**Major lung complications of systemic sclerosis**

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**Abstract**

Systemic sclerosis (SSc) is associated with high mortality owing to internal organ complications and lung disease is the leading cause of SSc-associated death. The most notable lung complications in SSc are fibrosis and pulmonary arterial hypertension (PAH). A major challenge for the management of lung disease in SSc is detecting those patients with severe pathology and those patients that are likely to benefit from available treatments. In the past few, strategies for managing lung fibrosis and pulmonary hypertension, including PAH, have greatly progressed. For lung fibrosis, the tools to assess risk of progression and severity of the disease have been refined. Clinical trial results support the use of immunosuppression, including high intensity regimens with autologous stem cell transplantation. New trials are underway to test other potential therapies including treatments that are approved for use in idiopathic lung fibrosis. For PAH, identifying individuals at high risk of disease development is critical. In addition, individuals who have borderline elevation of pulmonary arterial pressure need to be appropriately managed and followed up. Many approved drugs targeting PAH are now available and results from large-scale clinical trials provide robust evidence that various treatments for SSc-associated PAH are associated with good long-term outcomes.

## [H1] Introduction

Systemic sclerosis (SSc) is an uncommon disease characterized by fibrosis of the skin and internal organs and by vasculopathy. Amongst the autoimmune rheumatic diseases, systemic sclerosis has the highest mortality, which is mainly owing to the development of complications that affect the lungs [1,2]. The two most important lung complications in SSc are lung fibrosis, which reflects the tendency of SSc to cause scarring in the skin and internal organs, and pulmonary arterial hypertension (PAH), which reflects the cardinal proliferative vasculopathy that occurs in SSc [3,4]. SSc can be divided into two major clinical subsets on the basis of the extent of skin fibrosis: limited cutaneous SSc (lcSSc, affecting the face, neck and distal limbs) and diffuse cutaneous SSc (dcSSc, affecting the proximal limbs, abdomen and chest). These two major subsets also differ in the associated frequency and pattern of different SSc-associated autoantibodies and cardinal clinical characteristics [5].

The pathogenic mechanisms of lung fibrosis and pulmonary arterial hypertension are complex and incompletely understood but involve an interplay and cross talk between the cellular constituents of the lung. These complications are probably triggered by lung injury or damage in the epithelial and parenchymal compartments (for lung fibrosis) or the endothelium and pulmonary vasculature (for pulmonary hypertension) (Figure 1). Strategies for managing lung fibrosis and pulmonary hypertension, especially PAH, have considerably advanced in the past few years. Major challenges in managing both conditions include the detection of patients with clinically meaningful disease, the identification of patients who are likely to benefit from intervention and the formulation of an optimal management plan that includes the treatment goals, the choice and dose of treatments and the means for efficiently monitoring patients.

With regard to lung fibrosis, new developments in our understanding of the pathogenesis have led to pivotal clinical trials of historical treatments and novel therapies. The search continues for treatments that might be as effective but are safer than current therapies. Several targeted biological therapies are being tested as one possible avenue. Likewise, the development of antifibrotic agents has made substantial progress. In addition, researchers are defining new tools for assessing the severity of lung fibrosis in SSc and the risk of progression, which should help improve the accuracy of treatment decisions.

In pulmonary hypertension, detecting patients with SSc at high risk of developing PAH, as well as differentiating patients with PAH from patients with other forms of pulmonary hypertension (including post-capillary disease), is challenging. Once a patient is diagnosed with PAH, the effects of relevant co-morbidities including other lung or heart complications on the patient's disease are important to consider.

The publication of the results of new clinical trials into the treatment of lung complications in SSc have advanced practice and provide an evidence base to support current treatments. For both lung fibrosis and PAH, the concept of improving established disease and not just slowing progression is advancing. In this Review, we cover the major pulmonary aspects of SSc and discuss the current diagnostic approaches and treatment strategies.

## [H1] Pathogenesis

Lung involvement in systemic sclerosis is best defined in terms of extrapulmonary features such as respiratory muscle weakness or skin fibrosis of the chest wall that might restrict breathing and includes pleural effusion, and intrapulmonary manifestations. The two major complications within the lung are lung fibrosis and pulmonary hypertension although other processes involving the lung parenchyma can also develop. Other less common forms of parenchymal disease such as organizing pneumonia. Pulmonary vascular disease includes pulmonary arterial hypertension (PAH) and other forms of pulmonary vasculopathy such as thromboembolic disease and pulmonary veno-occlusive disease. These forms of pulmonary vasculopathy should be distinguished from post-capillary pulmonary hypertension. These various lung complications can have shared underlying disease mechanisms (Figure 1).

*[H2] Pathogenesis of lung fibrosis*

Fibrosis is a general term describing the excessive formation of scarred or thickened tissue with excessive extracellular matrix in response to tissue damage, inflammation or as part of a specific process termed fibrogenesis in which activated fibroblasts or myofibroblasts produce excessive extracellular matrix. SSc-associated lung fibrosis probably shares common pathogenic mechanisms with other parenchymal lung diseases and with other manifestations of SSc. Multiple cell types and mediators are implicated in lung fibrogenesis [6,7], including lung epithelial cells (pneumocytes), inflammatory cells of all immune lineages and mesenchymal cells (including lung fibroblasts and myofibroblasts) [29,30]. Myofibroblasts are activated profibrotic contractile cells that resemble fibroblasts but are characterized by the expression of α-smooth muscle actin; myofibroblasts are central to the development of fibrotic lung pathology (Figure 1).

Some clues about SSc pathogenesis have emerged from gene expression profiling studies of lung tissue and cultured fibroblasts [8,9] as well as of other cells isolated from biopsy samples or obtained through broncho-alveolar lavage [10] including lymphocytes, mononuclear cells and fibrocytes. Functional studies have confirmed that lung fibroblasts have a profibrotic phenotype in SSc [11] and researchers have identified candidate pathways and regulators, including TGFβ, CCL2 and IL13 that enhance extracellular matrix production and increase contractility and myofibroblast differentiation [12,13,14]. Studies of epithelial and endothelial cells from the lung tissue of patients with SSc-associated lung fibrosis also suggest a role for endothelial–mesenchymal and epithelial–mesenchymal transition in fibrotic lung pathology [15,16], meaning that the pathogenic population of myofibroblasts has multiple potential lineages of origin that might contribute to excessive extracellular matrix deposition and obliteration of normal lung architecture. In addition, serum levels of IL-6, monocyte chemotactic protein 1 (MCP1; also known as CCL2) and CXC-chemokine ligand 4 (CXCL4) are associated with the occurrence and/or progression of lung fibrosis in SSc, implicating these factors as potential markers or mediators of lung fibrosis. [17,18,19]

As with other parenchymal lung diseases, environmental factors probably contribute to pathogenesis. In SSc, epithelial injury and damage resulting from aspiration or micro-aspiration are potentially involved in lung fibrogenesis. In one mouse strain, that is genetically susceptible to lung injury, the introduction of a mildly acidic saline solution into the lungs caused fibrosis [20]. This finding was consistent with human studies that have demonstrated the presence of epithelial injury (as measured by serum levels of Mucin-1 (also known as KL-6) or clearance of aerosolized diethylenetriamine penta-acatate (DTPA) [21] in patients with SSc or have linked lung fibrosis severity with oesophageal reflux severity in SSc [22,23].

Epithelial injury might selectively activate profibrotic pathways including TGFβ signalling pathways, possibly via promoting conformational changes in the integrin–TGFβ complex. The involvement of epithelial injury and defective repair in lung fibrogenesis via increased TGFβ pathway activation is supported by the results from several relevant mouse models [24,25] through local activation of TGFβ via integrin pathways or via post-natal activation of canonical receptor mediated signaling. .

Experimental findings of genetically modified mice with fibroblast-specific attenuation of TGFβ signalling further support a pivotal role for TGFβ signalling in the development of lung fibrosis and explant fibroblast studies are supported by analysis of SSc lung tissue that includes multiple cell types that may interact in vivo. A subpopulation of lung fibroblasts is speculated to co-ordinate repair and be involved in the regulation of fibrogenic cells from peripheral blood including fibrocytes [26,27]. Other lineages such as endothelial cells and lung epithelial cell lineages might also contribute to the fibrogenic population of cells in SSc. In the past few years, studies of mouse models have attempted to incorporate human tissue or have explored effect on human skin ex vivo. These studies suggest that chronic administration of bleomycin may give more consistent results and support an important potential role for circulating fibrogenic cells [29,30].

Circulating and local resident monocyte–macrophage lineages are emerging as potential key effector cells in SSc lung fibrosis [16,31,32]. Analysis of genes expressed in the skin that are associated with severity of lung fibrosis [33] and a similar gene and protein analysis using a systems biology approach has contributed to a growing body of evidence implicating altered monocyte and macrophage function in the pathogenesis of SSc-associated lung fibrosis [34] based upon comparison of gene expression in different tissue substrates in SSc.

Genetic susceptibility might also be important in the development of lung fibrosis. A strong and consistent association exists between genetic risk factors (such as those identified by Immunochip analysis) and ANA patterns, providing support for a key role for the adaptive immune response in SSc pathogenesis [35]. Many genetic studies have been undertaken in SSc-associated lung fibrosis and a growing number of candidates have been identified from association studies or direct sequencing [36, 37,38,39]. In general, immunological or inflammatory candidates seem to be more consistently identified in independent cohorts than factors relating to fibrosis, although in a complex heterogeneous disease such as SSc, the genetic associations from single cohorts might shed light on candidate pathways or mediators involved in pathogenesis even if conventional genetic replications across cohorts is not possible. This heterogeneity might reflect gene–environment interactions, differences in cofactors and other genetic or epigenetic differences between different study cohorts. For example, the association of SSc and a polymorphism in *CTGF* was reported by two independent single center cohorts [40,41] but not in another large multi-national study population [43]. Findings from two meta-analyses support a role for this polymorphism in patients from UK or Japanese backgrounds but not other [42]s, which could explain previous negative results [43, 44]. Epigenetic factors are potential contributors to SSc fibrogenesis; for example, particular microRNAs, including miR-155, are associated with lung fibrosis [45] and bromodomain inhibitors having potential anti-fibrotic effects in SSc lung fibroblasts [46]. Additional complex gene-environment interactions likely contribute to lung pathology in SSc; for example, experimental studies support a role for the microbiome, with early antibiotic exposure associated with increased susceptibility to experimental lung fibrosis in a scleroderma mouse model [47].

*[H2] Pathogenesis of pulmonary hypertension*

The development of pulmonary hypertension in SSc and lung fibrosis have overlapping features. Vascular injury including pulmonary endothelial cell injury and endothelial dysfunction might be a key component in the development of both pathologies; vascular injury leads to an aberrant fibroproliferative or aberrant repair process that also results in an obliterative pulmonary vasculopathy [48]. SSc-associated PAH is histologically similar to idiopathic or hereditable PAH with muscularisation of intrapulmonary arterioles and medial thickening with perivascular inflammatory changes, although SSc-associated PAH has a lower prevalence of endothelial proliferative and plexiform lesions than other forms of PAH [49]. SSc-associated PAH could even be a phenocopy of heritable PAH. The TGFβ receptor family member bone morphogenetic protein receptor type-2 (BMPR2) is implicated in the pathogenesis of a number of forms of PAH, notably hereditable disease and idiopathic PAH; reduced levels of BMPR2 in the lung blood vessels is associated with structural changes in the lung [50]. Interestingly, mouse models of SSc that implicate endothelial injury as a trigger of SSc-associated PAH also point towards a possible defect in BMPRII expression and function that could represent a unifying mechanism and potential susceptibility factor for several forms of PAH [51]. Hence, SSc might be a susceptibility phenotype for PAH, which would explain why the risk of developing PAH is highest in established disease and continues through the course of follow up [52].

The mechanisms of PAH are likely complex and as with lung fibrosis probably involve multiple cell compartments that might contribute differently in different patients. Support for the role of immune cells in the development of SSc-associated PAH is emerging; on the basis of transcriptomic and serum analysis, macrophage or monocyte dysfunction, including M2 polarization, is associated with PAH development in SSc [53]. Endothelial cell to mesenchymal transition might also contribute to the fibroproliferative pathology seen in affected pulmonary vessels [54].

Other relevant pathogenic mediators include cytokines such as IL-6 and proliferative factors such as PDGF or CTGF that could be targeted with intracellular signalling inhibitors. The success of the antioxidant bardoxolone methyl in phase II trials of SSc-associated PAH points towards a possible role for cellular stress via mitochondrial dysfunction, oxidant stress and/or inflammation-induced damage in PAH pathogenesis. Recent studies implicate circulating adipsin, an adipokine that also regulates activation of the alternative complement pathway, in SSc-associated PAH pathogenesis [55], and some SSc-specific genetic susceptibility loci for PAH have been described [56] and analyzed [57], although no major associations have emerged. Thrombosis, which is an important contributor to CTEPH pathogenesis, is also evident in some patients with SSc- associated PAH, but not in patients without PAH (as observed using optical coherence tomography at initial time of diagnosis) [58]. Unfortunately, the risk to benefit ratio of anticoagulant use in patients with SSc-associated PAH is unfavorable, possibly because of the high frequency of gastrointestinal lesions in this population [59].

SSc-associated PAH might also share pathogenic mechanisms with other forms of pulmonary hypertension. In addition, factors that underlie other forms of pulmonary hypertension may be relevant. Thus, hypoxia is a key driver of group III pulmonary hypertension. Likewise, cardiac involvement is important for determining the development of pulmonary venous hypertension (PVHT) or group II pulmonary hypertension. It has been suggested, based on histological analysis, that SSc-associated PAH might often have components of PVOD, which could partially explain why some patients respond poorly to vasodilator therapy [60]. However, although PVOD is present in some patients with SSc-associated PAH on CT imaging, the overall frequency seems to be relatively low [61].

## [H1] Assessment of lung involvement

Systematic approaches for screening and assessing patients with SSc for lung involvement are associated with greater ascertainment of major organ-based complications and improved long-term survival [62] compared to historic cohorts without regular screening. Thus, a comprehensive assessment at initial diagnosis followed by a regular systematic assessment of cardiorespiratory function is recommended for all patients with SSc [63]. This strategy is important for the management of lung disease, for a differential diagnosis and to help evaluate the treatment response, which can be challenging owing to the multiple mechanisms of disease and comorbidity. The investigation of lung involvement in SSc generally starts with a clinical examination and simple imaging such as chest radiography followed by formal lung function testing and CT imaging. Lung function tests include measures of lung volume such as total lung capacity (TLC) and forced vital capacity (FVC) and measures of gas exchange determined by the diffusing capacity for carbon monoxide (DLCO), which can be expressed for the whole lung or corrected for the measured alveolar volume (termed the gas transfer coefficient). CT imaging is the best way for evaluating lung fibrosis whereas a right heart catheterization is required for a formal diagnosis of pulmonary hypertension, even if already suspected on the basis of clinical features or echocardiography.

Exertional dyspnoea is a common presenting symptom in patients with either pulmonary fibrosis or pulmonary hypertension. Worsening exertional dyspnoea in patients with SSc is an important symptom that should prompt further evaluation for lung complications. However, the differential diagnosis for patients with SSc and dyspnoea is broad, reflecting the multiplicity of disease-related mechanisms and other confounding factors that contribute to dyspnoea (**Box 1**).

Loss of exercise tolerance in patients with SSc is commonly multifactorial. The cumulative effect of SSc and comorbidities on exercise capacity has been quantified using the Frailty index, which reflected the severity of dyspnoea [64]. Determining the contribution of cardiopulmonary limitation to exercise intolerance is difficult because of two important confounding factors: anxiety and fatigue. In patients with anxiety, hyperventilation might cause dyspnoea or heighten dyspnoea severity, especially in well-informed patients who are sensitized to the dangers of cardiopulmonary involvement in SSc. Fatigue, a frequent source of disability in patients with SSc [65], might manifest as exercise intolerance and the distinction between limiting fatigue and limiting dyspnoea is often difficult to make.

In severe pulmonary fibrosis or PAH, prominent exercise intolerance can usually be confidently ascribed to lung involvement. However, in the remaining patients presenting with dyspnoea but without prominent exercise intolerance a form of exercise testing (the six-minute walk test) enables the assessment of cardiopulmonary function (using the point of oxygen desaturation as a measure of exercise tolerance), and this may identify other causes such as cardiac dysfunction [66,67].

### *[H2] Diagnosis of lung fibrosis*

All patients with SSc should be thoroughly examined for the presence of lung fibrosis at initial presentation and during follow up. Regular assessment increases the chance of detecting lung fibrosis early, thus enabling an early intervention. Currently, CT imaging is the best tool for detecting lung fibrosis and enables the pattern and extent of disease to be determined [68]. In addition, CT imaging seems to be more reliable than screening patients using lung function tests. The normal limits for lung function tests range from 80% to 120% of the average value for a person of the same sex, weight and

height (as predicted by a computerized lung function test algorithm) and this wide range means that many patients with pulmonary fibrosis do not show overt impairment at initial screening [69]. However, lung function tests should still be performed at baseline and are the cornerstone of longitudinal follow up [52].

Other methods for assessing patients with SSc are available, such as routine chest radiography, exercise tolerance testing and dyspnoea scores, but these methods have limited use for detecting early pulmonary fibrosis. Routine chest radiography lacks the sensitivity for detecting pulmonary fibrosis but might be performed to assess other pathologies. Measures of exercise tolerance also have a limited sensitivity, probably owing to the confounding effects of extrathoracic manifestations of SSc [70], although measuring exercise tolerance might be valuable in the exclusion of clinically meaningful disease once lung fibrosis has been identified. Likewise, dyspnea scores are of limited use in the diagnosis of lung fibrosis but are valuable for trials or the longitudinal follow up of patients [71].

Although researchers have developed risk scores for the prediction of lung complications in patients with SSc (as discussed in the next section), at present a systematic approach for the screening and follow up of patients with SSc is important and justified by the high overall risk of developing severe lung fibrosis [52].

*[H2] Screening and diagnosis of pulmonary hypertension*

The high risk of pulmonary hypertension in SSc, and the major effect that pulmonary hypertension has on survival and quality of life [72], justifies the screening of patients. Hence, screening patients with SSc for pulmonary hypertension is recommended in clinical practice and a number of screening approaches have been developed**.** Patients should be screened for pulmonary hypertension at least once a year as early diagnosis can enable early treatment that could improve the long term outcome.

One of the first advocated screening approaches, developed as a result of the French itinerAIR study, used echocardiographic thresholds to prompt routine right heart catheterization [73]. In the past few years, other approaches have been developed that integrate lung function, echocardiography and the presence of other relevant markers such as N-terminal pro-brain natriuretic peptide (Nt-proBNP) [74]. Results from comparative studies suggest that these screening tools all perform well in clinical practice [71,75,76]. For example, one approach is to use the DETECT algorithm, an evidence-based tool that integrates non-invasive clinical and laboratory variables and echocardiography, to assess the risk of PAH (Figure 2) [77] DETECT was developed in a large cross-sectional cohort [77] to integrate non-invasive tests and minimize missed diagnoses of PAH. When considering lung function tests, it is important to consider that concurrent emphysema might reduce the utility of measuring gas exchange (DLCO) in patients for screening as it may increase FVC and diminish DLco independent of pulmonary hypertension. [78,79]. The DETECT cohort included patients with mild PAH and specific determinants of PAH progression have been elucidated using data from this cohort [80] and align with variables such as Nt-pro-BNP and low DLco identified in other cohorts [52, 81,82]. The DETECT algorithm first examines six variables (FVC, telangiectasia, ACA positivity, electrocardiogram right axis deviation and serum levels of Nt-pro-BNP and urate) to generate a score. If this score is above a defined threshold, an echocardiogram is recommended and various echocardiograph measures (the tricuspid regurgitant jet velocity and right atrial area) are used to generate the final DETECT score. If the DETECT score surpasses a defined threshold, a right heart catheterization is recommended as the patient has a significant risk of PAH. The DETECT score was devised from data of patients with SSc who had a disease duration of over 3 years and

a predicted DLCO of <60% (the DETECT cohort) and so this approach is best suited for use in such patients. Otherwise, echocardiography, lung function testing and measurements of Nt proBNP (N-terminal pro-brain natriuretic peptide), together with clinical assessment, are the main tools for assessing the risk of PAH.

Defining the presence of other connective tissue diseases in patients with SSc-associated pulmonary hypertension is important as patients with overlap features might benefit from concurrent immunosuppression [83]. All screening programmes can help identify patients with borderline elevation of mean pulmonary arterial pressure (mPAP), which is associated with distinct characteristics [84] and a high risk of developing PAH during follow up and so such patients need to be carefully monitored [85,86]. Defining the presence of increased pulmonary artery wedge pressure (PAWP) in SSc-associated PAH is also important as this feature can affect the disease outcome and reduce response to PAH specific therapy [87]. Mixed phenotypes with elements of lung disease and possible post-capillary components probably also occur and need careful evaluation and treatment to ensure that treatable precapillary components are defined and addressed [88]. In a 2017 study, patients with SSc-associated PAH who had a preserved pulmonary vascular bed (as assessed using optical coherence tomography (OCT) at right heart catheterization to directly image the intrapulmonary vessel wall thickness and structure) showed a better response to PAH specific treatment **than** those patients with a damaged pulmonary circulation [58]. This finding is in line with other outcome studies suggesting that milder disease is associated with better outcomes than severe disease and fits with the current 2015 ERS/ESC recommendations for risk assessment and treatment [89].

Exercise testing could be an additional useful screening test for pulmonary hypertension but other musculoskeletal and extrathoracic manifestations might confound results [90,91]. More comprehensive risk prediction scores for pulmonary hypertension are in development but the value of these scores are presently limited and require validation. Identifying patients who have a very low risk of developing PAH, and hence who do not require intensive screening, can be more important than identifying those at high risk. MRI is emerging as a non-invasive tool that might help stratify patients [92] and diagnose the presence of pulmonary hypertension but is not yet used in routine assessment of PAH-associated SSc. Autoantibodies, especially anti-U3 RNP, ACA, anti-RNA polymerase III and anti-Th/To RNP antibodies, are helpful in defining increased or reduced risk of PAH and are helpful in risk stratification [93]. The extent and severity of concurrent lung fibrosis is important as it might suggest a diagnosis of group III pulmonary hypertension and needs to be carefully defined [94].

## [H1] Classification of lung involvement

### [H2] Classification of interstitial lung disease

The classification of interstitial lung disease is complex but historically this disease has been sub-classified on the basis of histological patterns observed in lung biopsy samples (Figure 3). The most common histological subtype that occurs in patients with SSc is non-specific interstitial pneumonia (NSIP) [67]. Although a sub-classification of NSIP was originally based upon histological patterns, correlations between lung biopsy and CT findings mean that patients with NSIP can be identified with high confidence using CT imaging [68]. NSIP can be further subdivided into reversible cellular NSIP and irreversible fibrotic NSIP subtypes based on the degree of inflammation present in the lung [95]. A minority of patients with SSc have another histological pattern referred to as usual interstitial pneumonia (UIP), which is the defining histological pattern of idiopathic pulmonary fibrosis. In idiopathic

lung fibrosis the UIP pattern is associated with a much faster progression and worse survival than NSIP, however, the major prognostic distinction observed between NSIP and UIP patterns of disease (histologically or by CT imaging) in idiopathic pulmonary fibrosis does not apply to SSc-associated ILD. The outcome of SSc-associated ILD is much better than idiopathic pulmonary fibrosis [96] and the mortality is similar for patients with SSc-associated ILD and a NSIP pattern and those patients with a UIP pattern [95,96].

Some patients with SSc can also have other forms of interstitial lung disease. For example, fibroelastosis is increasingly being recognized as a feature of connective tissue disease-associated ILD and can occur in association with pleural abnormalities and resembles idiopathics pleuroparenchymal fibroelastosis (a rare form of ILD with a poor prognosis). This form of ILD might be more progressive than other forms of SSc-associated ILD [97]. Currently, the precise frequency and clinical relevance of fibroelastosis in SSc-associated ILD is unknown [98]. Patients with overlap SSc, which represents up to 20% of patients with SSc [99], exhibit clinical features of the overlapping disease (for example, myositis or systemic lupus erythematosus (SLE)), which can include parenchymal lung disease. For example, myositis is associated with organizing pneumonia and SLE is associated with shrinking lung syndrome or lymphocytic interstitial pneumonias (LIP) [67].

Analyses of patient cohorts in the past few years has provided further insights into the timing and frequency of clinically important lung fibrosis development in SSc. Up to half of patients with dcSSc eventually develop severe lung fibrosis and many of these patients develop this complication within the first 3 years following diagnosis and can have considerable lung involvement at initial presentation [52,100]. This finding has important implications for treatment strategies aiming to prevent or attenuate worsening of disease. Overall, the frequency of lung fibrosis in patients with lcSSc is approximately half that of dcSSc (meaning approximately one quarter of patients with lcSSc are affected). Lung fibrosis is associated with different patterns of antinuclear antibodies (ANA), in particular anti-topoisomerase-1 antibodies. Approximately two thirds of patients that are positive for the anti-topoisomerase-1 ultimately develop moderate to severe ILD [5]. Other less common antinuclear antibodies (ANA) such as anti-U11/U12 ribonucleoprotein (RNP) antibodies or anti-Th/To RNP antibodies are also associated with lung fibrosis [101]. Interestingly, the presence of anti-centromere antibodies (ACA) or anti-RNA polymerase III antibodies (ARA) seems to be negatively associated with severe lung fibrosis [100,101] and so presence of these can be used to identify cases at lower risk in clinical practice and encourage further investigation of respiratory symptoms.

**[H2] Stratification by lung fibrosis severity**

In clinical practice the most important aspect for managing lung fibrosis in patients with SSc is identifying those patients with severe disease or at risk of disease progression. By studying the factors associated with disease progression in well characterized cohorts, researchers have defined several key risk factors for developing severe lung fibrosis [52], which can be used in clinical practice (**Box 2**) The most important of these factors is the extent of disease severity, particularly in patients in the early stages of SSc.

The importance of determining lung fibrosis severity has led to the development of a simple staging system that incorporates CT assessment and measures of FVC. In practice, with this staging system patients are first stratified into whether they have clearly mild or extensive fibrosis (<20% lung involvement or >20% lung involvement, respectively, by high-resolution CT). In patients for whom the

extent of fibrosis is indeterminable by CT imaging, they are instead stratified into these groups on the basis of FVC measurements (>70% for mild fibrosis and <70% for extensive fibrosis) [102]. A designation of mild or extensive fibrosis by this staging system is associated with symptoms of dyspnoea and impaired exercise capacity [103]. This staging system can also reportedly predict an increased risk of considerable future decline; for example, >20% lung involvement is associated with an increased risk of decline (as assessed by lung function tests) and decreased survival [104]. Other staging systems have also been suggested that are based on the analysis of large SSc cohorts [52] or clinical trial datasets [105,106] and include features (such as arthritis) that might reflect clinical subtypes of SSc at high risk of developing fibrosis [107]. Other factors that potentially predict future decline include markers of epithelial damage, such as serum mucin-1 and DTPA clearance, and circulating markers, such as CXCL4 and IL-6, although IL-6 is only predictive for patients with mild lung fibrosis [17,108]. At present, all of these measures are only useful in research settings pending further validation and standardization. In the future, composite markers that incorporate clinical and laboratory measures will probably be developed.

New approaches that use computer assisted quantitation of lung fibrosis are being developed [109,110] and might offer further insights into disease progression and the refinement of staging systems in the future. As outlined above, baseline tests including CT imaging, lung function tests, ANA testing and the assessment of clinical features facilitate the stratification of individuals at high risk of developing severe lung disease for whom treatment is a high priority. Such approaches are especially useful in planning treatments such as haematopoietic stem cell transplantation (HSCT), which is associated with a high risk of treatment-related mortality but also long-term benefits such as increased survival [111]. New data suggest that in patients with extensive lung fibrosis (as designated by the severity staging system) [112], serial lung function testing can be used to monitor disease progression and predict mortality; for example, a drop of >10% FVC at 12 months is the strongest single predictor of mortality). Additionally, a 5-9% decline in FVC alongside a 15% fall in DLCO at 12 months is also predictive of disease mortality. These thresholds might be useful in the evaluation of treatment responses, making treatment decisions and identifying patients for inclusion (or exclusion) in clinical trials [109]. Change in lung function, assessed by fall in FVC, is an important component of the newly developed composite response index for SSc clinical trials [113], and a decrease in lung function is associated with worse outcomes [114]. Finally, as discussed above, particular ANAs are also associated with an increased or decreased risk of lung fibrosis [100,101].

**[H2] Classification of pulmonary hypertension**

The classification of pulmonary hypertension in SSc follows that of pulmonary hypertension associated with other diseases and it is important to consider the multiple way in which pulmonary hypertension can develop. Pulmonary hypertension is conventionally divided into five groups on the basis of clinical and pathobiological features (Table 1). Overall, PAH (classified by the WHO as group I) is probably the most frequent form of pulmonary hypertension, but mixed forms (such as pulmonary hypertension with lung fibrosis and cardiac involvement) also exist. More than half of patients with SSc-associated pulmonary hypertension have PAH, but a considerable number of patients have post capillary pulmonary hypertension (WHO Group II) or pulmonary hypertension associated with lung fibrosis or hypoxia (WHO Group III) [52]. Pulmonary hypertension associated with lung fibrosis is generally defined as lung fibrosis affecting >20% of the lung volume, although precise estimates of the extent of lung fibrosis can be challenging in routine clinical practice [115] and fibrosis can be exacerbated by the co-

existent of emphysema [116]. In addition, some patients have concurrent pulmonary veno-occlusive disease (PVOD, WHO Group 1') or chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group IV). The incidence rate of pulmonary hypertension of any form is approximately 1-2% per year in patients with SSc [52]. However, the frequency of pulmonary hypertension varies across different reports depending upon the duration of follow up; the frequency might be 5% for a cohort with an average disease duration of 5 years, 10% for a disease duration of 10 years and 15% for a disease duration of 15 years [52]. This increase in frequency differs from other complications of SSc, such as renal crisis, that generally occurs in early disease and is consistent with SSc representing a susceptibility phenotype for the development of pulmonary hypertension.

## [H1] Treatment approaches

### *[H2] Treatment approaches for lung fibrosis*

Immunosuppression remains the cornerstone for treatment of SSc-associated lung fibrosis. The benefits of immunosuppression are largely supported by findings from observation studies and retrospective studies [116,117]. However, limitations of the open label and retrospective design of most studies underpins the need for prospective randomized studies. A limited number of prospective clinical trials have been performed and show immunosuppression has beneficial effects. The most notable of these studies is the Scleroderma Lung Study I (SLS I) that compared oral cyclophosphamide over 12 months with placebo [118]. In this study, oral cyclophosphamide was efficacious but only had a marginal treatment benefit and substantial toxicity. However, the fact that the benefit observed was only small reflected the inclusion of many patients with mild non-progressive lung disease whereas post hoc sub-analyses suggested that in extensive disease, cyclophosphamide therapy had major benefits in preventing disease progression, based on lung function testing. The results of a 2-year follow-up study suggested that the benefit of oral cyclophosphamide might continue to 18 months (the placebo subtracted difference at 18 months was 7%) but was possibly attenuated by 24 months [119].

The Fibrosing Alveolitis in Scleroderma Trial (FAST) trial had a similar design to the SLS I trial but investigated 6 months of intravenous cyclophosphamide followed by oral azathioprine. After 12 months, the benefits of this treatment were no different from placebo, although FVC showed a trend towards improvement in the treatment group compared with the placebo group that did not reach statistical significance [120]. In the Scleroderma Lung Study II (SLS II), mycophenolate mofetil (MMF) was as efficacious as oral cyclophosphamide in improving cough-specific measurements [121], which was also observed when the data from both SLS studies were combined, to include the placebo control from SLS I [122] However, the tolerability of MMF was superior to cyclophosphamide and MMF is now used as a first line treatment in most centers [123]. The optimal dose of MMF for the treatment of SSc-associated ILD is probably 3g/day, which was the target dose in the SLS II trial, although for patients who struggle to tolerate 3/g day, 2g/day might be considered. Further support for immunosuppression in SSc lung fibrosis comes from the American Scleroderma Stem Cell versus Immunosuppression Trial (ASSIST) [124], the Autologous Stem cell Transplantation International Scleroderma ASTIS [111] trial and, in 2018, the Scleroderma: Cyclophosphamide or Transplantation (SCOT) study [125], which all compared intravenous cyclophosphamide with HSCT. In all three studies, HSCT was superior to cyclophosphamide therapy alone. However, the transplant-related mortality with HSCT was lower in the SCOT study than in the larger ASTIS trial. The SCOT study had a focus on lung fibrosis outcomes and in this study there was some impressive apparent improvement in established lung fibrosis, based upon computer assisted

quantitative CT analysis, that point towards potential reversibility of lung fibrosis. However, HSCT remains a major undertaking and potential transplant-related mortality means that patients should be carefully selected for therapy, which emphasizes the value of staging or stratifying patients with SSc so that this therapy can be considered at a time when it might be best tolerated.

Although the SCOT study highlights the potential benefit of HSCT in treating SSc lung fibrosis, a similarly beneficial but less toxic treatment is necessary. Such a need is providing impetus for clinical trials that test biological strategies or the use of new agents in combination with immunosuppression such as MMF or B cell depletion with rituximab [126]. lung fibrosis such as IL-6R blockade can alter markers of fibrogenic macrophage differentiation or fibroblast activation [127] and tocilizumab (an IL-6 inhibitor) is being further tested in ongoing clinical trials of SSc [128]. The role of the adaptive immune compartment in SSc lung fibrosis development is supported by studies of lymphocytes isolated from bronchoalveolar lavage fluid [10] that show markers of T cell activation [10] and the association of lung fibrosis with specific antibody reactivities [5, 129]. Thus, both T cell and B cell lineages might be relevant in lung fibrogenesis, which could explain the apparent benefit of immunosuppressive therapies in some patients [130]. For example, B cell depletion is effective in the treatment of some patients who are refractory to other therapies, providing strong support for the contribution of B cells to the pathogenic micro-environment in SSc-associated lung fibrosis [131].

Emerging clinical trials undertaken to test novel therapies include blockade of TGFβ [132] and its activation by epithelial alphaν integrin [133] [https://clinicaltrials.gov/ct2/show/NCT02745145], the IL-13–IL-4 axis and IL-4 [134]. In addition, two anti-fibrotic agents that can retard disease progression in idiopathic pulmonary fibrosis are currently undergoing evaluation in SSc-associated ILD: pirfenidone and nintedanib. Pirfenidone has already been evaluated in a small phase II study (LOTUSS) [135] and the SLS III trial comparing MMF combined with pirfenidone treatment and MMF treatment alone is ongoing [136] [https://clinicaltrials.gov/ct2/show/NCT03221257] A large phase III trial investigating the safety and efficacy of nintedanib in SSc-associated lung fibrosis is ongoing [137,138, https://clinicaltrials.gov/ct2/show/NCT02597933]. However, trials of lung fibrosis in SSc are challenging and some studies have failed to recruit enough patients [139] or have had unequivocally negative results [140,141].

In addition to immunosuppression for patients with extensive fibrosis or those predicted to be at risk of lung disease progression, other general measures for the treatment of SSc-associated lung fibrosis include vigorous management of gastro-oesophageal reflux [142]. Combinations of antacids (acid suppressive agents) and prokinetics, as well as simple lifestyle measures, are used in the treatment of gastro-oesophageal reflux. Oxygen therapy can also be useful for reducing exertional dyspnoea and patients with severe lung disease might benefit from long term low dose oxygen therapy to reduce the risk of developing secondary pulmonary hypertension (WHO Group III). Oxygen therapy should be administered following general respiratory practice guidelines. Another important treatment approach in SSc-associated lung fibrosis is the management of infection. Prophylactic antibiotics should be considered for preventing community acquired infection in patients reporting frequent lower respiratory tract infections, and for preventing opportunistic infections such as pneumocystis in patients receiving long-term intensive immunosuppression [142].

*[H2] Treatment approaches for PAH*

PAH management has made substantial advances over the past 2 decades, especially regarding oral therapies and the growing evidence base for the use of drug combinations [143]. Therapies have progressed from a time when only intravenous epoprostenol was available [144,145] and outcomes were very poor, to the current availability of multiple licensed treatments that can be used in combination (Table 2). The early studies that led to the licensing of various PAH therapies, including bosentan and sildenafil, focused on short term gains in exercise capacity; in these studies, the response of patients with SSc-associated PAH or CTD-associated PAH was often less efficacious than patients with other forms of PAH, although most treatments seem to result in meaningful benefit in the majority of patients with SSc-associated PAH [146,147,148,149]. However, evidence in clinical practice suggests that these therapies have long-term benefits in SSc-associated PAH [142], which is supported by key event-driven clinical trials published in the past 3 years [150,151,152]: the SERAPHIN trial (which tested the oral endothelin receptor antagonist macitentan), the GRIPHON trial (which tested the prostcyclin-receptor agonist selexipag) and the AMBITION trial (which tested a combination therapy of ambrisentan (endothelin receptor antagonist) and tadalafil (a PDE5 inhibitor)).

Treatment strategies have defined key potential pathogenic and protective mechanisms in PAH. For example, endothelin (ET1), a potent vasoconstrictor and pro-proliferative peptide, is a probable pathogenic factor [147, 148]. Whereas the nitric oxide pathway (which mediates vasodilation through soluble guanylate cyclase) is probably a protective factor as soluble guanylate cyclase stimulators and inhibitors of phosphodiesterase 5 (an enzyme that breaks down guanylate cyclase) have shown some promise in the treatment of SSc-associated PAH [143]. Similarly, prostacyclin-dependent pathways are protective and defects in these pathways might be important in pathogenesis [144]. The effectiveness of combination therapies, such as ambrisentan and tadalafil suggests that multiple pathways and mediators are likely involved in the development of PAH in SSc [153]

All the pivotal trials of new PAH treatments over the past few years have included considerable numbers of patients with CTD-associated PAH or SSc-associated PAH, which has enabled subgroup analyses and helped to establish licensed drugs for PAH in SSc (Table 3). The findings of these trials generally support the efficacy of specific licensed PAH treatments in PAH-associated SSc and are in line with emerging registry and retrospective cohort data [59]. The results of the three large, long-term event-driven trials were positive and suggest that these treatments are efficacious in patients with CTD-associated PAH, which is in line with the efficacy observed in the overall cohort that included patients with idiopathic or heritable PAH [150,151,152,154,155]. Studies of riociguat (a soluble guanylate cyclase stimulator) have shown similarly encouraging results in terms of long-term survival [156]; although the phase III trial examined exercise capacity as a primary end point and and showed less benefit in PAH-CTD, the earlier studies examined the six-minute walk test distance for which the response of patients with CTD-associated PAH or SSc-associated PAH was less overall than of patients with idiopathic PAH or the overall cohort [156]. Evidence-based recommendations are available for the treatment of pulmonary hypertension [89] and SSc-associated PAH [63]. Current recommendations support an aggressive use of combination treatments in patients with SSc at high risk of PAH [89], which is now recommended by most expert centers. Patients with mild PAH or those patients with mixed PH phenotypes might require a less aggressive treatment. Emerging evidence from cohort studies support the beneficial effects of intensive combination therapy (including a substantial improvement in survival) in the most severe cases of SSc-associated PAH [157].

The presence of cardiac disease or lung fibrosis is important to consider in SSc-associated PAH as these pathologies might occur concurrently, potentially resulting in a phenotype with a mixed aetiology that can affect the outcome and treatment response. For example, pulmonary vasodilators might be disadvantageous if they worsen the ventilation–perfusion ratio in pulmonary hypertension associated with lung fibrosis and detrimental in patients with a degree of post-capillary pulmonary hypertension owing to cardiac involvement. However, data from the GRIPHON study and other emerging data suggest that some patients with a degree of group II pulmonary hypertension **in** associated with PAH might benefit from specific PAH. The occurrence of PVOD and the risks associated with PVOD are also important to consider. PVOD occurring in SSc might be a mixed phenotype rather than a pure form of PVOD and could possibly respond to careful use of vasodilators [61]. Patients with complex forms of pulmonary hypertension should be managed by experts in SSc and experts in pulmonary hypertension collaboratively in specialist units to ensure that affected patients receive optimal treatment.

*[H2] Role of lung transplantation*

Lung transplantation is a potential treatment option for some patients with SSc who have pulmonary hypertension or lung fibrosis. However, choosing whether to use this treatment is difficult as lung transplantation is associated with a high frequency of relevant comorbidity including gastroesophageal reflux disease [158,159]. Challenges related to previous treatment, steroid use and gastro-oesophageal reflux are important as they may impact on post-transplant complications and outcome. [160]. However, case series from the past decade suggest that transplantation has favourable outcomes in many patients with SSc and long-term survival is comparable to that observed in patients with other multisystem diseases; hence, for some patients with SSc, heart, lung or combined transplantation is an important therapeutic option [161,162].

## [H1] Conclusions

In this review, we highlight the ongoing challenges of lung complications in SSc but also provide clear evidence of the changing landscape in terms of understanding pathogenic mechanisms, assessing patients and providing treatments that effect outcomes [163]. The timing and frequency of lung fibrosis and pulmonary hypertension in SSc indicates that both complications are important and relatively frequent. An increasing understanding of pathogenetic pathways means that the expanding number of targeted biological or synthetic agents that target specific pathway or mediators can be tested and a better understanding of clinical trial design for lung fibrosis and PAH will ensure that the data obtained are robust and reliable. The situation is considerably more positive than a decade ago and tangible progress will probably be made over the next few years. The ultimate test will be increasing long term survival with better quality of life for patients with SSc, as observed after autologous stem cell transplantation [125].

Thus, despite the challenges of SSc there is reason to be optimistic because an unprecedented number of drugs are being tested in clinical trials for targeting lung and skin involvement in SSc, including treatments that might target fibrosis in both sites. Moreover, as the cost of PAH therapies becomes lower as generic formulations become available, opportunities arise to implement combination treatment at an early stage of disease. Identification of patients with a poor prognosis at an early stage of disease will enable better targeting of treatment and might start to diminish the high mortality seen

in some patients with SSc [164,165]. High-quality recommendations and guidelines are now available [63,166] that provide a roadmap for best practice and will undoubtedly be further updated as new evidence-based treatments for lung disease emerge. The future is bright as better tools for screening and diagnosis are being developed and a greater understanding of fundamental pathogenic mechanisms and identification of new potential therapeutic targets is being unveiled. Treatments for established lung complications are now available and various others are in clinical trials so that treatment approaches that prevent the progression of fibrosis and pulmonary hypertension will likely soon emerge as well as better ways to predict those at risk of major lung complications.

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**Key points**

- Lung complications are frequent in systemic sclerosis (SSc) and include lung fibrosis and pulmonary hypertension which have a substantial impact on disease outcomeand are both major causes of SSc-related death.
- Systematic valuation of patienst ensures that diagnosis of lung fibrosis and pulmonary hypertension is timely and permits treatment at earliest possible stage.
- There are multiple licensed therapies for pulmonary arterial hypertension and use of these agents alone and in combination has improved outcome and survival in event driven morbidity-mortality trials.
- There are no approved therapies for lung fibrosis but treatment with immunosuppression appears beneficial in recent clinical trails and is recommended for appropriate cases with severe or progressive lung fibrosis.

**Box 1: Potential causes of dyspnoea in patients with systemic sclerosis**

Parenchymal lung disease

- In addition to typical systemic sclerosis (SSc)-associated interstitial lung disease (ILD), some patients with overlap syndromes might present with patterns of lung involvement associated with other autoimmune rheumatic diseases [67], such as organizing pneumonia (a frequent feature in myositis **[**and airway involvement (seen in rheumatoid arthritis and Sjögren syndrome) [67].

Respiratory comorbidities

- Comorbidities including smoking-related emphysema, infection and pulmonary thromboembolism can cause dyspnoea.

Pulmonary vasculopathy

- Pulmonary arterial hypertension (PAH) can present with exertional dyspnoea. In some patients, pulmonary vascular disease is not sufficiently severe to manifest as PAH at rest but can cause exertional dyspnoea owing to a loss of pulmonary vascular reserve [71]. **[**

Cardiac involvement

- Dyspnoea might be caused by systolic or more commonly diastolic dysfunction, rate or rhythm disturbances [5] or from pericardial effusion. Cardiac involvement is frequent in SSc but can be challenging to diagnose and is not always symptomatic [66].

Cardiac comorbidities

- Coronary heart disease and valvular heart disease (especially aortic stenosis) can cause dyspnoea and might be associated with angina, but dyspnoea without concurrent angina may reflect otherwise unsuspected cardiac comorbidity in some patients.

Anaemia

- This condition might arise from a variety of mechanisms and cause dyspnoea and might also aggravate other manifestation such as PAH [5].

Arthritis

- Arthropathy, owing to either autoimmune disease or concurrent osteoarthritis, can, in isolation, cause exertional dyspnoea because of the increased work of locomotion

Muscle involvement

- Peripheral muscle limitation because of autoimmune muscle involvement is an often-underestimated contributor to exercise limitation [167]

Conditioning

- Cardiorespiratory and musculoskeletal conditioning is a common cause of subjective exertional dyspnoea in SSc [5], which might be amplified if loss of fitness is associated with significant weight gain.

**Box 2 Risk factors for severe lung fibrosis in systemic sclerosis [Au: Only one of these risk factors has a reference cited. Could you provide references for the other risk factors listed here?]**

- Diffuse cutaneous systemic sclerosis [50]
- Less than 3 years disease duration [50]
- Severe gastro-oesophageal reflux [22, 23]
- The presence of antinuclear antibodies (in particular anti-topoisomerase-1 antinuclear antibodies, but also anti-Th/To ribonucleoprotein (RNP) antibodies or anti-U11/U12 RNP antibodies) [94]
- A ‘severe’ score by the UK-RSA Staging system [96]
- Declining lung function [50]
- Evidence of epithelial damage (for example, elevated KL-6 or fast DTPA clearance) [25]

Table 1 Classification of pulmonary hypertension in systemic sclerosis

| WHO Group | Designation for management | Investigation and diagnosis | Approximate frequency in SSc | Treatment considerations | Features |
|---|---|---|---|---|---|
| I | Precapillary pulmonary arterial hypertension (PAH) | PAH is defined by mPAP ≥ 25 mm Hg with PAWP ≤ 15 mm Hg and PVR ≥ 3 WU without major lung fibrosis | PAH is the most common cause of severe pulmonary hypertension in SSc and probably accounts for ~60% of patients with SSc-associated pulmonary hypertension [77] | Supportive measures and targeted PAH specific medication can be given, often in combination | Borderline elevation of mPAP (21-14 mm Hg) is associated with high risk of developing established PAH [82] |
| I' | Pulmonary veno-occlusive disease (PVOD) | PVOD has a similar haemodynamics to PAH but presents with CT findings of septal lines, nodules and lymphadenopathy | The frequency of PVOD in SSc is unknown but up to 15% of patients with SSc-associated pulmonary hypertension might have elements of PVOD [61]. PVOD is rarely observed as the pure cause of pulmonary hypertension | Supportive measures and vasodilator therapy can be used but the latter should be used with care as this therapy might otherwise precipitate pulmonary oedema Immunosuppressive therapy might be beneficial for some patients. | The frequency of apparent PVOD varies between cohort studies and some patients might have both PVOD and Group I PAH [60,61]. |
| II | Post-capillary pulmonary hypertension | Group II pulmonary hypertension is characterized by elevated PAWP above 15 mm Hg in association with pulmonary hypertension mPAP > 25 mm Hg | In ~15% of patients with SSc-associated pulmonary hypertension, group II pulmonary hypertension is the major form [77] However, the frequency of group II pulmonary hypertension is difficult to determine. In the context of scleroderma renal crisis with systemic hypertension, this form is the most likely explanation for concurrent pulmonary hypertension and might later improve without specific therapy. | The cardiac cause (including systolic or diastolic failure, arrhythmia and valvular disease) should be treated. In some patients, vasodilator therapy with PAH specific therapies might be considered but these therapies might worsen heart failure and so need to be used with some caution. | The true frequency of this form of hypertension is unclear, and some studies suggest that there is often a post-capillary component to pulmonary hypertension in SSc, which might be apparent with a fluid challenge at right heart catheterisation. This form might sometimes co-exist with Group I PAH [66] |
| III | Pulmonary hypertension owing to lung fibrosis or hypoxia | In SSc, this form of pulmonary hypertension is difficult to classify as many patients have some degree of lung fibrosis. A diagnosis of pulmonary hypertension | Approximately 15% of patients with SSc-associated pulmonary hypertension are estimated to have Group III pulmonary hypertension | Treatment of any associated chest wall skin fibrosis, myositis and lung fibrosis should be prioritized. Subsequently, judicious use of vasodilator therapy might be considered, but should be used with caution as this therapy might | Lung fibrosis occurs in over 50% of patients of SSc and so fibrosis often co-exists with other forms of pulmonary hypertension. Therefore, simply demonstrating the presence of any lung fibrosis is not usually |

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|---|---|---|---|---|---|
| | | associated with lung fibrosis is normally made if specified thresholds of various tests of lung function are exceeded: for example, >70% predicted FVC (by spirometry) or >20% fibrotic lung volume involvement (by HRCT) . | | aggravate hypoxia owing to a decreased ventilation to perfusion ratio | sufficient for classifying patients into this group [52]. |
| IV | Thrombo-embolic pulmonary hypertension | All patients with suspected PAH should be investigated to exclude chronic thromboembolic disease as this form of pulmonary hypertension can be treated surgically. | Research studies suggest that intra vascular thrombosis is present in some cases of SSc-associated PAH but others develop more typical CTEPH [58]. | The management of thrombo-embolic disease should be in line with current recommendations and includes surgical treatment, medical therapy and, when suitable, balloon pulmonary angioplasty. Routine use of anticoagulants in PAH in SSc is not associated with better outcome and so is not recommended. | This is uncommon as a major cause of pulmonary hypertension in SSc but mural thrombosis (a thrombosis that partially blocks the blood vessel) might be observed in vessels by imaging [58]. |
| V | Uncommon and multifactorial pulmonary hypertension | Routine pulmonary hypertension investigation supplemented with extensive additional tests should be used to confirm multifactorial and/or uncommon causes | Rare causes of pulmonary hypertension might co-exist with SSc. In addition, individuals with pulmonary hypertension arising from multiple mechanisms might be considered as part of this group | Type V pulmonary hypertension is a heterogeneous group that includes forms with various mechanisms and pathologies and so the frequency will depend on what definition of mechanisms thatare included in this group. | Patients might have pulmonary hypertension with multifactorial elements but usually one of these factors predominates |

FVC, forced vital capacity; HRCT, high-resolution CT; mPAP, mean resting pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SSc, systemic sclerosis

Table 2 Summary of therapies approved for use in SSc-associated PAH

| **Drug** | **Delivery route** | **Evidence for efficacy in SSc-associated PAH [Au: For this column, could you please clarify on the findings of the studies presenting this evidence, and provide references]** | **Major adverse effects** | **Comments** |
|---|---|---|---|---|
| Endothelin receptor antagonists | | | | |
| Bosentan | Oral | Similar treatment effect seen in SSc subgroup to the overall treatment cohort in pivotal trials | Abnormal liver function tests, anaemia, oedema and nasal congestion | The first oral therapy licensed for SSc-associated PAH. Anecdotal improvement in long term outcome and preventing mortality [149] |
| Ambrisentan | Oral | Similar treatment effect seen in SSc subgroup to the overall treatment cohort in pivotal trials and ambrisentan in combination with tadalafil is highly efficacious | Anaemia, oedema, fluid retention and nasal congestion | Fewer drug interactions than other endothelin receptor antagonists [146] |
| Macitentan | Oral | Demonstrated high efficacy compared with placebo in a robust outcome study using morbidity-mortality endpoint. | Anaemia and nasal congestion. | Macitentan in combination with a PDE5 inhibitor is also highly efficacious [150] |
| Prostacyclin pathway targeting therapies | | | | |
| Beraprost* | Oral | No robust efficacy data available | Jaw pain, diarrhoea, hypotension and headache | Not licensed in Europe or North America. |
| Selexipag* | Oral | Robust long-term data from Griphon trial including cases on triple therapy with an endothelin receptor antagonist and PDE5 inhibitor. There was benefit in morbidity-mortality for cases treated with selexipag compared with placebo, even in cases already on dual combination therapy [151]. | Jaw pain, diarrhoea, hypotension and headache | |

| | | | | |
|---|---|---|---|---|
| Epoprostenol** | Intravenous | Demonstrated efficacy in a randomized open label study but no mortality benefit reported | Line sepsis, jaw pain, diarrhoea, hypotension, headache and rapid worsening if infusion interrupted | Epoprostenol is generally used in patients with severe pulmonary hypertension, particularly patients with class IV pulmonary hypertension [] |
| Iloprost** | Inhaled | Similar treatment effect seen in SSc subgroup to the overall treatment cohort in pivotal trials [167]. | Jaw pain, diarrhoea, hypotension and headache | Inhaled route not popular with many patients but other formulations not approved [169] |
| Treprostinil** | Subcutaneous or intravenous | Similar treatment effect seen in SSc subgroup to the overall treatment cohort in pivotal trials [OLD 163]. | Injection site pain (from subcutaneous administration), jaw pain, diarrhoea, hypotension and headache | Pain at site of injection is a major limitation [171] |
| PDE5 inhibitors | | | | |
| Sildenafil | Oral | Improved exercise capacity for SSc as in overall treatment groups in pivotal trial [148] | Hypotension, interaction with nitrates, visual disturbance, epistaxis, headache and priapism | Sildenafil is a widely use first line therapy and the generic formulation is relatively inexpensive. This therapy is often used in combination with an endothelin receptor antagonist [148] |
| Tadalafil | Oral | Improved exercise capacity for SSc similar to overall treatment groups in pivotal trial [154] | Hypotension, interaction with nitrates, visual disturbance, epistaxis, headache and priapism | Evidence base from studies including in combination, most robustly from the Ambition clinical trial [153] |
| Soluble guanylate cyclase agonist | | | | |
| Riociguat | Oral | Data for SSc are in line with overall treatment groups in pivotal trial showing benefit of active treatment compared with placebo [156] | Hypotension, epistaxis, headache and haemoptysis | Also licensed for CTEPH. Cannot be combined with a PDE5 inhibitor [156]. This therapy has the theoretical advantage of not |

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| | | | | depending upon endothelial production of nitric oxide for efficacy (unlike other approved therapies) [156] |

Prostacyclin pathway targeting therapies include prostacyclin agonists* and synthetic prostacyclins**.

CTED, chronic thromboembolic disease; PDE5, phosphodiesterase type 5 inhibitor

Table 3 Clinical trials of therapies in PAH that have included patients with SSc

| Treatment (trial name) | Primary endpoint | Total number of patients enrolled | Number of patients with CTD-associated PAH (%) | Patients with SSc-associated PAH (%) | Summary of resuts relevant to SSc associated PAH | Reference |
|---|---|---|---|---|---|---|
| Endothelin receptor antagonists | | | | | | |
| Bosentan (BREATHE-1 and study 351) | SMWT | 245 | 66 (27%) | 52 (79%) | These two pivotal trials in PAH led to approval of bosentan and included cases with SSc associated PAH that had qualitatively similar treatment benefit to overall cohort | 149 |
| Sitaxentan (STRIDE-1 and STRIDE-2) | SMWT | 425 | 110 (26%) | 63 (57%) | These two trials confirmed increase in SMWT in PAH cases treated with sitaxentan including those with SSc. Sitaxentan later withdrawn due to hepatotoxicity | 168 |
| Ambrisentan (ARIES-1 and ARIES-2) | SMWT | 384 | 117 (30%) | 76 (65%) | Both trials showed improved SMWT in PAH treated with ambrisentan compared with placebo. Similar benefit in SSc cases to overall cohort | 172 |
| Macitentan (SERAPHIN) | Morbidity and mortality | 742 | 224 (30%) | NS | The first event driven morbidity-mortality trial showed that adding macitenan to background therapy | 150 |

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|---|---|---|---|---|---|---|
| | | | | | or as first line treatment was superior to placebo. Umerically similar benefit for SSc-PAH to overall cohort | |
| PDE5 inhibitor | | | | | | |
| Sildenafil (SUPER-1) | SMWT | 278 | 84 (30%) | 38 (45%) | Significant improvement in SMWT for sildenafil treated PAH compared with placebo and similar effect in SSc-PAH to overall cohort | 148 |
| Soluble guanylate cyclase agonist | | | | | | |
| Riociguat (PATENT-1, and PATENT-2) | SMWT | 443 | 96 (22%) | 59 (61%) | Improved SMWT distance in PAH cases treated with riociguat compared with placebo, including those on background ERA. Numerically smaller gain in PAH-SSc but good long term survival in all PAH | 156 |
| Prostacyclin pathway targeting therapies | | | | | | |
| Epoprostenol[b] | SMWT | 111 | 111 (100%) | 111 (100%) | Open label study showed gain in exercise capacity (SMWT) but no mortality benefit. | 144,145 |
| Treprostinil[c] | SMWT | 470 | 90 (19%) | NS | Significant improvement in SMWT for subcutaneous treprostinil treated PAH compared with placebo and similar effect in SSc-PAH to overall cohort | 171 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Iloprost[c] (AIR) | SMWT | 203 | 35 (17%) | NS | Numerical gain in SMWT in active treatment compared with placebo but not reaching statistical significance. | 169 |
| Selexipag[b] (GRIPHON) | Morbidity and mortality | 1156 | 334 (29%) | 170 (51%) | Largest event driven morbidity-mortality trial performed t date showed that adding selexipag to background therapy or as first line treatment was superior to placebo. Numerically similar benefit for SSc-PAH to overall cohort | 151 |
| Combined therapy with an endothelin receptor antagonist and phosphodiesterase type 5 inhibitor | | | | | | |
| Bosentan added to sildenafil (COMPASS-2) | Morbidity and mortality | 334 | NS | NS | No evidence of significant benefit for combining sildenafil and bosentan compared with sildenafil alone | 172 |
| Ambrisentan and tadalafil (AMBITION) | Morbidity and mortality | 500 | 187 (37%) | 118 (63%) | Important study demonstrating that initial combination therapy was superior to either single treatment in PAH including PAH due to SSc and significant benefit was equivalent for SSc and non-SSc cases including idiopathic PAH | 154 |

[a]Range indicates separate values for ARIES-1 and ARIES-2 trials Prostacyclin pathway targeting therapies include prostacyclin agonists[b] and synthetic prostacyclins[c].

AIR, Aerosolized Iloprost Randomized; AMBITION, Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension; ARIES, Ambrisentan in Patients with Moderate to Severe Pulmonary Arterial Hypertension; BREATHE, Bosentan: Randomised Trial of Endothelin

Receptor antagonist Therapy for Pulmonary Arterial Hypertension; COMPASS, Combination Therapy in Pulmonary Arterial Hypertension; GRIPHON, Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension; NS, not specified in the trial report; PATENT, Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial; PDE5, phosphodiesterase type 5 inhibitor; SERAPHIN, Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; SMWT, six minute walk test; STRIDE, Sitaxsentan To Relieve Impaired Exercise in Pulmonary Arterial Hypertension; SUPER, Sildenafil Use in Pulmonary Arterial Hypertension

**Figure 1 Pathogenesis of major lung complications in systemic sclerosis**

Multiple cell types and mediators are probably involved in the pathogenesis of lung fibrosis and pulmonary arterial hypertension. Tissue damage initiated by epithelial injury or inflammation might result in a local environment within the lung parenchyma that results in the generation and persistence of myofibroblasts. Accumulation of excess extracellular matrix and destruction of the lung structure in the absence of repair and regeneration can most often lead to a NSIP pattern of lung disease. In the pulmonary circulation, endothelial damage might promote a proliferative vascular response that includes multiple cell types and results in endoluminal lesions and medial wall thickening. Vascular fibrosis and perivascular inflammation can subsequently occur. The pathogenic processes that occur following epithelial injury (leading to lung fibrosis) and pulmonary endothelial injury (triggering pulmonary arterial hypertension) seem to be shared. Hence, SSc might be a susceptibility phenotype for these complications and other facets of the disease process, and autoimmune, genetic or environment factors might determine which of the potential manifestations is predominant.

**Figure 2 Screening for pulmonary hypertension in systemic sclerosis**

This schematic is an example of one approach for diagnosing and screening patients with pulmonary hypertension, and is in line with current recommendations for the diagnosis and management of such patients [71,76] . All patients with systemic sclerosis (SSc) should have an initial assessment looking at clinical features, lung function (including measures of diffusing capacity for carbon monoxide (DLCO)) and transthoracic echocardiographic findings. The abundance of N-terminal pro-brain natriuretic peptide (Nt-pro BNP) should also be measured. For patients with a DLCO <60% and disease duration of >3 years, the DETECT score can be calculated [77]. These tests are repeated annually in all patients, and if a patient develops clinical features suggestive of possible new pulmonary hypertension these tests are repeated more often. If the results (from either the transthoracic echocardiographic findings, pulmonary function tests or DETECT score) exceed defined thresholds, right heart catheterization should be performed to confirm a diagnosis of pulmonary hypertension. A diagnosis of pulmonary arterial hypertension (PAH) requires a low pulmonary arterial wedge pressure (PAWP) and the absence of major lung fibrosis (which would otherwise be classified as group III pulmonary hypertension).

FVC, forced vital capacity; mPAP, meaning resting pulmonary arterial pressure;

**Figure 3 Histological and CT appearances of major lung complications in systemic sclerosis**

The most common histological pattern of lung fibrosis in SSc is NSIP, which might be mild (part a) or extensive (part b) and is characterized by relative preservation of lung architecture and often a homogeneous “ground glass” change within the lungs (GC arrow). NSIP might have cellular or fibrotic subtypes. By contrast, compared with NSIP, the less common UIP pattern of fibrosis (part c) has a much more altered architecture, a more variable severity of fibrotic lesions and a less homogeneous pattern with dense fibrosis and cystic changes, termed honeycombing (HC arrow). Pulmonary hypertension (part d) is characterized by enlargement of the pulmonary artery on CT imaging (PA arrow). A designation of PAH can only be made if only mild lung fibrosis is present as otherwise a classification of group III

pulmonary hypertension is made. It is also important to note whether CT features of pulmonary veno-occlusive disease (PVOD) are present such as septal lines, nodules or lymphadenopathy (not shown).

**Glossary terms**

***Dyspnoea.*** Breathlessness that is a major symptom of lung complications in systemic sclerosis but that also has other potential causes including cardiac disease, anaemia and deconditioning.

***Exertional dyspnoea.*** Subjective breathlessness that occurs on exertion and is a cardical feature of significant lung complications including lung fibrosis and pulmonary hypertension.

***Fibroblasts.*** Cells that produce extracellular matrix and that are activated inappropriately or excelssively in fibrotic disease.

***Myofibroblasts.*** Activated fibroblastic cells that have a contractile cytoskeleton that includes microfibrils containing alpha smooth muscle actin.

***lung function test.*** Collective term for the physiological measurement of lung volume, airways resistance and gas exchange in the lungs.

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**Competing interests**

C.P.D has received honoraria from Actelion, Bayer, Boehringer Ingelheim, Genentech-Roche, GSK. or and consultancy fees from Actelion, Bayer, Boehringer Ingelheim, CSL Behring, Genentech-Roche, GSK, Inventiva, Merck-Serono, Sanofi-Aventis.

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**Table of contents blurb**

**Major lung complications of systemic sclerosis**

Christopher P. Denton, Athol U. Wells and John G. Coghlan

The two major lung complications in systemic sclerosis, lung fibrosis and pulmonary arterial hypertension, share some pathogenic mechanisms. Strategies for managing patients with these complications has greatly advanced in the past decade and many tools and treatments are now available.