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Scleroderma Lung
Pathogenesis, Evaluation and Current Therapy

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Abstract

The lungs are frequently involved in systemic sclerosis ('scleroderma'), a rare, disabling disease of unknown origin, characterised by skin thickening and Raynaud's phenomenon. The pathogenesis of scleroderma is complex, but signs and symptoms of excessive fibrosis, vasculopathy and inflammation are almost universally present. Dyspnoea in scleroderma patients can be due to chest wall tightening from skin thickening, pleural disease, cardiac involvement, myositis of intercostal muscles, or so-called scleroderma lung disease. Scleroderma lung disease encompasses vascular (pulmonary artery hypertension) or interstitial lung disease, or both. A comprehensive work-up is required to delineate the underlying cause of dyspnoea in a scleroderma patient, and to establish the contribution of each component to the symptoms. This should include a 6-minute walk test, pulmonary function testing, high-resolution thoracic CT scanning, ECG, echocardiography and, if pulmonary artery hypertension is suspected, right-heart catheterisation; bronchoalveolar lavage is optional. Lung disease in scleroderma contributes significantly to excess morbidity and early mortality, especially when diffusion capacity drops below 40% and/or forced vital capacity below 50%. However, recent clinical studies have unequivocally demonstrated that scleroderma lung disease is amenable to treatment with new vasodilatory drugs that target specific pathways involved in vasoconstriction, or with cyclophosphamide for interstitial lung disease. Uncontrolled studies have suggested that these therapies also have an impact on survival, but controlled studies with a long follow-up are needed to corroborate this point.

Systemic sclerosis (SSc), also referred to as 'scleroderma', is a rare, heterogeneous condition of unknown aetiology characterised by microvascular injury and deposition of excess collagen in skin and internal organs.[1] A genetic predisposition may be present, but genetic factors have been difficult to identify because of the low incidence and prevalence of the disease.[2] Severe forms of the disease, and rapidly progressive diffuse SSc in particular, are associated with significant mortality (estimated to be 40–50% in 5 years) secondary to cardiac, renal and, particularly, pulmonary involvement.[3-11] Less severe chronic forms are nevertheless associated with significant morbidity, reduced quality of life and a major burden of disease.

Systemic sclerosis can be classified according to criteria established by the American Rheumatism Association (table I).[12] Presence of the major criterion (proximal scleroderma) or two or more of the minor criteria is necessary to establish a diagnosis of SSc. A further subclassification can be made into limited (cutaneous) SSc (lcSSc) and diffuse (cutaneous) SSc (dcSSc). lcSSc is characterised by skin involvement limited to the hands, feet, face and/or forearms and is associated with a high incidence of anticentromere autoantibodies (70–80%), existence for a number of years of Raynaud's phenomenon and a significant late incidence of pulmonary hypertension. The syndrome described by the acronym CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia) fits into this subset. dcSSc is characterised by skin involvement on the upper arms and trunk, and is associated with early incidence of interstitial lung disease, hypertensive crisis and renal failure, diffuse gastrointestinal disease and myocardial involvement. Antitoposiomerase antibodies are commonly found in the serum of patients with the diffuse subset. Both forms of the disease are associated with vascular abnormalities clinically manifest as Raynaud's phenomenon.

Table I. Preliminary criteria for the classification of systemic sclerosis (scleroderma) from the American Rheumatism Association scleroderma criteria cooperative study.[12] Presence of the major criterion or two or more minor criteria is required to establish the diagnosis

Major criterion
Proximal scleroderma
Minor criteria
Sclerodactyly
Digital pitting scars or loss of substance of the digital finger pad
Bibasilar pulmonary fibrosis

1. Terminology

'Scleroderma lung' refers to pulmonary involvement in patients with systemic sclerosis. Two clinical patterns are recognised: precapillary vascular disease and interstitial lung disease (ILD), which has become the leading cause of death in SSc since the introduction of ACE inhibitors to treat previously fatal renal crisis.[7] Vasculopathy may lead to pulmonary arterial hypertension (PAH) even in the absence of significant fibrosis, and PAH is a major predictor of mortality in diffuse systemic sclerosis, independent of ILD.[13] PAH, defined as a mean pulmonary artery pressure >25mm Hg at rest or >30mm Hg during exercise in the absence of left-sided heart disease defined as a pulmonary wedge pressure >15mm Hg, occurs in at least 10% of SSc patients, and is associated with high mortality.[14] PAH in the absence of pulmonary fibrosis, left ventricular failure or pulmonary embolism is termed 'isolated' PAH. Lung fibrosis has been found in approximately 70% of SSc patients at autopsy[15] (figure 1).

Most studies differentiate scleroderma-associated PAH and ILD as two separate pathological processes, concentrating on one or the other. However, many patients have both conditions, and appear to resemble patients with isolated restrictive lung disease in that they have a high prevalence of diffuse skin involvement and antitopoisomerase positivity.[16] A recent analysis by the EUSTAR (European League Against Rheumatism [EULAR] Scleroderma Trials And Research) group of core set data from 3656 SSc patients revealed that ILD was more frequent in dcSSc (53%) than in lcSSc (35%), whereas PAH was diagnosed in a similar frequency within the two subsets, namely in 22% of dcSSc patients and in 21% of lcSSc patients.[17] Isolated PAH in the absence of lung fibrosis was found in

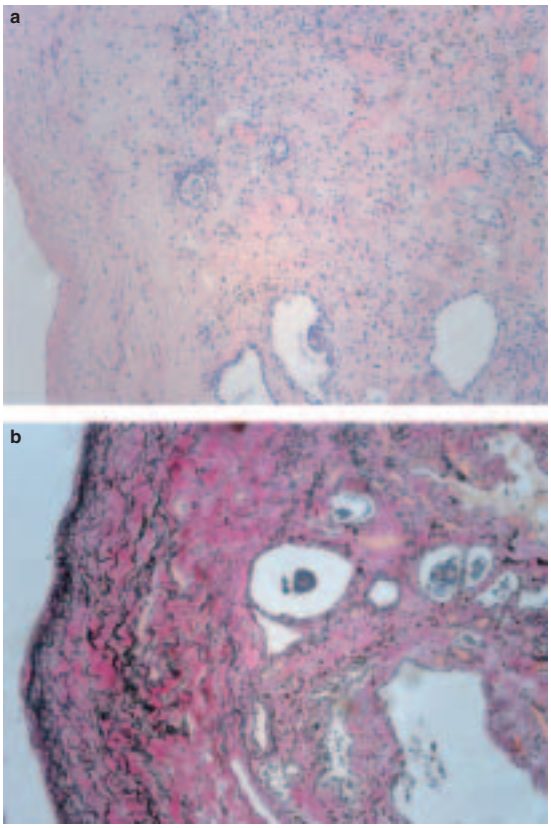

Fig. 1. Histological appearance of peripheral lung tissue and pleura of a 53-year-old male who died from end-stage lung fibrosis due to systemic sclerosis. (**a**) Haematoxylin and eosin staining shows that the normal alveolar pattern has vanished because of massive fibrosis, leaving only a few cyst-like spaces with some debris. There is only a very scanty, diffuse lymphocytic infiltrate. (**b**) Elastica van Gieson staining of the same tissue fragment shows dominant layers of elastic fibres in the pleura (black), obliteration of the alveolar spaces by fibrotic tissue (red), and distortion of the remnants of the elastic fibre skeleton of the lung (black). Only a few cyst-like spaces with some debris and one larger dilated bronchiolar space are present (original magnifications ×10).

26% of dcSSc with PAH and in 45% of lcSSc PAH patients.

Severe lung involvement, defined as forced vital capacity (FVC) <55% predicted, has been reported to occur in 16% of 953 patients with diffuse SSc, and within the first 3 years in half of those who were ever affected.[18] Prediction of end-stage lung disease in patients with early disease is difficult.[19] Furthermore, recognition of ILD in SSc may be delayed because the clinical signs are often mild and insidious. Moreover, the disease course of lung fibrosis associated with SSc may vary considerably, making treatment decisions difficult. Therefore, the challenge is to identify high-risk patients at a sufficiently early stage of the disease to stop further deterioration.

2. Pathogenesis

The pathogenesis of SSc is complex, but dominated by excessive collagen production and deposition, vascular damage, inflammation and autoimmunity.[20] SSc is the prototype fibrosing disease. Scleroderma skin and lung fibroblasts produce excessive amounts of type I collagen *in vitro*.[21] Numerous lines of evidence suggest that an inflammatory process, which may be autoimmune in origin, precedes the development of fibrosis. Antibodies to nuclear proteins are frequently present prior to the development of disease.[22] Reactivity to the nuclear auto-antigens topoisomerase I and the centromere proteins are rarely seen other than with this disease and are associated with particular HLA-D genotypes.[23] A recent study found that the serum of SSc patients contains stimulatory antibodies to the platelet-derived growth factor receptor; these antibodies selectively induced intracellular transcription factors and reactive oxygen species and stimulated type I collagen-gene expression and myofibroblast phenotype conversion in normal human primary fibroblasts.[24]

An inflammatory response with lymphocytic infiltration is evident early in the disease, and is well documented in skin[25] and lung.[26,27] The early active stage of SSc lung fibrosis is characterised by the induction of a large number of smooth muscle α-actin-positive myofibroblasts in the interstitium and by the excessive formation of irregularly shaped alveolar capillaries accompanied by an increase in the number of microvascular endothelial cells. As fibrosis progresses to end-stage lung disease, the population of myofibroblasts and capillary endothelial cells declines.[28] The similarity of the condition with aspects of graft-versus-host disease (GVHD) further suggests that immune allo-reactivity is capable of inducing excessive fibrosis.[29,30] An increased

frequency of microchimerism by haematopoietic cells derived from offspring has been reported in SSc patients.[31-34] Allogeneic cells could trigger immune responses analogous to GVHD and drive the secondary events of fibrosis. Immunological involvement in the pathogenesis of the disease is supported by the clear thymic and T-cell abnormalities found before the development of disease in the UC Davis spontaneous chicken model of scleroderma.[35-37] Despite this evidence, the relationship between autoimmune responses and the vascular pathology of SSc is unclear.[38] Vascular abnormalities may be evident many years prior to the onset of disease.[39] Similarly, the extent to which autoimmune responses and inflammation contribute to the maintenance of fibrosis remains unresolved. The perceived failure of immunosuppressive treatments to reverse established fibrosis suggests that once initiated, the fibrotic process becomes dissociated from the normal immune process and continues as an autonomous process. Alternative pathogenetic mechanisms may also be involved in SSc alveolitis, such as an imbalance of pro- and anti-inflammatory eicosanoids.[40]

Until recently, it was believed that pulmonary fibrosis in SSc patients was indistinguishable from idiopathic pulmonary fibrosis or usual interstitial pneumonia (UIP), but recent studies have demonstrated that histological and CT features of SSc lung disease are more similar to those found in idiopathic nonspecific interstitial pneumonia (NSIP).[41-43] UIP is characterised histologically by identification of a temporally and spatially heterogeneous pattern of ongoing lung injury, where areas of relatively uninvolved lung parenchyma are admixed with areas of severe fibrosis, with small aggregates of actively proliferating fibroblasts and myofibroblasts adjacent to areas of established fibrosis. Honeycombing and a subpleural distribution favour a diagnosis of UIP. In NSIP, fibrosis and inflammation are more diffuse in involved areas and of the same age throughout the affected lung. Fibrosis in SSc on CT appears less coarse, and the proportion of ground-glass opacification is greater than in patients with UIP, resembling that of NSIP.[44] In a quantitative study of ten open lung biopsies, the cytokine profiles of patients with UIP differed from those of patients with ILD associated with SSc, with the former patients having a predominance of gene expression for T-helper-2-type regulatory cytokines and the latter a more mixed phenotype.[45] Further studies are needed to prove that this reflects a fundamental difference in pathogenesis or merely reflects differences in stage of disease. Similarly, further studies are needed to investigate whether survival of SSc patients with NSIP is better than of SSc patients with UIP, as is the case in non-SSc patients.

PAH in SSc is characterised by the presence of plexiform lesions, composed of actively proliferating endothelial and smooth muscle cells, surrounded by an inflammatory mononuclear infiltrate around the plexiform lesions.[46] There is an increase in vasoconstrictor factors (thromboxane A_2, endothelin-1) and a decrease in vasodilator factors (prostacyclin, vasoactive intestinal peptide), together with an imbalance of antithrombotic and prothrombotic factors, contributing to vasoconstriction and thrombosis, respectively.[47]

3. Evaluation

All SSc patients (with or without dyspnoea) should be thoroughly evaluated for the presence of lung involvement, whether ILD, PAH or both. A 6-minute walk test gives a crude indication of a patient's exercise capacity, although myositis, wasting, anaemia and/or cardiac involvement may be confounding factors. The validity of the 6-minute walk test in SSc patients with ILD was recently demonstrated, although its utility as an outcome measure of lung disease appeared limited.[48] Further investigations should include pulmonary function tests, radiological evaluation (preferably CT), ECG and echocardiography; bronchoalveolar lavage (BAL) can also be considered (table II).

Pulmonary manifestations can be identified by pulmonary function testing in the majority of SSc patients.[49,50] In a group of 162 patients, 62% with diffuse disease and 72% with the lcSSc/CREST syndrome variant showed one or more pulmonary function abnormalities.[51] Pulmonary fibrosis leads

Table II. Recommended (annual) and optional work-up of systemic sclerosis patients to diagnose presence or progression of lung involvement (pulmonary arterial hypertension and/or interstitial lung disease)

Recommended (annual)
Lung function: (forced) vital capacity; forced expiratory volume in 1 second, diffusion capacity
High-resolution thoracic CT
ECG
Echocardiogram
6-Minute walk test
Optional
Arterial blood gas
Broncho-alveolar lavage
Right-heart catheterisation

to restrictive lung disease and interferes with gas exchange, resulting in decreased (F)VC, total lung capacity (TLC) and carbon monoxide diffusing capacity (DLCO). VC and static lung compliance declined at a greater-than-expected annual rate, consistent with progressive restriction.[49,50] The mean loss in percentage VC occurring over three 2-year time periods in 55 patients whose initial pulmonary function tests were performed during the first 5 years of scleroderma symptoms were 32%, 12% and 3%, respectively.[10] In the same study, patients with the lowest FVC (<50% predicted) had the worst prognosis, with a cumulative 10-year survival close to 50%.

DLCO is the lung function parameter that best reflects the extent of alveolitis in SSc.[52] Furthermore, a DLCO <70% is a predictor of early mortality, especially when accompanied by proteinuria and elevated erythrocyte sedimentation rate.[9] A reduction in DLCO, however, does not necessarily point to underlying ILD, but can also be a manifestation of pulmonary vascular disease or a combination of ILD and vascular disease.[53] In patients with pure fibrotic disease and secondary PAH, the ratio of the FVC to the DLCO approximates 1. The DLCO decreases at the same time and to the same degree as the decrease in FVC. In patients with isolated PAH, the DLCO is much lower than the FVC and the ratio of FVC to DLCO is usually >1.8. When there is a mixture of both fibrosis and vasculopathy, the FVC is moderately decreased but the DLCO is even lower, again resulting in a ratio that is often >1.8. It should be noted that pleural and extrapulmonary disease, including chest wall motion limited by skin tightness or involvement of intercostal muscles, may contribute to a reduced FVC.[54,55]

Radiological investigations include chest radiography and high-resolution CT (HRCT; figure 2). Chest radiography is less informative than HRCT of the lungs in the evaluation of the presence and extent of ILD in SSc.[56] With thin-section CT scanning, early signs of ILD can be detected in 90–100% of SSc patients in whom this develops.[57,58] Frequent findings on HRCT are ground-glass opacities, reticular linear opacities, subpleural and diffuse honeycombing, nodules, traction bronchiectasias and parenchymal bands (figure 2). In one study, HRCT could be used to differentiate inflammatory and fibrotic changes in 16 of 20 biopsy specimens taken from SSc patients.[59] Ground-glass opacification on HRCT is frequently used to diagnose alveolitis, and higher neutrophil and total cell counts are detected in BAL in patients with ground-glass abnormalities on HRCT.[57] Ground-glass opacification, however, may also be seen with pulmonary oedema, resolving inflammation and/or infection and may be confused with mosaic perfusion patterns seen in pulmonary vascular disease. In cases of

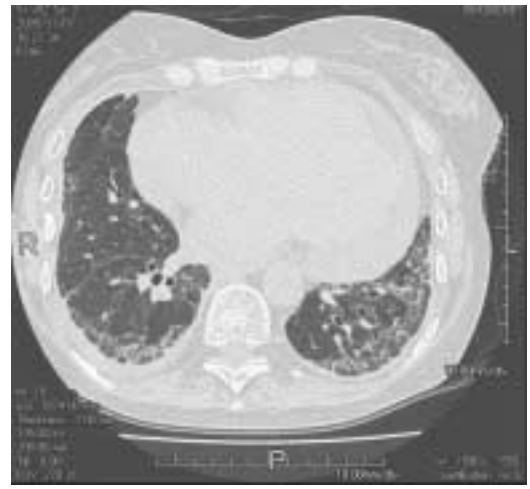

Fig. 2. High-resolution thoracic CT scan of a 50-year-old woman with end-stage lung fibrosis secondary to systemic sclerosis, showing bronchiectasias, thickening of bronchus walls and interlobular septa, bibasilar fibrosis and bilateral pleural effusion.

ground-glass appearance on HRCT, the patient should be examined in the prone as well as the supine position to exclude the possibility that the observed changes are not due simply to position.

BAL may be a valuable diagnostic tool to rule out infection or confirm the presence of alveolitis. Normal values for cell differentials in BAL fluid vary between laboratories. The following values are usually considered normal, being three standard deviations or greater above the mean of healthy control subjects: neutrophils ≤4%, eosinophils ≤3%, lymphocytes ≤14%, Langerhans cells ≤4% in smokers (generally absent in nonsmokers), with macrophages constituting the bulk of the remainder. Alveolitis occurs frequently in SSc, and BAL may be useful for identifying patients at risk of a further decline in pulmonary status.[60] A comprehensive analysis of BAL findings in relation to HRCT findings in 38 nonsmoking, untreated SSc patients demonstrated that neutrophil percentages increased strikingly in association with extensive lung fibrosis, whereas BAL eosinophil percentages increased in early as well as in advanced disease, notably when CT appearances suggested inflammation.[61] Differential cell count of BAL is a valuable prognostic parameter in ILD of SSc patients. Patients with diffuse SSc and granulocytosis in BAL had a significantly reduced DLCO compared with patients with a lymphocytic alveolitis or a normal BAL differential cell count over a follow-up of 2 years.[62] Similar findings were reported in a study of 79 SSc patients with pulmonary involvement, who were assigned to two groups according to whether their BAL cell differential count was normal (inactive BAL) or abnormal (active BAL, i.e. neutrophils >5% and/or lymphocytes >15%).[63] Active BAL was associated with more severe lung function impairment than was inactive BAL, and patients with active BAL deteriorated, both in terms of VC and DLCO, during follow-up if untreated.[63,64] In contrast, patients with active BAL who were treated with corticosteroids and/or cyclophosphamide stabilised or improved, in parallel with reductions in neutrophils and eosinophils, in serial bronchoalveolar investigations.[64]

In a study of 18 SSc patients with dyspnoea, BAL of the middle lobe or lingula was shown to underestimate the presence of active alveolitis and HRCT did not detect all sites of inflammation, although ground-glass opacification on HRCT accurately predicted alveolitis in the middle lung fields.[65] In three patients, a culture of BAL fluid identified unsuspected infection. On the basis of these results, the authors concluded that, in addition to HRCT, BAL with differential cell counting and culture from at least two segments of the lung should be performed for diagnosing SSc alveolitis. Nevertheless, because of variability in reporting of cell counts and difficulties in interpretation, treatment decisions should not be based on BAL findings alone.

Pulmonary hypertension can be reliably diagnosed with echocardiography only at high mean pulmonary arterial pressure, i.e. when the tricuspid gradient is markedly increased. In 10% of SSc patients, a tricuspid gradient cannot be assessed. In a Swedish cohort of SSc patients, an increased tricuspid gradient was found in 40% of patients, more commonly in patients with longer disease duration, higher age and ILD.[66] Right-heart catheterisation is still the gold standard for investigation of PAH. This investigation allows assessment of right atrial and ventricular pressures, pulmonary capillary wedge pressure and cardiac output. Knowledge of these parameters is essential for differential diagnosis of PAH secondary to myocardial disease, while thromboembolic disease should be excluded by ventilation-perfusion scanning or CT. Vasodilator challenge can be performed to assess pulmonary vascular responsiveness, although this is rarely positive in SSc-associated PAH. ECG is a simple tool to exclude cardiac causes of dyspnoea, while P-wave amplitude analysis on the ECG has been shown to be helpful in the assessment of pulmonary hypertension in patients with scleroderma.[67]

4. Treatment

Until recently there existed no proven effective disease-modifying therapy to prevent disease progression or reverse fibrosis in patients with SSc. Blinded randomised clinical trials of penicil-

lamine,[68] interferon-α,[69] fluorouracil[70] and chlorambucil[71] have been unable to demonstrate a clinically significant effect. Methotrexate showed beneficial effects on skin thickening but not on organ dysfunction in a small placebo-controlled crossover study[72] and a large multicentre, prospective placebo-controlled, randomised trial.[73] Corticosteroids are the cornerstone of the treatment of lung fibrosis associated with connective tissue diseases, but there is no evidence for their efficacy as monotherapy in SSc. Importantly, a retrospective case-control study showed that high-dose corticosteroid therapy, i.e. prednisone 15 mg/day or equivalent, is associated with the development of scleroderma renal crisis, which may lead to irreversible renal failure.[74] Of all immunosuppressive drugs, only cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function and increase survival in a number of non-randomised studies, particularly in early disease.[75-80] Although the studies were heterogeneous with respect to diagnoses, treatment protocols and assessment criteria, the consistent effects on skin and lung function, notably in patients with diffuse skin disease, and biochemical evidence of acute phase reactivity and/or active alveolitis, strongly suggest a disease-modifying effect for cyclophosphamide in SSc.[81,82] Genetic factors, such as interleukin (IL)-1α promotor polymorphism, may influence responsiveness to cyclophosphamide therapy, although this needs to be confirmed in different cohorts.[83]

Two prospective, placebo-controlled, multicentre clinical trials have been recently completed in SSc patients with alveolitis.[84,85] The North-American Scleroderma Lung Study investigated the effects of 12 months of oral cyclophosphamide 2 mg/kg versus placebo in 162 patients.[84] The main outcome measure was percentage predicted FVC. Secondary outcome measures included percentage predicted TLC and DLCO, and several measures of dyspnoea, quality of life and function. At 12 months, patients who were treated with cyclophosphamide had a statistically significant change in FVC compared with placebo-treated patients (decreases of 1.4% vs 3.2% predicted, respectively; $p = 0.05$). The vitality and health transition portions of the Short-Form 36 were significantly better in cyclophosphamide-treated patients versus placebo, as were the transitional dyspnoea index and the Health Assessment Questionnaire Disability Index. Interestingly, there was also a significantly greater improvement in skin score in patients with dcSSc treated with cyclophosphamide compared with placebo (−3.9 vs −0.2, respectively; $p = 0.03$). Not surprisingly, cyclophosphamide also led to a higher incidence of leukopenia and neutropenia, which were associated with pneumonia and gastroenteritis in two patients, respectively.

The FAST (Fibrosing Alveolitis in Scleroderma Trial), conducted in the UK, investigated the effects of prednisone (20mg every other day) and 6-monthly infusions of intravenous cyclophosphamide 600 mg/m^2, followed by oral azathioprine, versus matched placebo.[85] Forty-five patients were enrolled. Only 62% completed the 12-month follow-up. At 12 months, there was a statistically significant difference in FVC with active treatment versus placebo. This treatment difference was 4.76% favouring cyclophosphamide compared with placebo ($p = 0.04$). No differences were noted in the DLCO or secondary outcome measures (CT changes and dyspnoea scores). No significant treatment-related adverse effects (e.g. haemorrhagic cystitis) were noted in the active treatment group.

The results of these studies convincingly demonstrated for the first time a disease-modifying effect of cyclophosphamide on SSc lung disease, albeit small. The effectiveness of cyclophosphamide on alveolitis and skin disease in SSc has prompted studies to investigate the feasibility, safety and efficacy of dose-intensification of cyclophosphamide with or without additional lymphoablative agents, followed by autologous haemopoietic stem cell transplantation in severe SSc and other autoimmune diseases. The rationale for this new treatment modality is based on several converging lines of evidence.[86,87] First is the observation that patients with autoimmune disease who undergo allogeneic, and more recently autologous stem cell transplant, for

haemopoietic or other malignancy are frequently noted to experience a remission of their autoimmune disease. Secondly, the evidence from disease-susceptible strains of animals that autologous haemopoietic stem cells may cure the autoimmune disease and induce tolerance to the inciting agent. Lastly, there is a prevailing perception that immunosuppressive therapy acts with a clear dose-response pattern. Higher dose regimens requiring some form of blood progenitor rescue may, therefore, be superior in the treatment of some individuals with severe autoimmune disease.

In view of the poor prognosis of SSc, the presumed autoimmune origin and the lack of available therapies, this disease was considered suitable for initial investigation of the tolerability and efficacy of autologous haemopoietic stem cell transplantation.[88] An international collaborative committee was established in 1995 under the auspices of the European Group for Blood and Marrow Transplantation (EBMT) and EULAR, with subsequent inclusion of other active groups in North America. Entry criteria and treatment protocols were established in a phase I-/II-like study to assess feasibility, mortality and the preliminary response to such an approach.[89] The results of the first 41 SSc patients with at least 3 months' follow-up suggested a significant impact on skin score with a trend to stabilisation of lung function: 69% of patients achieved an improvement of ≥25% in skin score.[90] In a recent analysis of 65 patients (which included the first cohort), the transplant-related mortality was 12.3% at 1 year, and 7.7% when patients who did not meet the consensus guidelines on patient selection were excluded.[91] These data formed the basis of the ongoing prospective ASTIS (Autologous Stem cell Transplantation International Scleroderma) and SCOT (Scleroderma Cyclophosphamide Or Transplant) trials in Europe and North America, respectively, which were designed to test whether this novel approach indeed provides a survival advantage over conventional approaches in the long term.[92] So far, in the ASTIS study, 90 patients have been randomised.

Lung transplantation in SSc patients is a treatment option for SSc patients with end-stage lung disease, although its attendant risks are high. Survival in nine SSc patients (four with pulmonary hypertension, five with pulmonary fibrosis) at 4 years post-transplantation was 76%, similar to other patients undergoing lung transplantation.[93] In a retrospective review of 47 SSc patients who underwent lung transplantation in various US centres between 1987 and 2004, 7 early and 17 late deaths were observed.[94] The Kaplan-Meier 1- and 3-year survival rates were 67.6% and 45.9%, respectively, which were not significantly different from those of >10 000 patients receiving transplants for other lung conditions during the same period. In a recent study of 29 lung transplant recipients patients with SSc, 70 with idiopathic pulmonary fibrosis and 38 with idiopathic PAH, survival rates at 2 years after the procedure did not differ between the two groups.[95] These studies indicate that lung transplantation can be a valid life-saving therapeutic option in selected SSc patients with end-stage lung disease.

PAH is a potentially fatal complication of SSc, notwithstanding the fact that survival of selected patients with SSc-PAH has improved since the advent of new drugs to treat PAH. Survival in a current treatment era group comprising 45 patients was 81% and 71% at 1 and 2 years, respectively, which was significantly better than that of a historical group of 47 patients (68% and 47%, respectively; $p = 0.016$).[96] Recent clinical trials have convincingly shown that PAH is amenable to treatment. In a prospective randomised trial of 111 patients with PAH, significant improvements in exercise capacity and haemodynamics were documented in patients treated with continuous ambulatory epoprostenol, a prostacyclin analogue; the improvements observed were similar to those seen in primary hypertension.[97] Blockade of the endothelin receptor with oral bosentan for 16 weeks has also been shown to result in improved exercise performance as assessed by the 6-minute walk test (ultimate walking distance) and symptom improvement in a placebo-controlled prospective trial involving 213 patients with severe PAH (including 44 SSc patients).[98] In another study of 278 patients with symptomatic PAH, including patients with SSc, sildenafil, a

phosphodiesterase type 5 inhibitor, also improved exercise capacity, WHO functional class and haemodynamics.[99] Of the 222 patients completing 1 year of treatment with sildenafil monotherapy, the improvement from baseline at 1 year in the distance walked in 6 minutes was 51m. In North America and Europe, licensed therapies for PAH now include parenteral prostacyclin analogues (epoprostenol, iloprost), oral bosentan and sildenafil. New therapies include the oral endothelin type A receptor selective antagonists ambrisentan and sitaxsentan.[100,101] There are no systematic studies on the effects of immunosuppressive drugs on PAH.

While it is clear that advanced PAH is progressive and has high mortality, but can nevertheless be improved using the aforementioned drugs, it is less clear whether and how milder forms of PAH progress. Patients with severe PAH secondary to lung fibrosis pose a challenge, as intravenous administration of prostacyclin may have unwanted haemodynamic effects that result in exacerbation of symptoms.[102] A thorough evaluation of cardiopulmonary function is thus warranted to select the proper treatment strategy. In patients whose disease is non-responsive to pharmacological vasoreactive treatments, a surgical approach via atrioseptotomy can be considered.[103]

5. Conclusions

Pulmonary fibrosis and pulmonary vascular involvement are common and potentially life-threatening manifestations of SSc. Every patient with SSc deserves a thorough work-up in a specialised centre to investigate whether lung involvement is present and, if so, to what degree. Evaluation of SSc patients with dyspnoea should at least include pulmonary function tests, a 6-minute walk test, ECG, Doppler echocardiography and a thoracic CT (table II). Additional cardiac tests may be required to exclude coronary arterial or intrinsic cardiac disease. Patients with dyspnoea, and declining lung function in particular, are at risk of developing respiratory insufficiency and premature mortality. Cyclophosphamide is the only drug so far with proven efficacy in SSc-ILD, either as a daily oral regimen or by repeated intravenous bolus injections. Prostaglandins and drugs that block endothelin-1 receptors are effective in pulmonary vascular disease. The proven efficacy of these new treatments indicate that the old days of therapeutic nihilism in scleroderma lung disease are gone, and have set the stage for new clinical trials to further improve the outlook of patients with systemic sclerosis and lung disease.

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