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Review article

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# Systemic sclerosis interstitial lung disease: unmet needs and potential solutions

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## Abstract

Systemic sclerosis (SSc), or scleroderma, is a rare, complex, systemic autoimmune disease of unknown aetiology, characterized by high morbidity and mortality often resulting from cardiopulmonary complications such as interstitial lung disease and pulmonary arterial hypertension. Despite substantial progress in unravelling the pathways involved in the pathogenesis of SSc and the increasing number of therapeutic targets tested in clinical trials, there is still no cure for this disease, although several proposed treatments might limit the involvement of specific organs, thereby slowing the natural history of the disease. A specific focus of recent research has been to address the plethora of unmet needs regarding the global management of SSc-related interstitial lung disease, including its pathogenesis, early diagnosis, risk stratification of patients, appropriate treatment regimens and monitoring of treatment response, as well as the definition of progression and predictors of progression and mortality. More refined stratification of patients on the basis of clinical features, molecular signatures, identification of subpopulations with distinct clinical trajectories and implementation of outcome measures for future clinical trials could also improve therapeutic management strategies, helping to avoid poor outcomes related to lung involvement.

## Sections



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## Key points

- Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterized by high clinical heterogeneity, in which interstitial lung disease (ILD) is one of the main causes of morbidity and mortality.
- Despite many advances in the understanding of pathogenetic mechanisms and clinical definition, SSc–ILD management is still associated with several unmet needs.
- Discovery of new therapeutic targets and specific diagnostic and prognostic markers will help optimize the management of SSc–ILD.
- Stratification of patients by clinical features and molecular signatures, identification of subpopulations with distinct clinical trajectories, and implementation of outcome measures in clinical trials can also improve SSc–ILD management.

## Introduction

Systemic sclerosis (SSc), or scleroderma, is a rare, systemic autoimmune disease that is associated with high mortality, often resulting from cardiopulmonary complications such as interstitial lung disease (ILD) and pulmonary arterial hypertension. ILD occurs in up to 80% of individuals with SSc as observed on high-resolution computed tomography (HRCT), the gold standard imaging technique for the detection of ILD, with 25–30% of individuals with SSc developing a progressive clinical phenotype that results in respiratory failure and death[1–3]. Clinically, SSc–ILD can remain asymptomatic for a long time, although bilateral basal inspiratory and expiratory crackles ('Velcro' crackles) can be present on chest auscultation. In approximately 40% of people with SSc–ILD, progression of ILD occurs and is associated with dyspnoea on exertion and increasingly persistent dry cough. The most severe lung involvement and/or the later stage of SSc–ILD is clinically characterized by dyspnoea at rest, cyanosis and signs of right heart failure[1,2]. Despite the approval of drugs for the treatment of cardiopulmonary complications, only a small clinical improvement has been achieved, and improving survival and quality of life as well as determining the appropriate use of available DMARDs are important unmet needs.

SSc–ILD can range from a mild and self-limiting form to a more severe and rapidly progressive clinical phenotype[4,5]. Despite advances in the understanding of pathogenetic mechanisms and clinical definition, SSc–ILD management still has several unmet needs regarding pathogenesis, disease classification and progression, validated biomarkers for early diagnosis, management, appropriate treatment regimens and monitoring of treatment response, clinical evolution, and outcome measures for future clinical trial design. In this Review, we summarize relevant results from the past 7 years on the unmet needs in SSc–ILD and discuss potential solutions that might help to address them.

## Pathogenesis of SSc–ILD

### Vascular damage

SSc–ILD pathogenesis is characterized by the involvement of different types of non-immune and immune cells and their mediators, which modulate key molecular pathways involved in vascular damage, inflammation, autoimmunity and, ultimately, tissue fibrosis[6] (Fig. 1). The purported first pathogenetic event involves repetitive injury to the lung vascular tree, likely triggered by environmental factors and infections in genetically susceptible individuals. Evidence for this vascular injury hypothesis is derived from studies demonstrating the presence of antibodies against endothelial cells, type A receptor of endothelin 1 ($ET_AR$) and type I receptor of angiotensin II (AT1R). The binding of anti-$ET_AR$ and anti-AT1R antibodies to these receptors induces the production of transforming growth factor-β (TGFβ), induction of IL-8 by endothelial cells and their expression of vascular cell adhesion molecule 1 (VACM1), as well as collagen production from activated fibroblasts, thereby contributing to abnormal fibrosis[7]. Interestingly, TGFβ can induce endothelial–mesenchymal transition (EMT), a process that is greatly activated in SSc[8]. In vitro, TGFβ induces EMT in immunopurified murine lung endothelial cells mediated by tyrosine-protein kinase ABL1 and protein kinase Cδ[9]. These transdifferentiating cells, via endothelin 1 production, upregulate the expression of TGFβ1 and TGFβ2 as well as of TGFβ receptors, inducing a self-perpetuating EMT process[10].

The damaged vascular tree produces thrombin, which is involved in local hypercoagulation as well as in the activation and differentiation of fibroblasts into myofibroblasts, with subsequent deposition of extracellular matrix (ECM) proteins. Thrombin also enhances the release of profibrotic cytokines, such as TGFβ, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF) and monocyte chemo-attractant protein 1, by a variety of cells including lung fibroblasts, and induces endothelial cell apoptosis[11].

### Innate immune system

Both innate and adaptive immune systems are involved in the early stage of lung damage[12]. Following vascular damage and increased expression of adhesion molecules, the activation and proliferation of lung-resident immune cells and recruitment of inflammatory cells, including macrophages, monocytes, neutrophils, mast cells and natural killer cells, contribute to the fibrotic process. Endogenous ligands released as a result of oxidative stress and cellular injury, such as mitochondrial DNA, are thought to bind to Toll-like receptors (TLRs) and other pattern recognition receptors such as cyclic GMP–AMP synthase (cGAS)[13], and to stimulate dendritic cells (DCs) to produce IFNα and IL-6, which in turn activate T helper 2 ($T_H2$) cells to produce IL-4, IL-10 and IL-13 as well as stimulating profibrotic macrophages. IL-4 and IL-10 stimulation induces STAT3 and STAT6 hyperactivation in alveolar macrophages. Furthermore, IL-10 enhances IL-4-induced expression of CCL18, a strongly profibrotic cytokine. During lung fibrosis, macrophages show increased expression of both *SPP1* (which encodes sphingosine 1-phosphate phosphatase 1) and lipid-metabolism genes in early disease, switching towards expression of ECM-remodelling genes in later stages. *SPP1*-expressing macrophages might activate myofibroblasts[14,15]. Macrophages also undergo polarization to either classic M1 macrophages that secrete pro-inflammatory and/or profibrotic cytokines (IL-1β, IL-8, IL-10 and CXCL13) or to M2a macrophages that secrete profibrotic cytokines (CCL22, CCL18, PDGF-BB, TGFβ and IL-6)[16]. A monocyte–macrophage lineage expressing surface markers of both M1 and M2 phenotypes is present in patients with SSc–ILD associated with positivity for SCL70 antibody[17]. Plasmacytoid DCs (pDCs) are also involved in SSc–ILD through the high production of type I interferon as shown by single-cell RNA sequencing[18]. Type I interferon is responsible for the activation of monocytes, the differentiation and activation of T cells, B cells and DCs, and the stimulation of the expression of TLRs by DCs, and it is also able to increase the expression of fibrotic effectors, such as CTGF, in endothelial cells and fibroblasts[18] (Fig. 1).

### Adaptive immune system

Altered B cell subtypes and B cell dysfunction are early events in SSc–ILD pathogenesis[19]. Decreased frequency and impaired regulatory function of TIM1$^+$ transitional B cells[20] and increased expression of CD30$^+$ GM–CSF effector B cells with antibody-independent functions, together with IL-4 production and induction of DCs, are implicated in SSc–ILD[21]. B cell activation, characterized by increased CD19-mediated signalling together with decreased inhibitory CD22 signalling, with the production of pro-inflammatory cytokines and profibrotic growth factors such as IL-6, B cell-activating factor (BAFF) and TGFβ, also contributes to lung fibrosis[22,23].

Activation and polarization of CD4$^+$ T cells with $T_H1$-to-$T_H2$ cell and $T_H17$-to-regulatory T cell imbalance are involved in SSc pathogenesis and associated with active lung disease through the production of profibrotic cytokines IL-4 and IL-13. Moreover, expanded topoisomerase I-specific CD4$^+$ T cells are strongly polarized towards a pro-inflammatory $T_H17$ phenotype and associated with active alveolitis and progression of ILD via IL-13 and IL-4 production[24]. CD8$^+$ T cells from the lungs of individuals with SSc produce IL-4 and oncostatin M and might activate latent TGFβ[25]. Finally, the chronic stimulation of myofibroblasts, through the production of profibrotic molecules and subsequent tissue hypoxia, might induce epigenetic modifications in these cells, which further fuels fibrosis[26].

### Genetics

Genome-wide association studies have identified numerous risk loci mainly localized in non-coding regions and mostly affecting the innate and adaptive immune systems, with some variants also

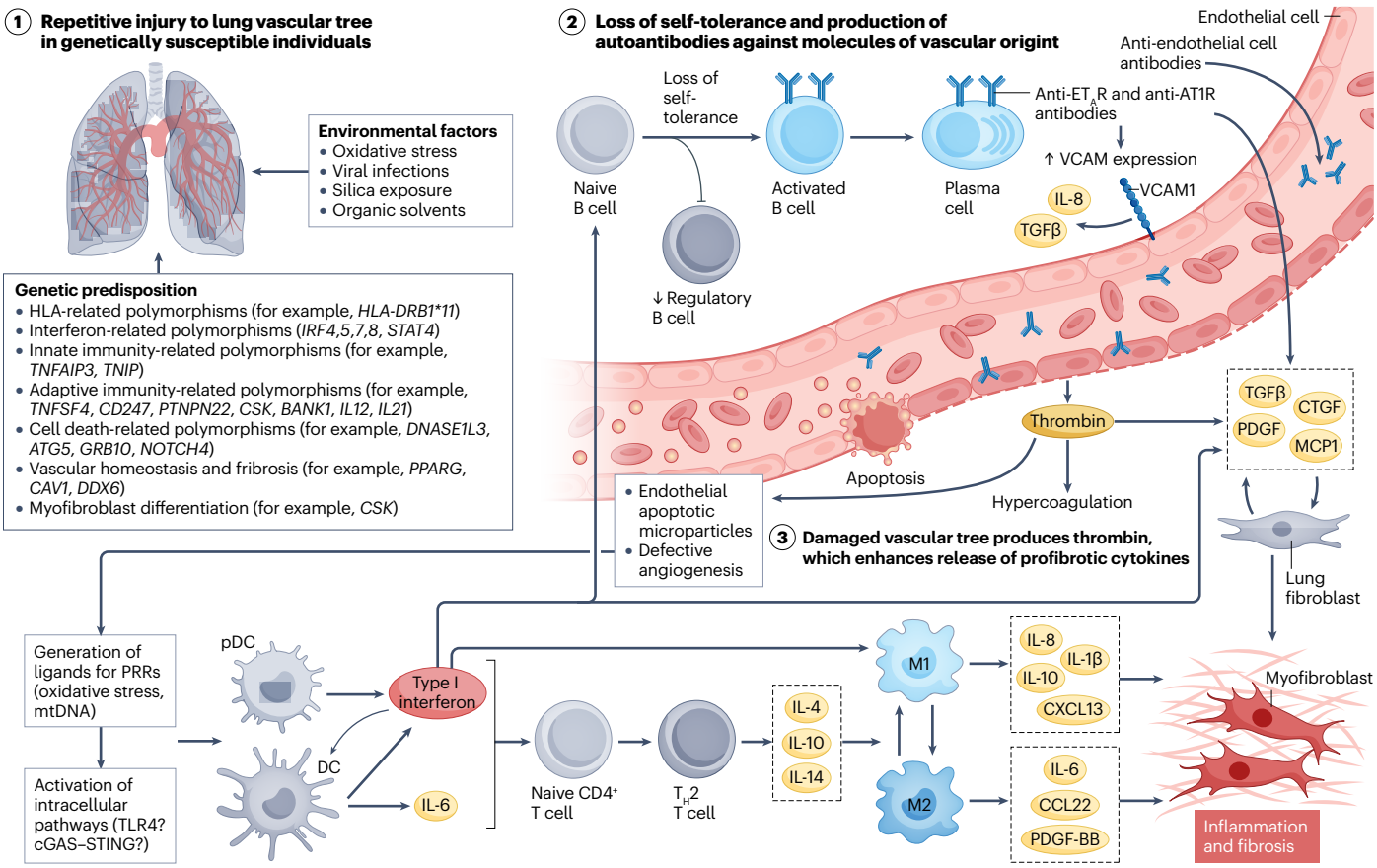


**Fig. 1 | Pathogenesis of SSc interstitial lung disease.** Systemic sclerosis (SSc) interstitial lung disease pathogenesis is complex and involves both immune and non-immune cells. The purported first pathogenic event involves repetitive injury to the lung vascular tree, likely triggered by environmental factors and infections in genetically susceptible individuals, leading to loss of self-tolerance and production of autoantibodies against molecules of vascular origin, with subsequent production of chemokines responsible for local inflammation and activation of both the innate and adaptive immune systems. Transforming growth factor-β (TGFβ) can induce endothelial–mesenchymal transition, a process that is greatly activated in SSc. The damaged vascular tree produces thrombin, which is involved in local hypercoagulation as well as in activation and/or differentiation of fibroblasts into myofibroblasts, with subsequent deposition of extracellular matrix proteins. Thrombin also enhances the release of profibrotic cytokines, such as TGFβ, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF) and monocyte chemo-attractant protein 1 (MCP1), by a variety of cells including lung fibroblasts, and induces endothelial cell apoptosis. Activation of B cells, production of autoantibodies and activation of Toll-like receptors (TLRs) leads to type I interferon production and stimulation of plasmacytoid dendritic cells (pDCs) to further produce type I interferon and IL-6, which stimulate T helper 2 ($T_H2$) cells to produce IL-4 and IL-13 that stimulate type 1 macrophages (M1) and type 2 macrophages (M2) to produce profibrotic factors. The production of TGFβ, CTGF and PDGF-BB stimulates fibroblasts to produce collagen and other extracellular matrix molecules, leading to local fibrosis. Anti-AT1R, antibody against angiotensin type 1 receptor; anti-$ET_AR$, antibody against endothelin 1 type A receptor; cGAS, cyclic GMP–AMP synthase; DC, dendritic cell; mtDNA, mitochondrial DNA; PRR, pattern recognition receptor; STING, stimulator of interferon gene; VCAM1, vascular cell adhesion molecule 1.

## Box 1

# Classification and stratification of SSc–ILD

Systemic sclerosis (SSc) interstitial lung disease (ILD) can be classified into specific histopathological patterns, including non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia, organizing pneumonia, lymphoid interstitial pneumonia and diffuse alveolar damage, which are characterized by varying degrees of inflammation and fibrosis. NSIP is the most common histopathological pattern, whereas the occurrence of interstitial pneumonia is less frequent than that of NSIP.

On the basis of the extent of lung fibrosis on high-resolution computed tomography (HRCT) combined with the results of pulmonary function tests (PFTs), ILD can be stratified into limited disease (extent of lung fibrosis of <20% on HRCT or indeterminate lung involvement on HRCT and forced vital capacity (FVC) ≥70% of predicted) or extensive disease (extent of lung fibrosis of ≥20% on HRCT or indeterminate lung involvement on HRCT and FVC <70% of predicted).

On the basis of the risk of progression, individuals with SSc–ILD can be stratified into low risk (no elevation of acute phase reactants, presence of anti-centromere antibody) or high risk (older age at disease onset, male sex, African American ethnicity, diffuse cutaneous SSc subtype, shorter disease duration, low baseline FVC and/or diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$), extensive disease on baseline HRCT, presence of anti-SCL70 antibody, elevated acute phase reactants).

On the basis of disease severity, ILD can be stratified into subclinical ILD (ILD with minimal (5–10%) extent on HRCT and no ILD-related clinical symptoms (dyspnoea or cough) and normal baseline PFTs (including FVC and $DL_{CO}$) or no clinically meaningful decline in PFT if serial PFTs are available) or clinical ILD (mild-to-severe ILD on HRCT and one or more of the following features: abnormal baseline PFTs (including FVC and/or $DL_{CO}$) and/or clinically meaningful decline of PFTs (including FVC and/or $DL_{CO}$), ILD-related symptoms or impact of ILD on daily life).

affecting autophagy pathways, vasculopathy and fibrosis, all of which are involved in SSc susceptibility. Variants of risk genes involved in the type I interferon and TLR2 pathways, such as *IRF5*, *IRF7*, *IRF8* and *TLR2*, could lead to exacerbation of the production of pro-inflammatory cytokines by macrophages, thereby recruiting DCs devoted to capturing, processing and presenting antigen to T cells, with subsequent overactivation of T cell responses and autoantibody production. Variants of risk genes of apoptotic pathways, such as *RAB2A*, *ATG5* and *DNASE1L3*, can lead to impaired autophagy and apoptosis of endothelial cells. Variants of genes involved in vasculopathy, such as *DDX6* and *DNASE1L3*, are associated with altered VEGF secretion, blood vessel remodelling, impairment of macrophage clearance of apoptotic bodies, release of nuclear components that are targets of SSc autoantibodies and increased damage-associated molecular pattern sensing. Lastly, genes such as *CSK*, *CAV1* and *GRB10* are involved in fibroblast proliferation and activation and in myofibroblast differentiation, contributing to abnormal fibrosis[27].

Genetic background only partially explains the development of SSc. The overall twin concordance rate for SSc is low (4.7%) compared with that for other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (25%). Notably, the concordance rate for the positivity of anti-nuclear antigen autoantibodies is higher in monozygotic twins with SSc than in dizygotic twins with SSc[28]. In a cross-sectional epigenomic study on 27 twin pairs who were discordant for SSc, differentially methylated functional loci were identified, revealing distinct epigenetic architectures in diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc[29]. Results from a meta-analysis on the role of occupational exposure (to heavy metals) and environmental exposure (to silica, solvents, silicone breast implants, epoxy resins, welding fumes, pesticides, hair dyes and drugs) suggest roles for all these factors in SSc development[30]. However, further studies are needed to confirm the role of environmental factors in epigenetic regulation.

### Airway basaloid cells

Compared with healthy individuals, those with SSc–ILD or with idiopathic pulmonary fibrosis (IPF) have aberrant basaloid cells and severe loss of alveolar type I cells. Basaloid cells, which are epithelial in nature, are enriched in the expression of fibrosis-associated genes and involved in the EMT, thereby contributing to lung fibrosis[18,31].

## Classification of SSc–ILD

### Histopathological classification

SSc–ILD can be classified into specific histopathological patterns, including non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia, lymphoid interstitial pneumonia and diffuse alveolar damage, which are characterized by a varying extent of inflammation and fibrosis (Box 1). Radiological findings of NSIP (the most common pattern) include the presence of ground glass opacity (GGO) with peripheral, subpleural and bibasal distribution, with conserved lung architecture. The presence of reticulation and traction bronchiectasis indicates 'fibrotic' NSIP. UIP is characterized by a disrupted lung architecture with dense patchy areas of fibrosis and fibrotic cystic changes (honeycombing), associated with a worse prognosis than NSIP[32]. Moreover, in some individuals with SSc–ILD who directly exhibit end-stage lung fibrosis, ILD cannot be classified as they do not fulfil the definition for any specific pattern. A lung biopsy is not required to diagnose ILD, as HRCT could predict the underlying histopathology, unless a discrepancy between clinical symptoms and HRCT findings is observed, supporting the suspicion of other pathological conditions such as infection and malignancy.

## Screening and early diagnosis of SSc–ILD

Early diagnosis and treatment of SSc–ILD could improve the natural disease course and survival rates. However, there is still no consensus on screening guidelines for early diagnosis and evaluation of SSc–ILD. The currently available tools include chest auscultation, pulmonary function tests (PFTs) with diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$), and HRCT of the lungs. Patient-reported symptoms and 6-min walk distance (6MWD) are only supporting tools and are not included in ACR–EULAR classification criteria[33]. Clinical manifestations, such as dyspnoea on exertion and dry cough, are non-specific and can also be present in individuals with other cardiopulmonary pathological conditions. Furthermore, at SSc diagnosis, many patients are asymptomatic for ILD, and PFTs with $DL_{CO}$ can give normal results in individuals

with early SSc–ILD, resulting in missed diagnoses. A decrease in $DL_{CO}$ can also indicate pulmonary hypertension and/or other disease manifestations, including anaemia, or smoking. Currently, HRCT of the lungs remains the non-invasive 'gold standard' investigation technique for early diagnosis of ILD but there is still no consensus on screening for SSc–ILD detection with HRCT, a diagnostic tool of well-characterized radiation exposure (Box 2).

Findings of reduced survival in patients with mild lung fibrosis and normal range of forced vital capacity (FVC) strongly suggest that all individuals with SSc should undergo baseline PFTs and lung HRCT screening to diagnose ILD early and tailor further management[34]. Particular attention should also be paid to individuals with a decline of FVC within the 'normal range', which could possibly represent a clinically meaningful decline[35]. Results from a retrospective study to assess the performance characteristics of PFTs for the detection of ILD in individuals with early dcSSc (a population at high risk for the development of ILD) confirmed that HRCT should be part of the ILD screening algorithm in these patients because its combination with FVC <80% of predicted or $DL_{CO}$ <80% of predicted improved the sensitivity to 85% from 63% obtained for FVC <80% of predicted alone[36]. A prospective study that evaluated a dedicated HRCT protocol consisting of only nine slices with a basal–apical gradient for the detection of SSc–ILD showed that the protocol had high accuracy and sensitivity[37].

In a Delphi study conducted in the USA to develop consensus recommendations on the global assessment of SSc–ILD and to build on the latest EULAR scleroderma treatment guidelines[38] and the European consensus statement[39], it was recommended that all individuals with SSc should be screened with HRCT at baseline to detect early asymptomatic ILD[40]. The presence of anti-centromere antibodies was the key clinical variable inversely associated with the performance of HRCT in the US-based Collaborative National Quality and Efficacy Registry study[41]. An unresolved question is when to repeat ILD screening in patients without lung parenchymal involvement by HRCT at the first evaluation and how to proceed. Because individuals with SSc can develop ILD in the first 3–5 years of the disease, these patients should be closely followed-up with PFTs every 4–6 months, and a clinically meaningful decline in FVC or $DL_{CO}$ (as suggested by the OMERACT definition) or the presence of new respiratory symptoms suggestive of ILD should recommend further HRCT[42,43], with variations in different countries[44]. At the ACR 2022 Congress, the validated ILD-RISK score was presented as a tool for prediction of the presence of ILD at the time of diagnosis and to evaluate the performance during follow-up, thereby limiting unnecessary HRCT[45]. Lung ultrasonography is a promising imaging tool with some potential for diagnosis and follow-up of SSc–ILD, but it is not yet ready for application in daily clinical practice as suggested by the OMERACT Ultrasound Group[46–50]. Nevertheless, the results of a meta-analysis suggested that the evaluation of individuals with SSc by lung ultrasonography could be a valuable tool to discern those patients needing to receive additional HRCT to detect lung involvement, thereby reducing exposure to ionizing radiation[51]. Results from another meta-analysis suggested that the presence of B-lines (discrete laser-like vertical hyperechoic lines arising from the pleural plane, extending to the bottom of the screen without attenuation and synchronizing with respiration) is a surrogate for ILD, although the value of pleural evaluation (irregularity, thickening and fragmentation) requires further investigation[52]. Lung ultrasonography might also be useful for the detection of ILD[53,54]. However, further studies are needed to achieve consensus in scoring and the evaluation methodology of lung ultrasonography. Lastly, MRI has a possible role in the evaluation and follow-up of SSc–ILD, although it is currently only a research methodology[55].

## Stratification of SSc–ILD

### Stratification based on the radiological extent of ILD

Because of ILD heterogeneity, the radiological extent of ILD is an important factor. A simple staging algorithm can rate ILD as limited or extensive based on the extent of fibrosis on HRCT combined with PFT values[56]. Limited SSc–ILD is characterized by an extent of lung fibrosis <20% on HRCT or indeterminate lung involvement on HRCT and an FVC ≥70% of predicted, whereas extensive disease (which is associated with higher mortality) is characterized by an extent of lung fibrosis ≥20% on HRCT or indeterminate lung involvement on HRCT and an FVC <70% of predicted (Box 1). This classification system predicts mortality but is unable to predict a therapeutic response to SSc–ILD. Consequently, it should not be applied to therapeutic decision-making. In this study, HRCT scans were scored at five levels for total disease extent, extent of reticulation, proportion of GGO and coarseness of reticulation. Lung bases were not included in the evaluation, even though individuals who differed in the extent of ILD were enrolled. Quantification of the radiological extent of SSc–ILD has also been addressed. CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) is a useful tool for quantification of lung involvement, with the GGO score being predictive of $DL_{CO}$ worsening[57]. A method to quantify lung involvement in SSc–ILD based on the ratio between the weight of interstitial opacities and the total lung weight enables accurate calculation of lung involvement[58]. Evaluation of SSc–ILD staging using a hybrid method incorporating PFTs and a novel CT methodology, which provides a volumetric analysis of structures such as airways, lobe volumes and vasculature, can differentiate moderate-to-severe ILD from limited ILD at baseline[59]. When patients are stratified based on the extent of lung fibrosis on HRCT, evaluation of the radiological involvement should include the lung bases. Furthermore, when individuals with a limited form of ILD mainly involving the lung bases are included in clinical trials, the radiological and functional end points chosen to reflect ILD progression should evaluate the whole lung as in the SENCIS trial[60], which identified SSc–ILD progression with higher sensitivity than studies using different HRCT scores[61]. Comparisons between studies should therefore consider variation in methodology and scores.

## Box 2

## Major unmet needs in SSc–ILD

Systemic sclerosis interstitial lung disease (SSc–ILD) is associated with unmet needs in the following areas:

- Understanding pathogenesis
- Disease classification and progression
- Validation of biomarkers for early diagnosis
- Management
- Agreement on appropriate treatment regimens and monitoring of treatment response
- Prediction of clinical evolution
- Agreement on outcome measures for future clinical trial design

### Stratification by risk and rate of progression of ILD

SSc–ILD can be stratified by risk and by the rate of progression and severity. Possible risk factors for ILD progression include older age at disease onset, male sex, African American ethnicity, dcSSc, shorter disease duration, low baseline FVC and/or $DL_{CO}$, extensive disease on baseline HRCT, presence of anti-SCL70 antibody, elevated acute phase reactants, and gastro-oesophageal reflux. By contrast, anti-centromere antibodies can be considered protective for ILD progression[2,56,62–67]. Prospective study results using data from the European Scleroderma Trials and Research (EUSTAR) data base with long-term follow-up showed that 23–27% of individuals with SSc–ILD had progressive ILD in any 1 year of a 5-year period from baseline, whereas 33% did not have any years of progressive ILD[62]. Only 8% of individuals with progressive SSc–ILD had a pattern of rapid, continuously declining FVC, whereas 58% had a pattern of slow lung function decline. Higher skin score, male sex, and the presence of reflux and/or dysphagia symptoms were the strongest predictors for FVC decline[62]. The American Thoracic Society guidelines of 2021 placed SSc–ILD within a subgroup of ILDs other than IPF that might potentially manifest progressive pulmonary fibrosis based on physiological, radiological and histopathological features of the disease[63]. Furthermore, in a USA cohort observational study of 254 individuals with SSc, 7 distinct FVC trajectories were identified according to baseline FVC value and pattern: very low, slow decline (5.5%); very low, improve (13.8%); low, fast decline (9.5%); low, stable (19.7%); low–normal, improve (31.1%); normal, improve (16.1%); and normal, stable (4.3%), highlighting the highly variable course of pulmonary function over a 12-year period[68].

### Stratification by severity of ILD

Heterogeneous rates of disease progression and treatment response suggest the need for validated definitions of ILD clinical subsets to enable the selection of appropriate therapeutic options. Sometimes, in early SSc–ILD, symptoms related to lung involvement are difficult to assess, especially considering the adaptability of patients to the new condition to avoid dyspnoea. However, evidence indicates that patients who lack dyspnoea and cough can still experience marked physiological progression of ILD when untreated[69]. Notably, studies have used different definitions of the subclinical condition using different clinical variables, thus limiting their comparability. One definition of clinical ILD is mild-to-severe ILD on HRCT and one or more of the following features: abnormal baseline PFTs (including FVC and/or $DL_{CO}$) and/or clinically meaningful decline of PFTs (including FVC and/or $DL_{CO}$, ILD-related symptoms, or impact of ILD on daily life), whereas subclinical ILD is characterized by a minimal (5–10%) extent on HRCT, no ILD-related clinical symptoms, and normal baseline PFTs (including FVC and $DL_{CO}$) or no clinically meaningful decline in PFTs, if serial PFTs are available[70]. These definitions differ from those used in a retrospective study of 294 treatment-naive patients with SSc, defined as mild-to-moderate or severe on the basis of FVC. In this study, ILD progressed over 1–2 years in 25% of patients defined as mild[71], and immunosuppressive treatment with mycophenolate mofetil (MMF) decreased the risk of developing clinical ILD[72]. Nevertheless, in an international survey of treatment practices in subclinical SSc–ILD, almost 50% of respondents would not treat subclinical ILD[73]. Instead, respondents noted that these individuals should be strictly monitored by performing serial PFTs and eventually repeating HRCT. Our opinion is that PFTs should be performed every 6 months as there is currently no universally accepted algorithm for monitoring SSc–ILD progression, with most experts suggesting that PFTs should be assessed at least every 3–6 months for the first 5 years of the disease[74]. Clinical presentation, management and survival vary between geographical regions[75,76], highlighting the need for standardization of medical practice in the global management of ILD. Biomarkers could help to identify patients at high risk of progression of ILD and to provide prognostic information useful for treatment decision-making[77–79]. At present, autoantibody status (anti-SCL70), elevation of C-reactive protein (CRP) and the presence of dcSSc provide important information about lung involvement and survival in these patients[5,80], with Krebs von den Lungen 6 (KL6) serum protein being routinely used in clinical practice in some countries to predict ILD severity and prognosis in SSc[81].

## Box 3

## Candidate patients for treatment

Candidate patients for treatment include those with the following phenotypes:

Forced vital capacity (FVC) <80% of predicted or FVC >80% of predicted in a patient at high risk with interstitial lung disease (ILD) or respiratory symptoms (dyspnoea).

Extensive ILD (>20%) on high-resolution CT (HRCT).

Limited ILD on HRCT (<10%) or indeterminate ILD (>10% and <20%) plus abnormal results of pulmonary function tests (PFTs; FVC <70% of predicted).

Mild ILD on HRCT and/or on PFTs (FVC <80% of predicted) or subclinical ILD in patients at high risk of progression (with early rapidly progressive diffuse cutaneous systemic sclerosis).

Progressive fibrotic phenotype of ILD, end-stage ILD, hypoxaemia at rest and desaturation on exercise at presentation.

Decline of FVC >10% of predicted or decline of diffusing capacity of the lungs for carbon monoxide >15%, or both, regardless of the extent of lung involvement for 12 months.

Worsening of ILD on HRCT with symptoms, at follow-up.

## Candidates for treatment, appropriate treatment regimens and monitoring of treatment response

### Candidates for treatment

Because of the highly heterogeneous nature of SSc–ILD, it is important to identify individuals with early ILD, especially those with a progressive ILD pattern, and to determine the ideal timing to initiate treatment as well as the appropriate treatment regimen and duration. Based on available data, patients who are candidates for treatment include all those with clinical ILD regardless of the extent of lung fibrosis on HRCT, all patients with abnormal PFT changes, patients with early rapidly progressive dcSSc with mild ILD on HRCT and/or on PFTs, and those with rapidly progressive fibrotic ILD or asymptomatic ILD at high risk for progression[5,42,60,70] (Box 3).

Asymptomatic individuals with high-risk factors for moderate-to-severe ILD should be treated early to improve morbidity and mortality, although the uncertain disease course in these patients means that consensus on the management strategy is still lacking. Results of an international survey of rheumatologists and pulmonologists demonstrate that screening and treatment of ‘subclinical’ ILD (defined as ILD with

minimal or mild fibrosis on HRCT, absence of symptoms, and normal PFTs) vary between countries and physicians. Up to 52% of participants would consider treating those patients if they were affected by dcSSc, and/or had anti-SCL70 antibodies, and/or if the disease duration was <18 months, and/or if GGO was present on HRCT, with MMF being the first-choice drug[73]. High-quality randomized controlled trials (RCTs) are needed to produce evidence-based guidelines with the objective of harmonizing therapeutic management of subclinical SSc–ILD, which remains an unmet need.

### Appropriate treatment regimens

The most common treatment for SSc–ILD is immunosuppression. In the Scleroderma Lung Study I (SLS), treatment with oral cyclophosphamide for 1 year with follow-up for another year improved lung function, dyspnoea, skin thickening, functional ability and health status, with effects continuing for several months after discontinuation[82]. However, except for a sustained influence on dyspnoea, all these effects waned and were no longer apparent at 24 months. In SLS II, MMF was as effective and safe as oral cyclophosphamide, with improvement of lung function over 24 months, and with lower toxicity[83]. Therefore, some experts recommend MMF as first-line therapy. Furthermore, treatment with cyclophosphamide for 1 year, followed by placebo for a second year, or with MMF for 2 years was associated with a reduction in the extent of lung fibrosis on HRCT[84]. In addition to improved lung function and radiographic fibrosis, a clinically meaningful improvement in self-reported dyspnoea was also observed, underlying the importance of patient-reported outcome measures (PROMs) as indicators of treatment response in SSc–ILD[85]. By contrast, in the FAST study comparing intravenous cyclophosphamide plus low-dose prednisolone for 6 months, followed by oral azathioprine for 6 months, with placebo for 12 months, the benefits of active treatment were no different from those of placebo probably because of the limited sample size or the disease being in a relatively stable phase[86]. In a phase II trial, tocilizumab (an anti-IL-6 drug) achieved preservation of FVC compared to placebo in patients with early dcSSc[87]. Furthermore, a post hoc analysis of the focuSSced trial showed that tocilizumab is effective in preserving lung function, irrespective of the extent of ILD and lung fibrosis at baseline[74]. The immuno-inflammatory, early fibrotic phase of dcSSc might represent a therapeutic window of opportunity to preserve lung function. In the RECITAL study, a head-to-head trial of rituximab versus cyclophosphamide in patients with early, treatment-naive, anti-SCL70$^{+}$ dcSSc with ILD, rituximab was as efficacious as cyclophosphamide, with fewer adverse effects[88,89]. Nintedanib, a tyrosine-kinase inhibitor used for the treatment of IPF, is also now considered a therapeutic option for patients with SSc–ILD. The results of the SENCIS trial showed that nintedanib can reduce the annual rate of decline of FVC in these patients, and its use in those with a progressive fibrotic phenotype could be a valid option in monotherapy or in combination therapy[60]. An expert consensus has suggested that nintedanib (as monotherapy or in combination with MMF, cyclophosphamide or tocilizumab) could be a therapeutic option for patients with progressive fibrotic ILD that persists despite immunosuppressive therapy, for patients with aggressive ILD (defined as relative FVC decline of >10% in 1 year) or with advanced disease at initial presentation (FVC <50% of predicted), and for patients with contraindications or intolerance to immunosuppression[40]. Treatment with pirfenidone does not seem to stabilize or improve lung function in SSc–ILD[90], although an initial upfront combination of pirfenidone with MMF seems to lead to more rapid improvement of lung function in the first 6 months, albeit with a similar overall improvement over 18 months compared with MMF plus placebo[91]. Autologous haematopoietic stem cell transplantation (AHSCT) can also be considered a therapeutic option, particularly for patients with rapidly progressive SSc who are at risk of organ failure. Notably, AHSCT is associated with a high risk of treatment-related adverse effects and mortality, so careful selection of patients is required to minimize this risk[92–94]. Lastly, lung transplantation can be considered for a minority of individuals with end-stage lung disease as well as for refractory disease[95].

On the basis of our clinical experience, we argue that immunosuppressive treatment should be considered for patients with clinical ILD and lung inflammation on HRCT (whatever the extent of that inflammation) or abnormal PFT changes, or with early, rapidly progressive dcSSc with mild ILD according to HRCT and/or PFTs, whereas treatment with nintedanib as first-line monotherapy or combination therapy should be considered mostly for patients with established lung fibrosis or a progressive fibrotic phenotype. Regarding immunosuppression, MMF should be the first-line therapy because of its lower toxicity with respect to cyclophosphamide. In cases of intolerance to MMF and in patients with early and rapidly progressive ILD, intravenous cyclophosphamide or rituximab could be treatment options. For patients with SSc–ILD refractory to immunosuppressive therapy, treatment with rituximab or tocilizumab is an alternative. Tocilizumab should be given as first-line therapy for patients with early dcSSc with elevated CRP and/or positivity for anti-SCL70 antibody or those with mild ILD or subclinical ILD and high risk of progression. Upfront combination therapy with immunosuppressive drugs and antifibrotics could also be considered for patients with early SSc–ILD characterized by both lung inflammation and fibrotic changes on HRCT or for patients with early SSc–ILD at high risk of rapid progression into a fibrotic phenotype. Therapeutic management for patients with dcSSc at high risk of development of ILD but without ILD or for patients with subclinical ILD at low risk of progression is less clear. Unfortunately, no RCTs have evaluated the effect of early treatment in these patients, making their management an unmet need. However, we recommend for these patients a very strict follow-up for early lung involvement by performing 6-monthly PFTs with $DL_{CO}$. AHSCT should be considered for patients with early progressive dcSSc at risk of organ failure and with no cardiac disease, whereas for patients with end-stage disease only of the lungs, lung transplantation is a possible alternative. The efficacy and safety of the various treatment regimens for SSc–ILD still need to be further determined[96–98].

### Response to treatment and predictors of response

The development of drugs that target specific molecules implicated in the pathogenetic mechanisms of SSc–ILD has changed its treatment profoundly. However, it is still necessary to identify, for each patient, the drug with the best likelihood of response combined with the best toxicity profile. Little evidence is available on the prediction of response to treatment in SSc–ILD. CXCL4 might have an important role in perpetuating profibrotic and pro-inflammatory activity in this disease, and changes in plasma CXCL4 concentrations are associated with lung function improvement in patients with SSc who receive immunosuppressive therapy[99]. A composite serum interferon–inducible protein score can predict response to immunosuppressive therapy with MMF or cyclophosphamide in patients with SSc–ILD[100]. Global RNA sequencing of peripheral blood cells from patients enrolled in the SLS II study and treated with MMF demonstrated that higher baseline expression of lymphoid lineage modules predicted better FVC course,

whereas higher baseline expression of myeloid lineage and inflammation modules predicted worse FVC course, consistent with the primary mechanism of action of MMF on lymphocytes[101].

## Definition and predictors of progression of ILD and mortality

One of the main unmet needs in SSc is the early identification of patients at high risk of progression of SSc–ILD (which is associated with increased mortality) as well as the lack of a valid and homogeneous definition of progression, which hinders the comparison of clinical studies. Currently used definitions include the EUSTAR consensus, which defines progression as an absolute FVC reduction of ≥10% or absolute FVC reduction of ≥5% to <10% and a $DL_{CO}$ reduction of ≥15%[102]; the OMERACT consensus, which defines progression as a relative FVC reduction of ≥10% or relative FVC reduction of ≥5% and <10% and a relative $DL_{CO}$ reduction of ≥15%[43]; and the ERICE consensus, which defines progression as a relative FVC reduction of ≥10%, or a relative FVC reduction of ≥5% and a $DL_{CO}$ reduction of ≥15%, or a relative FVC reduction of ≥5% and worsening of HRCT, or a relative FVC reduction of ≥5% and worsening of symptoms, or worsening of HRCT and of respiratory symptoms, all over 24 months despite treatment[103]. Selection of homogeneous cohorts of patients at the highest risk of progression of ILD might help the design of future clinical trials. Another definition, progressive pulmonary fibrosis, was defined by an international, multidisciplinary committee of experts as at least two of three criteria occurring within the past year with no alternative explanation[63]. The first criterion is worsening respiratory symptoms; the second is physiological evidence of disease progression, defined as an absolute decline in FVC of >5% within 1 year of follow-up or an absolute decline in $DL_{CO}$ (corrected for haemoglobin) of >10% within 1 year of follow-up. The third criterion is radiological evidence of disease progression, defined as increased extent or severity of traction bronchiectasis and bronchiolectasis, new GGO with traction bronchiectasis, new fine reticulation, increased extent or increased coarseness of reticular abnormality, new or increased honeycombing, or increased lobar volume loss.

Identification of predictors of progression and circulating biomarkers that can be used in clinical practice is an important aim[104–106]. In the Genetics versus Environment in Scleroderma Outcome Study (GENISOS), a prospective, observational cohort of 266 patients with early SSc, the presence of anti-SCL70 antibody was the only variable associated with differential FVC levels predicting the rate of FVC decline within the first 3 years of follow-up[107]. A decline in either FVC or total lung capacity of >15% during a 6-month interval could also indicate a progressive phenotype. Lastly, an initial modified Rodnan skin score (mRSS) of >12 points in individuals with SSc with recent-onset skin disease (<1 year) and/or an increase in mRSS of >12 points during a 6-month interval could indicate that mRSS is a helpful tool to classify ILD early for treatment initiation[102]. The pneumoproteins KL6, surfactant protein D and CCL18, which are increased in individuals with SSc–ILD, can be considered as biomarkers for short-term progression of SSc–ILD[77]. The evidence-based SPAR prediction model of rapid lung worsening consists of the combination of lower $SpO_2$ (partial oxygen saturation) after 6MWD testing and arthritis (ever), which have been considered as independent baseline predictors for progression of mild SSc–ILD at 1-year follow-up from real-life data in two independent SSc cohorts[108]. Lastly, the ILD-GAP model (sex, age, FVC and $DL_{CO}$) generated to predict mortality risk in individuals with ILD, enhanced with KL6 serum level, can provide a better estimation of disease progression in ILD[109].

## Patient selection and outcome measures for future clinical trial design

An unmet need for RCTs is the ability to identify appropriate outcome measures of ILD activity without relying on severity and extent of organ involvement (Box 2). Primary outcome measures in SSc–ILD studies approved by regulatory agencies are focused on functional lung volume, particularly FVC[76]. Similarly, OMERACT has endorsed FVC for use in clinical trials in SSc–ILD[11]. As a secondary outcome measure, a few studies have used the extent of lung involvement on HRCT, whereas $DL_{CO}$ is not considered a validated outcome measure of SSc–ILD because it can be influenced by pulmonary vascular disease. Other outcome measures of lung function and physiology, including total lung capacity, 6MWD, hospitalization, exacerbation, mortality, time to death and death, were included as outcomes in some trials but without success. Given the lack of validated prognostic biomarkers for SSc–ILD, pulmonary function and extent of lung involvement are currently recommended.

Trials in SSc–ILD currently measure the effects of the disease process on lung volumes but do not assess the disease process itself as a direct measure of SSc–ILD activity is still missing. The use of fluorodeoxyglucose PET–CT could help to assess severity and predict lung function outcomes as it shows higher lung fluorodeoxyglucose uptake in individuals with SSc–ILD than in those without[110,111]. An important point that should be addressed in future clinical trial design is patient stratification in a homogeneous cohort for their SSc–ILD not only from a clinical perspective but also from a trial-enrichment strategy, thus giving RCTs further comparability and validity. Patients should ideally have similar features of lung involvement such as lung disease onset, HRCT pattern and lung progressive disease status (defined according to the latest standardized criteria).

Trial-enrichment strategies could facilitate the assessment of progressive SSc–ILD by the inclusion of patients likely to contribute meaningfully to the primary end point and therefore likely to benefit from treatment. Composite end points, including clinical and physiological parameters, are important to facilitate clinical trial enrichment as well as to define progressive SSc–ILD, performing better than any isolated single outcome measure[112]. For instance, the cyclophosphamide treatment effect observed from using the composite outcome of FVC% of predicted and patient-reported outcomes was stronger than the effect observed using FVC% alone[113].

An outcome measure should correlate with disease course and activity and should be a crucial part of a treatment being investigated in a clinical trial, enabling differentiation between first-line efficacious drugs and background therapies. The choice of a standardized comparator under treatment with immunosuppressive therapy (MMF or cyclophosphamide) or background use of glucocorticoids is another point to consider for future trial design for SSc–ILD. In this context, in the SENCIS trial, the group of patients treated with both nintedanib and MMF had a slower decline in lung function than those treated with only MMF or nintedanib, underlying the fact that background therapy with MMF should be allowed in future trials[60].

PROMs are important for routine clinical assessment and shared decision-making and for clinical trials as they provide evidence of the effects of the disease and new treatment interventions on patient quality of life. However, at present, the lack of a specific and validated PROM for SSc–ILD is an important unmet need. A comprehensive PROM for overall SSc, the Systemic Sclerosis Impact of Disease (ScleroID) questionnaire, was developed and validated by OMERACT criteria in a large European observational clinical cohort study. However, further

**Table 1 | Ongoing clinical trials for SSc–ILD**

| Trial identifier | Intervention | Mechanism of action | Number of patients | Primary end point | Secondary end point | Duration of study | Date of completion |
|---|---|---|---|---|---|---|---|
| NCT02370693 | Bortezomib | Proteasome inhibitor | 30 SSc–ILD | AEs | mRSS and change in FVC | 48 weeks | Unpublished |
| NCT04837131 | Ixazomib | Oral proteasome inhibitor | 12 SSc–ILD | AEs | Change in mRSS, FVC, $DL_{CO}$, TLC, dyspnoea index | 28 weeks | April 2024 |
| NCT03198689 | Brentuximab vedotin | Anti-CD30 monoclonal antibody | 11 dcSSc active | mRSS | Change in FVC and $DL_{CO}$ | 48 weeks | February 2023 |
| NCT04948554 | ACE-1334 | TGFβ1 and TGFβ3 inhibitor | 210 SSc with/ without ILD | AEs | Pharmacokinetics, pharmacodynamics of ACE-1334 | 48 weeks | May 2028 |
| NCT05270668 | PRA023 | anti-TL1A monoclonal antibody | 100 SSc–ILD | AEs, FVC annual change | Change in HRCT, ACR CRISS | 50 weeks | June 2024 |
| NCT05177471 | Ruxolitinib | JAK inhibitor | 20 SSc–ILD | Change in FVC | Change in $DL_{CO}$, skin fibrosis | 12 months | July 2022 |
| NCT05925803 | Anifrolumab | Type I interferon receptor inhibiting IgG1κ monoclonal antibody | 306 SSc | CRISS-25 | Change in mRSS, FVC, $DL_{CO}$, HRTC | 52 weeks | December 2027 |
| NCT05878717 | Belimumab | B cell-activating factor monoclonal antibody | 300 SSc–ILD | Absolute change of FVC | Change in mRSS, $DL_{CO}$, FACIT | 52 weeks | February 2027 |
| NCT05085444 | CAR T cell therapy | CD19/BCMA CAR T cell therapy | 9 refractory SSc | AEs, TEAEs | Progression-free survival, overall survival | 90 days/ 2 years | October 2024 |
| NCT05321082 | BI 1015550 | Phosphodiesterase 4B inhibitor | 1,041 progressive fibrosing ILDs | Absolute change in FVC | Change in $DL_{CO}$, symptoms | 52 weeks | November 2024 |

AEs, adverse events; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CRISS, Composite Response Index in Systemic Sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; $DL_{CO}$, diffusing capacity of the lungs for carbon monoxide; FACIT, Functional Assessment of Chronic Illness Therapy; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; JAK, Janus kinase; mRSS, modified Rodnan skin score; SSc, systemic sclerosis; TEAEs, treatment-emergent adverse events; TLC, total lung capacity.

studies are needed to validate ScleroID as a potential PROM for future clinical research trials in SSc–ILD[114].

## Untapped pathological pathways

An ongoing aim is to prevent the development of severe lung fibrosis or to reverse it. Several molecular pathways and cellular targets involved in SSc pathogenesis are currently under evaluation as potential therapeutic targets. Bortezomib, a proteasome inhibitor, blocks TGFβ and FGF2 signalling in vitro and prevents the development of skin and lung fibrosis in a mouse model of pulmonary fibrosis[115,116]. A small phase II trial with bortezomib in SSc is ongoing (NCT02370693) but the results have not yet been reported. ACE-1334 is a TGFβRII–IgG1 fusion protein that inhibits TGFβ1 and TGFβ3 but not TGFβ2. ACE-1334 has shown robust antifibrotic activity in multiple preclinical models of fibrosis, and a phase I–II trial in SSc is currently recruiting patients (NCT04948554). PRA023 is an IgG1 humanized monoclonal antibody that blocks TNF-like ligand 1A (TL1A, a signalling protein that promotes inflammation and fibrosis), and a phase II study of PRA023 in SSc–ILD is currently recruiting patients (NCT05270668). Ruxolitinib, a Janus kinase (JAK) inhibitor, has antifibrotic effects in the skin and lungs of a bleomycin-induced mouse model of SSc–ILD[117], and a small observational study is currently ongoing (NCT05177471). PDE4 inhibitors that preferentially target PDE4B have antifibrotic effects in a mouse model of bleomycin-induced pulmonary fibrosis, reversing the decrease in pulmonary function[118], and a phase III study of the PDE4B inhibitor BI 1015550 is currently recruiting patients with progressive ILD (NCT05321082). Belimumab, a recombinant human IgG1λ monoclonal antibody that specifically binds to soluble BAFF and inhibits the survival of B cells[119], is under investigation in an ongoing phase II trial (NCT03844061).

Despite the availability of immunosuppressive and antifibrotic drugs, treatment of SSc–ILD needs to improve the way that lung fibrosis is currently targeted, raising the question of whether untapped pathological pathways can identify prodromic damage before it is clinically detectable. Data from single-cell RNA sequencing of IPF and SSc–ILD lung tissue and tissue obtained from donors without pre-existing lung disease showed different patterns of interferon signatures between the two fibrotic diseases. In patients with IPF, IFNγ signalling was amplified, whereas in SSc–ILD, type I interferon signalling was upregulated[18]. In individuals with early SSc, type I interferon signalling in the peripheral blood correlates with both inflammation and fibrosis[120]. The type I interferon signature remains an active mechanism in advanced SSc–ILD as patients with the UIP histopathology pattern also have upregulated of type I interferon.

Numbers of pDCs in the bronchoalveolar lavage of individuals with SSc–ILD are greater than in healthy individuals and correlate with the severity of lung fibrosis in HRCT[121]. Numbers of pDCs are greater and pDCs are more transcriptionally active in SSc–ILD lung tissue than in IPF lung tissue. A proteome-wide analysis of pDCs showed that CXCL4 concentrations correlated with both fibrotic and vascular manifestations[122]. Functional inhibition of pDCs was effective in preventing skin activation and fibrosis in preclinical models of SSc[123]. Release of mitochondrial DNA can lead to activation of the type I interferon pathway through cGAS, a specific cytosolic receptor for free DNA, which in turn activates the endoplasmic reticulum membrane protein stimulator of interferon genes (STING) and type I interferon

production. Consistent with these findings, mitochondrial DNA concentrations are increased in SSc plasma, with the ability to function as damage-associated molecular patterns and interact with pattern recognition receptors[124].

Type I interferon signals through IFNAR1 and IFNAR2, which in turn activate JAK–STAT signalling pathways, resulting in the expression of pro-inflammatory and profibrotic cytokines. JAK inhibitors have the potential to block deleterious interferon and other profibrotic cytokine activation in SSc[125]. Anifrolumab, an anti-IFNAR1 monoclonal antibody, improves skin thickening in adults with SSc through sustained inhibition of the type I interferon gene signature and suppression of T cell activation and collagen accumulation[126]. Clinical trials of interferon-neutralizing agents or agents that inhibit the upstream regulators and/or the downstream effects of interferon signalling in carefully selected patients with an 'interferon signature' are required to determine whether such a strategy has a beneficial role in SSc–ILD.

Alveolar epithelial cell damage (loss of alveolar type 1 epithelial cells, presence of aberrant basaloid cells) occurs in SSc–ILD and can lead to architectural distortion and ECM deposition[18]. Rapid clearance of $^{99m}$Tc-DTPA, a marker of the extent of epithelial damage, predicts a rapid FVC decline, independent of disease severity[127]. Currently, very few drugs target the epithelium and those that do mostly target proteins expressed by epithelial cells. Galectin 1 and galectin 3 are expressed on epithelial cells and elevated in individuals with lung fibrosis[128], and a phase II study investigating the efficacy and safety of GB0139 (an inhaled galectin 3 inhibitor) in patients with IPF did not meet its primary end point of change from baseline in the rate of decline of FVC; development of GB0139 was therefore discontinued[129]. Lastly, chimeric antigen receptor (CAR) T cells targeting CD19 showed promising results in a patient with severe, refractory SSc, with a rapid improvement of heart, skin and joint involvement and stabilization of lung fibrosis[130]. A phase I trial using CAR T cells to target B cells in patients with refractory SSc was initiated in 2021 and is anticipated to be completed in 2024 (NCT05085444). These data are summarized in Table 1.

## Conclusions

SSc is a rare, highly heterogeneous, systemic autoimmune disease with high mortality. ILD is one of the main causes of morbidity and mortality in individuals with SSc. Early diagnosis and treatment of SSc–ILD, together with systematic management and strict monitoring of the treatment response, are of high importance. Validated diagnostic and prognostic markers are needed to identify and stratify patients at risk for SSc–ILD and for the progression of ILD. Efforts are ongoing to define the profiles of patients considering the specific patho-phenotype of ILD, disease onset and standardized clinimetric core sets, and well-designed clinical trials are needed to identify those who should be treated early and aggressively with old and new drugs to avoid a poor outcome associated with lung involvement.

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## Author contributions

All authors researched data for the article. All authors contributed substantially to the discussion of content. V.L., F.D.G., R.G. and F.C. wrote the article. V.L., F.D.G., R.G. and F.C. reviewed and/or edited the manuscript before submission.

## Competing interests

The authors declare no competing interests.

## Additional information

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