusion capacity of the lung for carbon (DLCO) shows a disproportionate decline. High-resolution computed tomography is more sensitive than a radiograph, and should be used for screening.

Alveolitis is usually associated with ground-glass opacification. Bronchoalveolar lavage is also useful in diagnosing acute ILD. The presence of neutrophilia and eosinophilia in bronchoalveolar lavage fluid at initial evaluation is correlated with active disease. PAH often remains undetected until it is advanced. Traditional diagnostic methods include measurement of DLCO and echocardiography (transthoracic or Doppler), which estimates pulmonary artery pressure. It is recommended that Doppler echocardiography is performed on a yearly basis. Cardiac catheterization directly measures baseline pulmonary artery pressures and cardiac output and rules out left-ventricular dysfunction. Creatine phosphokinase (CPK) elevation and electromyography abnormalities are seen in patients with myositis [15]. In patients with renal involvement, 24-h creatinine clearance of less than 60 ml/min or a fall of 20 ml/min from the previous value indicates impending scleroderma renal crisis. This is manifested as hypertension, microscopic hematuria or proteinuria, azotemia or microangiopathic hemolytic anemia and elevated plasma renin levels [16].

Treatment of scleroderma

Treatment of scleroderma is a challenging task for the physician. The causes are manifold. First, the disease manifestations are varied and are a cumulative effect of progressive fibrosis, obliterative vascular changes and immune system activation and autoimmunity. Hence, multiple drug therapy targeting the different pathogenetic mechanisms is needed. Second, the disease is heterogenous and has different subsets (limited, diffuse and localized), which differ in clinical presentation, autoantibody profile and outcome. Even within a disease subset, presentation varies depending on the organ systems involved. Diagnosis of the subset of disease is important in the early stage and treatment differs accordingly. Third, the disease runs an unpredictable course and may be rapidly progressive in some patients with diffuse variety. Since there are no predictive factors, close monitoring is required with initiation of appropriate therapy as and when needed. Fourth, there are no established criteria or markers to assess improvement on therapy, especially of internal organ damage. Finally, in patients presenting with established disease, irreversible fibrosis and vascular damage has already set in. Therapy at this stage may only be symptomatic.

Although difficult to treat, survival rates have improved considerably over the years because of better understanding of pathogenetic mechanisms and their translation into the evolution of targeted therapies directed at the molecular level of disease pathogenesis, such as endothelin receptor blockade, PD5 inhibitors and tyrosine kinase inhibitors [17,18]. Owing to different pathogenetic mechanisms involved in the disease process, involvement of multiple organ systems and manifestations varying in different individuals, therapy for scleroderma is thus organ- and pathogenesis-targeted and patient tailored.

Targeting pathogenetic factors

Vascular derangements

Vascular injury is probably the earliest event occurring in scleroderma. This causes endothelial cell activation and release of endothelin-1, which causes potent vasoconstriction, intimal proliferation,

vascular smooth muscle proliferation and fibrosis. This leads to obliteration of the lumen and tissue hypoxia [19]. Vasculopathy accounts for manifestations such as Raynaud's phenomenon, digital ulcers, PAH, glomerular dysfunction and esophageal dysmotility. Drugs are now available that target the different events in vasculopathy.

Calcium channel blockers

Calcium channel blockers lead to arteriolar vasodilatation and increase the peripheral blood flow. This class of drugs is useful in patients with Raynaud's phenomenon, has been tested in several clinical trials and has led to moderate improvement in both the frequency and severity of the ischemic attacks [20]. They have also been shown to improve early myocardial perfusion and function abnormalities. Relatively high doses may be useful in patients with PAH with reversible vasospasm. Side effects associated with the use of this class of drugs are hypotension, vasodilatation, peripheral edema and headache, especially at higher doses.

α 1-adrenergic receptor antagonist

Prazosin in doses of 1–3 mg/day has been shown to have a moderate effect in Raynaud's phenomena. However, side effects are frequent [21]. OPC-28326 is a selective α -adrenergic antagonist with preferential binding to the α (2C)-adrenergic receptor subtype. It may improve digital skin perfusion in patients with Raynaud's phenomenon at doses from 10 to 40 mg [22].

Prostacyclin analogues

An imbalance between prostacyclin (PGI_2) and thromboxane A2 has been observed in patients with systemic sclerosis. In addition to reducing functional vasospasm, PGI_2 inhibits platelet aggregation and leukocyte activation. Thus, vascular effect persists for a longer time. PGI_2 and its analogues are widely used in the treatment of Raynaud's phenomenon and PAH. Intermittent intravenous (IV) infusions of iloprost (a stable analogue of prostacyclin) improves Raynaud's phenomenon in patients with systemic sclerosis and decreases the severity and frequency of the attacks [23]. It is also useful for digital ulcers. Intravenous iloprost improves kidney vasospasm. It may also have a preventive effect on the development of PAH [24]. The oral route has not been shown to be as effective as the IV route. PGI_2 (epoprostenol) is efficacious in patients with PAH. Continuous IV infusion with epoprostenol results in improvement in the exercise capacity and cardiopulmonary hemodynamics, and benefits survival in patients with PAH secondary to scleroderma [25]. It is now considered to be a first-line therapy in patients with severe PAH. In addition, improvement in Raynaud's phenomenon and digital ulcers has been seen. Treprostinil, a prostacyclin analogue suitable for continuous subcutaneous infusion, has been shown to have modest effects on hemodynamics and symptoms in PAH [26]. Both epoprostenol and treprostinil are US FDA-approved for the treatment of PAH. However, they are associated with numerous adverse effects and require continuous parenteral administration. The utility of inhaled iloprost is limited by the frequency with which the medication must be dosed. The inhalation route may be used in patients in whom IV infusions cannot be given because of physical limitations secondary to

Raynaud's, digital ulcers or sclerodactyly. Beraprost is the first orally active prostacyclin analogue. Studies have shown that it prevents recurrence of digital ulcerations in patients with scleroderma.

Angiotensin-converting enzyme inhibitors

Vasculopathy of scleroderma leads to intimal thickening of the renal interlobular and arcuate arteries and results in a decrease in renal perfusion following endothelial injury or episodic vasospasm of the renal arterioles. Decreased renal perfusion leads to hyperplasia of the juxtaglomerular apparatus and renin production. Renin then cleaves angiotensinogen to form angiotensin I. This is then acted upon by the angiotensin-converting enzyme (ACE) to form angiotensin II.

This is a potent vasoconstrictor and acts directly on vascular smooth muscle cells. ACE inhibitors block this conversion and thus improve renal perfusion. ACE inhibitors have revolutionized the treatment of scleroderma renal crisis with improved outcome [27]. They are now well established in the treatment of scleroderma renal crisis. They are effective in controlling blood pressure and improve overall prognosis. However, 5-year survival in patients who develop full-blown scleroderma renal crisis remains low (65%). There is no evidence at present to support the use of ACE inhibitors prophylactically. A recent study also suggests that prophylactic use of these agents may be followed by a worse outcome in patients who develop scleroderma renal crisis [28]. In addition to their effectiveness in scleroderma renal crisis, they are also effective in treating patients with myocardial involvement and have also been shown to decrease the pulmonary vascular resistance in patients with PAH. Some studies have shown improvement in digital blood flow in patients with Raynaud's phenomenon. Recently, the angiotensin II receptor type I antagonist, losartan has been found to be efficacious in decreasing the severity and frequency of attacks of Raynaud's phenomenon [29]. Further studies need to be conducted to assess the disease-modifying effects.

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors act by targeting the nitric oxide (NO) pathway. NO is produced by NO synthases located in the vascular endothelium and alveolar epithelial cells. NO stimulates the conversion of GTP to cGMP, which leads to dilatation of vascular smooth muscles both at arterial and venous levels and also antiproliferative effects. Reduction of cGMP by phosphodiesterases (PDEs) leads to vasoconstriction and smooth muscle proliferation. In PAH, PDE expression is upregulated and leads to increased catabolism of NO-derived cGMP. Thus, inhibition of PDE serves to enhance NO-mediated vasodilatation. Sildenafil was the first commercially available oral PDE inhibitor. It is indicated for patients with mild-to-moderate PAH [30]. There are no data to support its use in asymptomatic individuals. It should not be used as a first-line agent in patients with severe PAH. It has also been shown to be effective in patients with digital ulcers [31]. Tadalafil is another orally administered PDE inhibitor approved for use in patients with PAH. Another study has shown the effectiveness of tadalafil in both the healing and prevention of digital ulcers and improvement in Raynaud's phenomenon, and may be a useful add-on therapy in this subset of patients [32].

Endothelin receptor antagonists

Endothelin-1 is a potent vasoconstrictor and is a dual receptor blocker of endothelin receptor type A (ETA) and endothelin receptor type B (ETB). It has been implicated in the pathogenesis of PAH in systemic sclerosis and its levels have a strong correlation with disease severity and prognosis.

Bosentan is the first endothelin receptor antagonist approved in the USA and Europe for treatment of primary PAH and PAH related to collagen vascular disease. It is found to be effective in reducing the mean pulmonary arterial pressure and other hemodynamic measures, improving exercise capacity and delaying the progression of PAH [33]. It has also been shown to be effective in reducing the frequency of new digital ulcers and has been approved in Europe for the same. Efficacy for the prevention and treatment of ischemic ulcers has been evaluated in two well-designed studies, RAPID-1 [34] and RAPID-2 [35]. It was concluded that bosentan may be useful in patients with recurrent digital ulcers. Adverse effects are hepatotoxicity with potential for teratogenicity. Regular liver function monitoring is recommended. However, studies have shown that bosentan is not effective in scleroderma-associated Raynaud's phenomenon without pre-existing digital ulcers. Other endothelin receptor antagonists being evaluated are sitaxsentan and abrisentan. These agents differ from bosentan in their selectivity for ETA, which allows for preservation of the vasodilatory action of ETB while antagonizing the vasoconstrictive effect of ETA. Sitaxsentan has recently been withdrawn from the market in view of concerns about hepatotoxicity. An idiosyncratic hepatotoxicity has been reported in some individuals that does not appear to be associated with identifiable risk factors.

Endothelin 1 has also been shown to induce fibrosis by binding to ETA and ETB receptors on fibroblasts, and indirectly by inducing fibrogenic cytokines. Thus, blocking the actions of endothelin 1 may have therapeutic implications in scleroderma/ILD. However, clinical trials studies have failed to show any benefit of bosentan in scleroderma/ILD [36].

Targeting fibrogenesis

Injury to epithelial lining cells and endothelial cells in organs predisposed to fibrogenesis leads to a state of dysrepair. This disturbs the normal epithelial–mesenchymal interaction and promotes fibrogenesis. Thus, therapies may be targeted to promote epithelial/endothelial regeneration or target the fibrotic pathway.

There is increased proliferation of fibroblasts in scleroderma and a subsequent increase in collagen synthesis and extracellular matrix proteins. The two main cytokines mediating these effects are TGF- β and PDGF. There is an increase in expression of their receptors TGF- β R1, TGF- β R2 and PDGFR and activation of their signaling pathway. Imatinib mesylate is a small-molecule tyrosine kinase inhibitor capable of selective dual inhibition of TGF- β and PDGF pathways [37]. It inhibits rather specifically fibroblast activation and synthesis of extracellular matrix and has potent antifibrotic potential. Case reports and open-label trials suggest potential efficacy of imatinib in diffuse systemic sclerosis, although adverse effects are common (edema, muscle cramps, diarrhea, bone marrow toxicity and congestive heart

failure). Several clinical trials are ongoing in scleroderma-related PAH, skin involvement and ILD. Their results will better define the role of tyrosine kinase inhibition. Other agents are nilotinib and dasatinib.

Other therapies are in the experimental phase. Some target epithelial/endothelial repair, such as hepatocyte growth factor, keratinocyte growth factor and cell-based therapies, such as mesenchymal stem cells and pluripotent stem cells. Others target mesenchymal cell activation and survival, such as peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists [38].

Targeting the immune system

Both humoral and cell-mediated immunity are implicated in the pathogenesis of scleroderma. Hence, immunosuppressive therapy has an important role, as in other connective tissue disorders [39].

D-penicillamine

D-penicillamine works by interfering with intermolecular cross-linking of collagen and may be effective in retarding skin thickening. A large randomized double-blind trial involving patients with early diffuse cutaneous scleroderma demonstrated that a low dose of 125 mg every other day may be as effective as higher doses of 750–1000 mg/day [40]. In a recent study, a dose of 750 mg/day in patients with rapidly progressive diffuse systemic sclerosis caused a significant reduction in skin thickening and improvement of renal, cardiac and pulmonary involvement [41]. Monitoring is required for side effects, such as autoimmune phenomenon (pemphigus and myasthenia gravis), hematological abnormality and proteinuria.

Steroids

The use of steroids is restricted to patients in the early edematous phase of the disease and is of limited use once the fibrosis sets in. Other indications are in arthritis and serositis, in which low doses may be effective, and myositis and myocarditis, which requires relatively higher doses.

Intravenous pulse therapy with methyl prednisolone is used in patients with active ILD. Caution is needed when initiating high-dose steroid therapy as it may precipitate normotensive renal failure in some patients.

Methotrexate

Several randomized clinical trials have demonstrated either trends towards or actual significance for improvement in skin thickening and global assessment favoring methotrexate [42]. It is well tolerated by the majority of patients and is recommended by EULAR/EULAR Scleroderma Trial and Research Group as a treatment of early diffuse scleroderma.

Cyclosporine

Used in doses of 2.5–4 mg/kg, studies have shown beneficial effects of cyclosporine in skin thickening and lung and esophageal involvement. However, moderate side effects limit its use, especially arterial hypertension [43].

Cyclophosphamide

Intravenous pulse cyclophosphamide (CYC) therapy is considered for patients with ILD and alveolitis in scleroderma. It is also useful for reduction of skin thickening in patients with early diffuse scleroderma with rapidly progressive disease. In a recent meta-analysis, it was concluded that CYC treatment does not induce a statistically significant improvement in lung function in systemic sclerosis ILD. However, use in early ILD, before irreversible fibrosis sets in, may be beneficial, and trials in early scleroderma lung disease are needed to assess the real efficacy of CYC [44].

Other therapies that have been tried include antithymocyte globulin, recombinant IFN- γ , mycophenolate, IV immunoglobulins, leflunomide and rapamycin. To date there are only anecdotal case reports available for these drugs.

Combination disease-modifying antirheumatic drugs therapy may be beneficial in patients showing poor response to a single drug and to avert side effects of high doses of usage of a single drug.

Autologous stem cell transplant

To date, no therapy has demonstrated a reversal in the natural course of the disease. Studies have failed to show any long-term benefit of immunosuppressive therapy. In autologous stem cell transplant (ASCT) high-dose chemotherapy is used to eradicate the immunocompetent cells, especially the T cells.

Autologous stem cells are then used to reconstitute the immune system, naive to previously implicated autoantigens. In Phase I/II trials, autologous hematopoietic stem cell transplantation (HSCT) has demonstrated impressive reversal of skin fibrosis, improved functionality and quality of life, and stabilization of internal organ function, but initial studies were complicated by significant treatment-related mortality. Treatment-related mortality was reduced by better pretransplant evaluation to exclude patients with compromised cardiac function and by treating patients earlier in the disease, allowing selected patients the option of autologous HSCT treatment. There are currently three ongoing randomized trials of autologous HSCT for systemic sclerosis: American Systemic Sclerosis Immune Suppression versus Transplant (ASSIST), Scleroderma Cyclophosphamide Versus Transplant (SCOT) and Autologous Stem cell Transplantation International Scleroderma (ASTIS). The results from these trials should clarify the role of autologous HSCT in the currently limited therapeutic arsenal of severe systemic sclerosis [45].

Treatment of manifestations

Scleroderma is a multisystem disease characterized by skin fibrosis and visceral involvement. Clinical manifestations include Raynaud's phenomenon, skin thickening, PAH, lung fibrosis, renal disease and involvement of other organ systems. Hence, there is no single medication, but treatment is for a constellation of manifestations (TABLE 3).

Raynaud's phenomenon & digital ulcers

Severe Raynaud's may cause digital ulceration and gangrene, and hence prevention is of utmost importance. Avoidance of cold and smoking is advisable. Calcium channel blockers, such as nifedipine, nicardipine, amlodipine and diltiazem, have been used successfully and lead to a decrease in the severity and frequency of attacks of Raynaud's. Sustained release preparations of nifedipine and diltiazem are available with better tolerability. High doses of

Table 3. Treatment of scleroderma manifestations.

Manifestation	Treatment
Raynaud's phenomenon	Calcium channel blockers Angiotensin type II receptor blocker (losartan) Prostacyclin analogues (intravenous iloprost) Phosphodiesterase inhibitors Surgical sympathectomy
Digital ulcers	Same as above Endothelin receptor antagonists (bosentan)
Skin fibrosis	Immunosuppressives (D-penicillamine, methotrexate, cyclosporine, tacrolimus, relaxin, IVIG)
Arthritis	NSAIDs Low-dose steroids DMARDs (methotrexate)
Myositis	Immunosuppressives (steroids, methotrexate and azathioprine)
Gastrointestinal involvement	Proton pump inhibitors Prokinetic agents Calcium channel blockers
Scleroderma renal crisis	ACE inhibitors Antihypertensives Dialysis Renal transplant
Pulmonary hypertension	Calcium channel blockers Prostacyclin/analogues Endothelin receptor blockers Phosphodiesterase inhibitors Combination therapy Imatinib Lung transplant
Interstitial lung disease	Immunosuppressives (steroids, cyclophosphamide) Imatinib Lung transplant
Advanced stage multisystem disease	Immunosuppressives (ATG, ALG and MMF) Autologous stem cell transplant

ACE: Angiotensin-converting enzyme; ALG: Antilymphocyte globulin; ATG: Antithymocyte globulin; DMARD: Disease-modifying antirheumatic drug; IVIG: Intravenous immunoglobulin; MMF: Mycophenolate mofetil.

40 mg of nifedipine and 360 mg of diltiazem may be required. Losartan, a specific type II angiotensin receptor antagonist, has recently been shown to be useful in the treatment of Raynaud's phenomenon. At a dose of 50 mg/day it resulted in a reduction in the frequency and severity of Raynaud's and was well tolerated.

Prostaglandins are potent vasodilators. As detailed above, IV iloprost has been effective in reducing the severity and frequency of Raynaud's phenomenon and also increases digital ulcer healing. However, the cost involved and inconvenient method of administration limit its use. Other drugs that have been tried include aspirin, dipyridamole, pentoxifylline and topical nitroglycerin, with variable results. In intractable Raynaud's and those with digital ulceration, sympathetic blocks – that is, stellate ganglion block and lumbar sympathetic blocks – may be useful. Surgical sympathectomy can be performed both using an open and videoendoscopic technique. The endoscopic technique being relatively safe, less time-consuming and producing better cosmetic results, is preferred over the conventional open procedure. Both have shown good results. Recently, surgical digital sympathectomy, which involves dissection of the perivascular fibrous tissue along with denervation of the digital arteries, has also been used. This procedure thus targets both the mechanical and vasospastic components of Raynaud's phenomenon [46]. Chemical sympathectomy, which involves injection of 5% phenol to the second thoracic sympathetic ganglion, is minimally invasive and an effective treatment modality. Sometimes, digital tip amputation may be required. More recent therapies include endothelial receptor antagonists, such as bosentan, for prevention of digital ulcers, and phosphodiesterase inhibitors, such as sildenafil and tadalafil, for treatment of Raynaud's and ulcer healing.

Skin

D-penicillamine has been shown to reduce the skin scores in patients with scleroderma when taken at a low dose of 125 mg every other day. There is no difference between high and low dose and no effect on scleroderma renal crisis. IFN- α has no role, and IFN- γ has been shown to have, at best, a modest role in skin sclerosis. Adverse effects include a flu-like syndrome. Cyclosporine and tacrolimus have also demonstrated a beneficial role in reducing the skin tightness in patients with scleroderma. Recombinant human relaxin has also shown beneficial effects in some studies. Intravenous immunoglobulin may have a role in the treatment of scleroderma patients with rapidly deteriorating skin disease and further studies are needed.

Joints & muscles

Arthritis and arthralgias benefit from NSAIDs. Short courses of low-dose steroids of 5–10 mg/day may be beneficial. In patients with severe polyarthritis, methotrexate is a good option. In patients developing digital contractures and deformities, physiotherapy, splinting and, in irreversible cases, surgical correction is warranted. Symptomatic myositis due to systemic sclerosis or overlap syndrome is treated with high-dose steroids with the addition of an immunosuppressive, such as methotrexate or azathioprine, with fairly good treatment outcomes.

Gastrointestinal

GI tract involvement is exceedingly common in scleroderma, with esophageal involvement being most common, followed by anorectal disease, small bowel and colonic involvement. Proton pump inhibitors are highly effective in reducing symptoms of gastroesophageal reflux and preventing complications such as fibrosis and stricture formation. These drugs should be used routinely in anyone with suspected scleroderma and reflux esophagitis. Prokinetic agents, such as metoclopramide and cisapride, may be used in combination. Nifedipine given for Raynaud's lowers esophageal sphincter pressure and may worsen the symptoms of reflux esophagitis. Symptomatic treatment of esophagitis includes intake of small meals, sitting upright after eating and avoiding heavy meals at bedtime. Bacterial overgrowth, resulting from intestinal stasis, is best managed with broad-spectrum antibiotics, such as ampicillin, tetracycline, ciprofloxacin and metronidazole.

Antibiotics are given in 2–3-week courses, with alternating antibiotic-free periods of 1–2 weeks to reduce the development of resistant strains. In advanced cases of malabsorption, parenteral nutrition may be required.

Scleroderma renal crisis

Scleroderma renal crisis occurs in 5–10% of scleroderma patients [47]. Patients with rapidly progressive diffuse skin thickening are most vulnerable. It is characterized by malignant hypertension with rapidly progressive renal failure. High-dose corticosteroids may precipitate scleroderma renal crisis and should be avoided in early diffuse disease. The hypertension is renin-mediated and treatment with ACE inhibitors has revolutionized the therapy of renal crisis of scleroderma with improved outcome [47]. Prompt initiation with ACE inhibitors (captopril or once-daily agents as oral therapy) is recommended. The dose should be gradually increased to achieve a reduction of 10–20 mmHg/24 h. In addition, low-dose prostacyclin infusion controls the blood pressure and benefits renal perfusion. Additional antihypertensives may be used, including angiotensin receptor blockers and calcium channel blockers. Mortality approaches 10%, and half of the patients require renal replacement therapy. Of these, 50% may be weaned off. In some, this may take up to 2 years, and hence the transplant option should be considered at least after 2 years. Renal transplant offers superior survival compared with long-term dialysis.

Pulmonary hypertension

Patients with systemic sclerosis can develop pulmonary hypertension caused by PAH, ILD or left ventricular disease.

Therapy in PAH is directed at the obliterative vasculopathy of the pulmonary circulation and benefits the first category of patients as mentioned above [48]. The prevalence of PAH associated with scleroderma that shows acute vasodilatation during hemodynamic testing is only approximately 1%. In the majority of these patients the vasoreactivity wanes over time. Thus, vasodilator therapy using high-dose calcium channel blockers is of limited utility in a small subset of patients only. The

prostacyclin analogue epoprostenol and treprostinil are the mainstay of therapy, as discussed previously. Although they improve hemodynamics, there are no effects on survival. Oral prostacyclin analogues have also been used, but efficacy remains questionable. The endothelin receptor antagonist bosentan was the first oral therapy approved for the treatment of PAH. Recent guidelines from the EULAR recommend bosentan as initial therapy for PAH scleroderma. Other selective endothelin receptor antagonists, such as sitaxsentan and ambrisentan, have recently been approved for the treatment of PAH. However, sitaxsentan has recently been withdrawn from the market in view of concerns about hepatotoxicity, as mentioned previously. Sildenafil was the first phosphodiesterase inhibitor approved for patients with mild-to-moderate PAH. Tadalafil may be a useful alternative to sildenafil in the treatment of PAH scleroderma given its safety profile and ease of administration. Since the different therapies in scleroderma target different pathogenetic mechanisms, the combination of two or three drugs (bosentan, epoprostenol and sildenafil) has also been reported in refractory cases. Amongst the novel therapies imatinib has a potential role, as discussed previously. The role of imatinib in PAH is secondary to its effect in downregulating the plasma concentrations of PDGF, the latter being implicated in the abnormal proliferation and migration of pulmonary artery vascular smooth muscle cells [49]. Symptomatic treatment with digoxin, diuretics and supplemental oxygen and anticoagulation may be required in patients presenting with right heart failure secondary to PAH. Despite medical therapy, the prognosis of scleroderma-associated PAH is poor, and only lung transplant is curative. However, in view of multisystem involvement and associated comorbidities, many patients may not be suitable candidates for the same. A consensus panel convened by the American College of Chest Physicians developed guidelines for the diagnosis and treatment of PAH that were published in 2004. These have subsequently been updated to include the newer agents and combination therapies [50].

Interstitial lung disease

Interstitial lung disease is the leading cause of morbidity and mortality in scleroderma. Although diffuse cutaneous scleroderma is more frequently associated with ILD, it also occurs in patients with limited scleroderma and even in patients without any cutaneous sclerosis (scleroderma sine scleroderma). Prognosis of ILD remains poor. D-penicillamine, relaxin and endothelin receptor antagonists have not been found to be effective. Oral or IV CYC in combination with high-dose steroids is effective in the initial stages of alveolitis and once irreversible fibrosis sets in, efficacy is doubtful [51]. Even though both routes of administration are well-tolerated, the overall beneficial effect of CYC on pulmonary function is at most modest [52]. However, the efficacy of CYC depends on the stage of lung disease and once irreversible fibrosis sets in, no drug can revert it. Thus, early detection of ILD and early institution of therapy with CYC should be encouraged. Imatinib offers a promising future option, as discussed above. It has been combined with IV CYC in one study and was found to be well tolerated [53]. The combination of immunosuppressives with antifibrotic agents

may be a good future option in the treatment of scleroderma fibrotic lung disease. Lung transplant remains a viable option for patients with end-stage scleroderma lung disease, and the results are no different from patients with idiopathic pulmonary fibrosis subjected to the same.

Heart

Pericarditis is treated with NSAIDs and low-dose steroids. If effusion is massive it requires pericardiocentesis. Myocarditis responds to steroids with inotropic support. Advanced left ventricular failure secondary to the fibrotic disease process is poorly responsive and uniformly fatal. It may be accompanied by arrhythmias, which may show an inconsistent response to anti-arrhythmic agents.

Localized scleroderma

Localized scleroderma, also known as morphea, is characterized by collagen deposition limited to the skin but may extend to involve deeper structures. However, systemic involvement is lacking. The specific clinical entity depends on the extent, type and depth of lesions and includes plaque morphea, generalized morphea, bullous morphea, linear scleroderma (including 'en coup de sabre' and hemifacial atrophy) and deep morphea [54]. Morphea is ten-times more prevalent than systemic sclerosis and its prognosis is generally good. Superficial forms resolve within 3 years and are more benign. Involvement of subcutaneous tissue, muscle and bone in addition to skin may lead to functional disabilities and cosmetic disfigurement.

However, unlike most forms of localized scleroderma, which lack extracutaneous manifestations, a subset of linear scleroderma referred to as en coup de sabre has been associated with several neurologic abnormalities [55]. It characteristically involves the frontoparietal scalp and forehead. Facial hemiatrophy may develop as a result of hypoplasia of the underlying bone and soft tissues. Progressive hemifacial atrophy (Parry–Romberg syndrome) is a related disorder characterized by progressive hemifacial atrophy without cutaneous sclerosis. Of the neurological abnormalities, complex partial seizures have been reported most frequently. Others are hemiparesis, trigeminal neuralgia, encephalitis, nerve palsies and migraine. Neuroradiologic abnormalities include cerebral atrophy, white matter lesions, intraparenchymal calcification, meningeocortical alterations and skull atrophy.

Diagnosis

The diagnosis of morphea is based on clinical examination. Sometimes confirmation by skin biopsy may be needed when lesions are unclear.

Laboratory findings

Eosinophilia occurs in 7–10% of patients with linear or generalized morphea and in a higher percentage of patients with deep morphea [56,57]. Hypergammaglobulinemia is seen in patients with more severe skin disease and is more common during clinical progression. Acute-phase reactants are elevated in patients with deep morphea and uncommonly elevated in the other groups.

CPK may be elevated in the deep morphea group. Several auto-antibodies may be positive in localized scleroderma. ANA positivity ranges from 23 to 63%. In one of the largest series on juvenile scleroderma, ANA positivity was 42.3% with a higher prevalence in the deep morphea-linear scleroderma group than in the plaque morphea generalized morphea subtype [56]. In the same study, anti-Scl-70, ACA and dsDNA antibody was positive in <5% of the patients, and rheumatoid factor and ACA were positive in approximately 15% of patients. Rheumatoid factor showed a correlation with arthritis. However, ACA positivity did not manifest as thromboembolic episodes. In another study, prevalence of ANA was similar as above in the adult group, but less in the childhood group with morphea (i.e., 23%) [57].

Some studies have shown high prevalence of antihistone antibodies in patients with linear scleroderma [58]. In another study, a high prevalence of topoisomerase II was found in patients with localized scleroderma, distinct from topoisomerase I seen in patients with systemic sclerosis [59].

Skin biopsy

Morphea and scleroderma cannot be differentiated on the basis of histopathological findings. Early lesions have thickened collagen bundles in the dermis and inflammatory cell infiltrate between the collagen bundles and around blood vessels, which may extend into the subcutaneous fat and glands. Late lesions show a paucity of inflammatory cells, extension of the collagen bundles in the subcutaneous tissue and replacement of fat cells and atrophy of the glands.

Assessment of skin lesions & disease activity in localized scleroderma

A new computerized method (computerized skin score) has been shown to be a reliable method to assess the skin lesions in patients with localized scleroderma. It is reproducible, easy to use and the use of computerized skin score software makes it applicable worldwide [60].

Infrared thermography

It detects active disease but has low specificity, especially in the detection of older lesions with atrophy of skin and subcutaneous fat [61]. In such cases, laser Doppler flowmetry can discriminate real active lesions from false-positives [62]. Some studies show that ultrasound in scleroderma may be used to assess disease activity as reflected by altered echogenicity and vascularity changes, and also to detect deeper extension of lesions beyond the dermis [63].

MRI

Among the major imaging techniques, MRI can show the true depth of the lesions. In the early inflammatory stages of the disease, MRI shows thickening of the dermis and infiltration of the subcutaneous tissue with an increase in signal intensity on short-tau inversion recovery images and contrast-enhanced T1-weighted images, and hypointense signal on unenhanced T1-weighted images. Involvement of fascia and musculature beneath the skin

is reflected by similar signal intensities [64]. Neuroimaging is also indicated for patients with the linear scleroderma en coup de sabre variety. Abnormalities may be seen in CT and MRI even in the absence of neurological disease.

Treatment

Treatment of localized scleroderma has remained a great challenge, with no single effective drug or drug regimen. The choice of treatment depends on the type and severity of the lesion, rate of disease progression, stage of disease and the age of the patient. The aim of treatment is to improve the lesions, delay progress and prevent disabilities and cosmetic disfigurement. In the acute inflammatory phase, a number of therapeutic modalities are available. In the chronic phase of the disease, emollients, physiotherapy and surgery have a role.

Immunosuppressives

Methotrexate and corticosteroids are the most commonly used drugs for the treatment of localized scleroderma. The dose and duration differs depending on the severity of the lesions. Topical, intralesional, oral and IV corticosteroids have been used depending on the severity of the lesions. Topical steroids are used in the inflammatory phase of the disease. Intralesional steroids may be useful, especially in linear scleroderma [65]. Oral steroids and pulse IV therapy are used for recent-onset disease, rapid progression, deep lesions, generalized forms and those located near the joints and face [66]. Methotrexate has been used alone and in combination with oral and IV steroids for the indications mentioned above and is generally well tolerated. Most patients who relapse after stopping treatment generally respond well to second and even third courses of methotrexate. Treatment with colchicine [67], sulfasalazine [68], antimalarials [69], D-penicillamine and mycophenolate [70] has also been described in anecdotal fashion. Appropriate monitoring is required for immunosuppressive drugs in view of the potential side effects.

Topical tacrolimus is a calcineurin inhibitor and inhibits T-cell activation and the production of cytokines. Studies have shown that tacrolimus 0.1% ointment is effective in the treatment of early inflammatory lesions of active plaque morphea [71].

Imiquimod cream has been used for local application. Imiquimod is an IFN- γ inducer and inhibits TGF- β , which is involved in fibrosis. Studies of imiquimod cream 5% in the localized form of the disease resulted in a reduction of induration and dermal thickening [72].

Intralesional IFN- γ given to patients with localized scleroderma had no effect on the regression of the lesions but may avert development of new lesions [73].

Phototherapy

UV irradiation has been used either alone or in combination with psoralens in the treatment of a number of dermatological conditions [74]. It has shown to have both antifibrotic and immunosuppressive effects, which accounts for its therapeutic effects. Acute rash of phototherapy includes dermatitis solaris. Risk of epitheloid skin cancer (squamous and basal cell carcinoma) is low.

UV-B only penetrates the epidermis and upper capillary dermis, whereas longer wavelength UV-A reaches the subcutaneous tissue. The effect of UV is increased by local systemic application of a photosensitizing agent (photochemotherapy). The photosensitizer 8- or 5-methoxypsoralen is given 2 h prior to UV-A irradiation (oral PUVA) or applied locally over the lesion (bath PUVA) prior to UV-A irradiation.

In morphea, bath PUVA has shown improvement and even clearance of fibrotic plaques. Broadband UV-A is also able to soften areas of localized scleroderma and acral sclerotic skin lesions in patients with scleroderma. Thus, phototherapy is a promising therapy for morphea and skin sclerosis in scleroderma. However, it is not effective in late stages once joint contractures and atrophy set in. Thus, it is important to start phototherapy in the early stage of disease.

Vitamin D analogues

Calcitriol has a dose-dependent inhibition on fibroblast proliferation and collagen synthesis. It also has immunoregulatory properties. Oral calcitriol has beneficial effects in localized scleroderma [75]. Calcipotriol or calcipotriene, a calcitriol analogue, has been shown to inhibit the growth of fibroblasts from scleroderma skin. It has been used alone and in combination with UV-A phototherapy and is highly effective in childhood plaque morphea [76].

Laser therapy

Pulsed-dye laser therapy has been used in patients with plaque scleroderma with improvement in skin flexibility and pigmentation [77].

Autologous fat transplant

Autologous fat transplant may be useful in patients with linear scleroderma. However, results may vary depending on the site of transplant [78].

Conclusion

Scleroderma is a heterogeneous disease with diverse clinical manifestations, autoantibody profile and an unpredictable disease course. Although the diagnosis is established in most cases, early disease detection and therapeutic intervention is emphasized to prevent the potentially irreversible fibrotic stage of the disease. Immunosuppressive therapy may be beneficial in the early stages of active inflammation. With a clearer insight into disease pathogenesis, newer therapeutic modalities targeting the fibrotic and vascular pathogenetic mechanisms are underway and may hold promise for the future.

Expert commentary

Scleroderma is a heterogeneous disease varying in clinical presentation, autoantibody profile and outcome. The ACR criteria for diagnosis of scleroderma are intended to provide uniformity while comparing patient subsets from different centers and are not meant for diagnostic purposes. Revision of ACR criteria as suggested is well justified as inclusion of nailfold capillary

abnormalities and presence of ACA as minor criteria may diagnose a significant number of patients with limited scleroderma who otherwise might be excluded.

Diagnosis of scleroderma is usually straightforward and clinical. Sometimes a skin biopsy may be warranted in diagnosing scleroderma-mimicking conditions that may also present with skin thickening. Autoantibodies in scleroderma are useful in differentiating disease subsets, especially in early disease. ACA and anti-Scl-70 antibodies positivity in patients with Raynaud's predict future development of disease in these patients. They are also useful for differentiating from other connective tissue diseases that may share a number of features with scleroderma. In scleroderma *per se*, antibody subsets may be associated with distinct disease manifestations. ACA predict a limited skin involvement and the absence of pulmonary involvement and the presence of anti-Scl-70 antibodies predict diffuse skin disease and lung fibrosis. Antifibrillar and anti-RNA-polymerase autoantibodies are also predictive of diffuse skin involvement and Anti-Th/To and PM-Scl, by contrast, with limited skin disease and myositis, respectively. Hence, the importance of serology in scleroderma is unmatched. With time, advances in diagnostic techniques with improved sensitivity have led to the early detection of internal organ involvement in scleroderma, which translates into early institution of therapy at a potentially reversible stage of disease.

In contrast to most connective tissue disorders, immunosuppressive therapies in scleroderma have been disappointing and have failed to influence the natural course of the disease. They have at most been effective in the very early stages of disease when very few would seek medical attention.

However, in recent years some newer therapies have revolutionized the treatment of some of the disease manifestations, such as prostacyclin and its analogues, endothelin receptor antagonists and phosphodiesterase inhibitors for pulmonary arterial hypertension, Raynaud's and digital ulcers and autologous stem cell transplantation as a potential curative modality. Antifibrotic therapies are still in the inception stage. Trials are ongoing with imatinib and if results are encouraging it may offer hope for a cure even at the relatively advanced stage of disease.

Localized scleroderma or morphea being localized to skin has a better outcome compared with scleroderma. Most superficial lesions regress with time. However, deeper involvement may lead to disfigurement and cosmetic problems, which may be an important issue in children. Phototherapy appears to be a promising antifibrotic therapy for localized skin fibrosis of scleroderma. Although it may not completely reverse the fibrotic process, it may halt further progression. Antifibrotic therapies for scleroderma may also benefit this subset of patients once they are proven effective.

Five-year view

Although diagnosis of scleroderma is simple, treatment is perplexing. The disease passes through various stages. The early stage is characterized by active inflammation and is potentially reversible.

Once the fibrotic stage sets in, it leads to end-organ damage and virtually no therapy is effective at this stage. Hence diagnosis and referral at the early stage of disease is the cornerstone

of effective treatment. Awareness of most connective tissue disorders is increasing amongst practitioners as rheumatology is now being recognized as a distinct subspecialty of medicine. With this heightened awareness we hope for the early institution of therapy and improved outcome for these patients in the near future.

Although many of the pathogenetic events of scleroderma are now extensively studied and have been exploited into targeted therapies, we still have a long way to go. Drug trials in scleroderma are not easy as it is a rare disease, all patients are not in the same stage at one point of time and there are no uniform markers or disease scoring systems to assess improvement with therapy. These issues need to be addressed for long-term effective drug trials and meaningful interpretation of results.

Although newer drug therapies have come in, they have their limitations. Affordability and ease of administration remains an important issue with prostacyclin and its analogues. Although effective in the treatment of PAH, Raynaud's and digital ulcers, continuous parenteral infusions and high cost limit their use. Oral iloprost and cisaprost have not been found to be as effective. Thus, there is a need for the development of other analogues that may be effective through the oral route. Antifibrotic therapy is still in inception and trials are ongoing with imatinib that should come to light in the near future. Other antifibrotic drugs still need to be

tested in clinical trials. However, not all trials translate into favorable patient outcomes. Well-conducted and controlled clinical trials are needed for relatively newer immunosuppressives, such as mycophenolate and leflunomide, for which anecdotal reports have shown encouraging results. Tadalafil has shown promising results in intractable Raynaud's and digital ulcers and may be a therapy of choice in the future. Combination therapies with endothelin receptor antagonists, PD5 inhibitors and prostacyclin need further studies as an effective therapy for PAH. Recently, B-cell depletion therapy offers a therapeutic target in patients with diffuse systemic sclerosis. In an open-label trial, rituximab (anti-CD 20) showed a marked effect on skin thickening, functional ability and disease activity. Thus, B cells may be an effective target in future therapies.

Autologous stem cell transplant is the only curative modality that can currently be offered in systemic sclerosis. As mentioned above, there are three ongoing trials and results are awaited that will clarify its role as a potential curative modality in the near future.

Treatment of localized scleroderma remains a sensitive issue as the disorder is more common in children, and early institution of therapy is needed to prevent cosmetic damage and disability. There is no therapy that is fully curative as with most connective tissue disorders, and treatment of this disorder is also likely to remain a challenge in the near future.

Key issues

- Scleroderma is a heterogenous disorder with diverse clinical presentations and a varied autoantibody profile.
- In practice, the diagnosis of scleroderma is clinical. Investigations aid in defining subsets of disease, extent of organ involvement and diagnosing scleroderma-mimicking conditions.
- Treatment of scleroderma remains elusive. No drug has been shown to halt the disease process.
- Earlier treatment was largely symptomatic and directed to the organ system involved.
- Immunosuppressives are only effective in the early stages of disease.
- Recent therapies targeting vascular dysfunction, such as endothelin receptor antagonists, prostacyclin analogues and PD5 inhibitors, have improved the outcome of disease.
- Antifibrotic therapies are underway. Imatinib, a tyrosine kinase inhibitor, holds promise as an antifibrotic agent, and others are in the pipeline.
- Autologous stem cell transplant may be a potentially curative option in properly selected patient groups in the near future.
- Localized scleroderma is a distinct entity and runs a benign course. However, treatment needs to be started early before skin atrophy and joint contractures set in.

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Diagnosis and treatment of systemic and localized scleroderma

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Activity Evaluation

Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

- A 43-year-old woman presents to your office and complains of symptoms consistent with Raynaud's phenomenon. You notice that she also has sclerodactyly and wonder whether this patient has scleroderma. You order some laboratory tests. Which of the following tests is best matched with its relationship to scleroderma?

 - A Anticentromere antibodies → poor prognosis
 - B Anti-Scl-70 antibodies → higher risk for gastrointestinal disease
 - C Anti-PM-Scl antibodies → combined polymyositis and scleroderma
 - D Anticardiolipin antibodies → suggests diagnosis other than scleroderma
- Her laboratory evaluation confirms the diagnosis of scleroderma, and further workup reveals evidence of pulmonary and renal disease. What should you consider regarding initial treatment for manifestations of disease at this point?

 - A Oral iloprost has supplanted calcium channel blockers in the treatment of Raynaud's phenomenon
 - B Prazosin is better tolerated than other therapies for Raynaud's phenomenon
 - C Angiotensin-converting enzyme (ACE) inhibitors are effective treatments for scleroderma renal crisis
 - D Sildenafil should be reserved for patients with severe pulmonary arterial hypertension (PAH)
- What should you consider regarding treatment targeting the immune system for this patient?

 - A D-penicillamine and methotrexate maintain efficacy even during the fibrotic stage of scleroderma
 - B Cyclosporine can help to lower blood pressure
 - C Cyclophosphamide is most effective during the fibrotic stage of scleroderma
 - D Autologous hematopoietic stem cell transplantation (HSCT) has been demonstrated to reverse skin fibrosis and stabilize internal organ function
- Two years later, the patient from question 1 brings her sister, who was recently diagnosed with morphea, to see you. What should you consider regarding the diagnosis and management of morphea?

 - A Morphea is much rarer than systemic sclerosis
 - B Anticentromere antibodies are more common in morphea than systemic sclerosis
 - C Methotrexate and corticosteroids are the most commonly used drugs in the treatment of morphea
 - D PUVA is ineffective for sclerosis in morphea