Article published online: 2024-05-07

Interstitial Lung Disease Associated with Systemic Sclerosis

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Semin Respir Crit Care Med 2024;45:342–364.

Abstract

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by a tripod combining vasculopathy, fibrosis, and immune-mediated inflammatory processes. The prevalence of interstitial lung disease (ILD) in SSc varies according to the methods used to detect it, ranging from 25 to 95%. The fibrotic and vascular pulmonary manifestations of SSc, particularly ILD, are the main causes of morbidity and mortality, contributing to 35% of deaths. Although early trials were conducted with cyclophosphamide, more recent randomized controlled trials have been performed to assess the efficacy and tolerability of several medications, mostly mycophenolate, rituximab, tocilizumab, and nintedanib. Although many uncertainties remain, expert consensus is emerging to optimize the therapeutic management and to provide clinicians with evidence-based clinical practice guidelines for patients with SSc-ILD. This article provides an overview, in the light of the latest advances, of the available evidence for the diagnosis and management of SSc-ILD.

Keywords
- interstitial lung disease
- systemic sclerosis
- SSc-ILD
- fibrosis
- immunosuppression
- connective tissue diseases

Systemic sclerosis (SSc) is a rare, complex, and heterogeneous autoimmune disease of the connective tissue, characterized by a tripod combining vasculopathy, fibrosis, and immune-mediated inflammatory processes.[1] It manifests as diffuse fibrosis, the variability of which explains the extent of clinical heterogeneity and defines the severity of the disease.[2] The fibrotic and vascular pulmonary manifestations of SSc, particularly interstitial lung disease (ILD), are the main causes of morbidity and mortality.[1,3] Although management options have long been limited to cyclophosphamide (associated with significant morbidity) or treatment abstention and follow-up, the armamentarium of drugs available to treat SSc-ILD has recently expanded. Several randomized controlled trials (RCTs) have recently been conducted with both immunosuppressants and antifibrotics, with the aim of stabilizing the progression of SSc-ILD. As a consequence, there is renewed interest in the early detection and diagnosis of ILD in patients with SSc, and a screening strategy with special emphasis on imaging needs to be implemented.[4] This article provides an overview, in the light of the latest advances, of the available evidence for the diagnosis and management of SSc-ILD.

Epidemiology and Risk Factors

Prevalence and Mortality Rates

The prevalence of ILD in SSc ranges from 25 to 95% according to the methods used to detect it (e.g., lung function tests, CT scan, or autopsy).[5] Pulmonary involvement may be present at the time of diagnosis, sometimes severe from the outset, or may develop at a later stage, with a predilection for appearing in the first 5 years following diagnosis.[5] Moreover, the

article published online
May 7, 2024

Issue Theme Pulmonary Complications of Connective Tissue Diseases; Guest Editors: Cormac McCarthy, MD, PhD, FRCPI, and David N. O'Dwyer, MB BCH BAO, PhD

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0044-1786698.
ISSN 1069-3424.

proportion of patients with ILD among those with SSc depends on the length of follow-up. For example, in a large study in which patients were followed up for 15 years, 42% of patients with diffuse SSc and 22% of patients with limited SSc developed clinically significant pulmonary fibrosis.[6]

Contributing to almost 35% of deaths, ILD was the leading cause of mortality in patients with SSc in two studies published in 2007 to 2010.[2,7] In a more recent study of 2,719 certificates of death related to SSc, 31% of deaths had a cardiac cause and 18% had a respiratory cause, including 16.6% due to ILD.[8] ILD was a predictive factor for low survival among SSc patients with a hazard ratio (HR) of 1.26, 95% confidence interval (CI) of 1.08 to 1.46.[8] These findings support the view that early detection of lung involvement is imperative in all patients with SSc.

In a recent French nation-wide study based on hospital insurance claims, 34% of SSc patients had ILD, with a 5-year overall survival of 70.8%.[9] In another nation-wide study on the burden of SSc in the United States, using death certificate data, the age-adjusted mortality rate decreased by 3% per year from 6.6 in 2003 to 4.3 per 1,000,000 population in 2016.[10] While SSc mortality related to ILD or to pulmonary arterial hypertension remained stable during this period of time, the death rate for SSc-ILD and concomitant pulmonary hypertension increased between 2003 and 2016.[10]

Risk Factors

Risk factors associated with the presence of ILD in patients with SSc include the presence of the diffuse cutaneous form of SSc compared with limited cutaneous SSc,[4,11,12] Afro-Caribbean ethnicity,[13] male gender,[14–16] low values of forced vital capacity (FVC)[6] and diffusion capacity of the lung for carbon monoxide (DLCO),[14] and the presence of anti-Scl-70/anti-topoisomerase I antibodies[11,12] as opposed to anti-centromere antibodies which are more commonly linked to the development of pulmonary hypertension. Interestingly, in the large EUSTAR cohort, the autoantibody-only model outperformed the cutaneous-only sub-setting for risk-stratifying people with SSc,[12] similar to an earlier study from the same cohort.[11] In other words, the antibody status is more relevant than the limited or diffuse phenotype of cutaneous involvement to inform the risk of ILD in patients with SSc (AUC: 0.76 [0.75–0.77] vs. 0.71 [0.70–0.72]).[12] However, these risk factors are neither absolute nor necessary, and it is important to note that ILD can develop in all patients with SSc. Due to its influence on mortality, identification of SSc-ILD requires a high level of awareness in all patients with or without respiratory symptoms.

It is also necessary to look for risk factors linked to the occupational environment, and in particular exposure to crystalline silica increasing the risk of SSc and of ILD in the so-called Erasmus syndrome.[17–20] Such exposures are generated, for example, during the cutting of "artificial stone" widely used for kitchen benchtops (or countertops).[21] Several studies also indicate that exposure to organic solvents, in particular trichloroethylene and other chlorinated solvents, is linked to the incidence of SSc, particularly in males.[19,22,23] ILD is considered more widespread and more severe in individuals suffering from SSc in an exposed occupational context.[24,25] Exposure to silica may be associated with more severe evolution of ILD in SSc.[24,26] Patients with SSc should be screened for occupational exposures at the time of diagnosis, as they represent risk factors for progression.[26]

Pathophysiology

The pathological hallmark of SSc is an aberrant and excessive deposition of extracellular matrix, especially collagen, which may affect all major organs. Several factors associated with fibrogenesis have been described, including epithelial and endothelial cell dysfunction, recruitment, proliferation and differentiation of fibroblasts, myofibroblast activation, and overproduction and crosslinking of extracellular matrix molecules, which are largely orchestrated by cytokines, coagulation factors, chemokines, and growth factors especially transforming growth factor-β (TGF-β).[27,28] Once the process of fibrogenesis has been initiated, a self-amplifying loop takes place,[29] through phenotypic changes in alveolar epithelial cells and fibroblasts through exposure to the microenvironments within the extracellular matrix and mechanical stress.[30] Fibroblasts in the fibrotic lung have probably multiple origins, including the proliferation of resident pulmonary fibroblasts, the recruitment and mesenchymal transition of epithelial alveolar cells, endothelial cells, pericytes, and circulating fibrocytes.[31]

Although the pathophysiology of SSc remains to be fully elucidated, microvascular and endothelial damage are considered the initial steps. The autoimmune response then leads to inflammation, and to a progressive process of fibrosis. In the skin, microvascular involvement is characterized by abnormalities of the capillaries best seen by capillaroscopy, Raynaud phenomenon, digital ulcers, renal crisis, and ischemia.[28] In the lung, it is less clear whether the initial event may be an injury to the alveolar epithelial cell (as reflected by the release of surfactant protein D or Krebs von den Lungen-6 [KL-6]) or to the pulmonary microvasculature.[32] However, microvascular changes appear very early in the course of disease, accompanied by both interstitial and alveolar inflammation. Although damage to endothelial cells occurs at an early stage, the origin of this damage remains poorly understood. One hypothesis suggests that oxidation may play a key role in the pathophysiology of this disease[33] and that autoimmunity may be involved in the pathogenesis of lung damage,[34] since several functional autoantibodies identified in SSc represent potential culprits for the vascular injury.

Research groups have identified the presence of antibodies directed against endothelial cells in the plasma of patients with SSc and pulmonary fibrosis, although the pathogenic effect of these antibodies has not been formally established.[35] Activation of endothelial cells leads to the activation of the coagulation process, in particular the activation of thrombin, a phenomenon occurring early in the course of lung disease, as well as production of endothelin-1, in turn stimulating fibroblast activity.

Early inflammation of the alveoli is also present, as shown by increased cellularity in the bronchoalveolar lavage (BAL)

fluid, with an increase in the percentage of neutrophils and eosinophils, and sometimes a change in the lymphocyte ratio toward a decrease in the CD4/CD8 ratio. Antibodies specifically targeting the α-subunit of the platelet-derived growth factor receptor (PDGFR) may induce the production of oxygen-free radicals and collagen by fibroblasts, promoting their transformation into myofibroblasts. Whether such mechanism plays an important role in SSc-ILD in humans remains to be confirmed.[36] A more detailed description of the pathogenesis of SSc can be found elsewhere.[32] The interplay between potential triggers (environmental factors, infections), autoimmunity and inflammation, and genetic and epigenetic predisposition, is still poorly understood in SSc-ILD.

Diagnosis

Clinical Presentation

Because SSc can affect multiple organs with varying severity and with different timeframes, a comprehensive assessment is warranted at diagnosis of SSc to phenotype the disease. SSc initially manifests with Raynaud phenomenon, which may be present 5 to 10 years before non-Raynaud manifestations in limited cutaneous SSc, and 1 to 2 years before the development of non-Raynaud manifestations or develop in parallel to organ manifestations in diffuse cutaneous SSc.[1] The American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria for SSc are described in ►**Table 1**.[37]

The clinical pulmonary manifestations of SSc-ILD are nonspecific, with initially an often-mild symptomatology characterized by dyspnea and dry cough. Basal crackles typical of pulmonary fibrosis are not always present. In severe cases, reduced mobility of the chest due to sclerosis of thoracic soft tissue may be seen upon clinical examination.

Pulmonary involvement in SSc is usually detected upon systematic screening of a patient suspected or known to have SSc, but may be the initial and revealing presentation of the disease,[38] particularly in the clinical entity known as SSc *sine scleroderma*.[39] This *forme fruste* of SSc described in particular in patients exposed to mineral particles shares with limited cutaneous SSc the same clinical and biological manifestations, with perhaps a greater frequency of respiratory manifestations,[39] placing the pulmonologist at the forefront for its recognition. Diagnostic criteria for scleroderma *sine scleroderma* have been proposed but are not validated.[16]

Pulmonary Function Tests

A restrictive functional profile is generally present, with reduced FVC.[40] However, FVC can be normal even in patients with obvious fibrosis on high-resolution computed tomography (HRCT).[41,42] Indeed, in several studies, a large proportion of patients with SSc-ILD diagnosed using HRCT had normal spirometry, indicating that pulmonary function tests alone are an inadequate screening tool for SSc-ILD.[41–44]

DLCO is also decreased.[40] However, a reduced DLCO may also be the result of pulmonary hypertension and/or emphysema.[45–47] It is therefore important that DLCO be interpreted in the context of the overall CT scan and clinical function to optimize diagnostic management.

In a recent, large, prospective study of all patients SSc resident in Norway, patients with ILD at baseline had a mean FVC of $94 \pm 20.9\%$ of predicted value, and a mean DLCO of $69.4 \pm 20.2\%$ of predicted. The extent of fibrosis on CT at baseline was $10.9 \pm 14.2\%$ of total lung volume.[42] This lung function profile probably denotes the benefit of systematic screening for ILD and early detection. As a comparison, in the landmark study by Goh et al published in 2008, the mean FVC was $78.7 \pm 18.6\%$ of predicted, and the mean DLCO was $55.1 \pm 16.8\%$.[48]

Table 1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis[37]

Items	Sub-items	Weight
Skin thickening of the fingers of both hands extending proximal to the MCP joints *(sufficient criterion)*		9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Whole finger, distal to MCP	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*		2
Raynaud phenomenon		3
SSc-related autoantibodies (anti-centromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anti-centromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3
Patients with a total score of ≥ 9 are classified as having definite systemic sclerosis		

Abbreviation: MCP, metacarpophalangeal joints.

Imaging

The most sensitive and specific way to diagnose SSc-ILD is by HRCT, and experts recommend that HRCT should be performed in all patients at the time of initial diagnosis of SSc.[49] Detailed practical recommendations for performing HRCT scans and interpreting the results for patients with SSc-ILD can be found elsewhere.[49,50]

ILD as such is present in less than 50% of patients; however, reticulation and ground-glass attenuation, which are generally predominant in the posterior and subpleural areas, are observed in around 90% of cases. The most common pattern seen on HRCT is non-specific interstitial pneumonia (NSIP) (70–80%) (►**Fig. 1**),[51] followed by a pattern of usual interstitial pneumonia (UIP) (10%). Ground-glass opacities are usually the predominant abnormality and are more consistent with sparse fibrosis than alveolitis.[52] With time, ground-glass opacities are progressively replaced by fibrosis.[53–55] Honeycombing may also be present in up to a third of cases.[54] The "four corners sign," a pattern of fibrotic ILD on CT that focally or disproportionately affects the bilateral posterosuperior lower lobes and anterolateral mid-upper lobes, is suggestive of SSc-ILD as compared with other ILD diagnoses.[56]

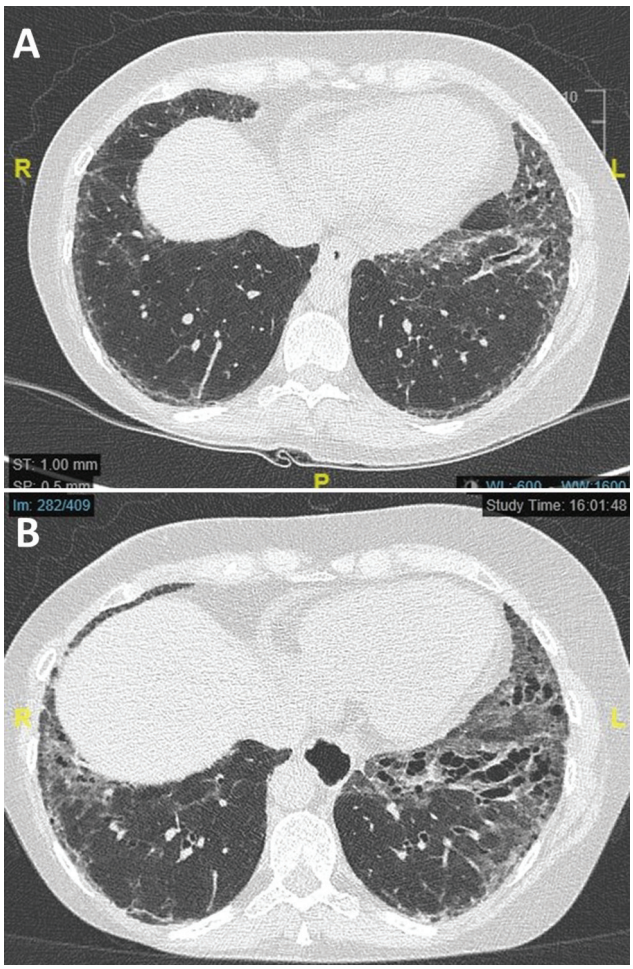

Fig. 1 Chest HRCT in a male patient with SSc-ILD, demonstrating peripheral reticular lesions and ground-glass opacities in areas associated with fibrotic lesions (bronchiectasis), with subpleural sparing in favor of a nonspecific interstitial pneumonia pattern. Note that esophageal dilatation is seen in the lower part of the lungs.

The extent of CT lesions is inversely correlated with FVC, and is strongly linked with mortality, with a HR of all-cause mortality of 2.45 (95% CI, 1.57–3.92; $p = 0.0005$) in patients with disease extent > 20% of total lung volume (►**Fig. 2**) compared with those with extent ≤ 20%.[48] The extent of fibrosis is associated with mortality independently of the CT pattern.[57] CT can also contribute to measuring lung volumes as shown in patients with various ILDs, including SSc-ILD.[58]

The CT scan may also reveal esophageal dilatation (which is pathological when it exceeds one-third of the height of the thorax) or, more rarely, soft tissue calcifications (which may also be seen in polymyositis), pointing to SSc in the context of unexplained ILD.[59,60] Mediastinal lymph node enlargement may be present but is generally multiple, not bulky, moderately hypermetabolic, and located at the base of the mediastinum lymph node chains.[61]

Pleuroparenchymal fibroelastosis lesions affecting the visceral pleura and subpleural parenchyma can also be seen on HRCT in 18% of cases, and are associated with a poor prognosis,[62] independently of underlying ILD severity.[63] In SSc patients with precapillary pulmonary hypertension, CT signs of pulmonary veno-occlusive disease are frequently observed, including lymph node enlargement, centrilobular ground-glass opacities, and septal lines.[64] Emphysema is independently associated with SSc. Combined pulmonary fibrosis and emphysema[65] is present in ~7 to 18% of patients with SSc-ILD, and is associated with worse survival than SSc-ILD without emphysema.[47,66]

Unsupervised, radiomics-based risk stratification using routine CT images identified clinically and prognostically distinct SSc-ILD patient clusters.[67] For example, in one study, elastic registration of CT scans combined with a deep learning classifier aided in the diagnosis of morphologic and functional worsening of ILD in patients with SSc.[68] Such radiomic profiling may help identifying patients at risk of progression complementary to clinical and conventional CT prognostic information.

Bronchoalveolar Lavage

BAL reveals abnormalities in almost half of patients with SSc, even in the absence of any radiological or HRCT abnormalities.[69] It is characterized by an increase in the total number of cells collected, an increase in the relative number of neutrophils and/or eosinophils, and, more rarely, an increase in lymphocytes (with a decrease in the CD4/CD8 ratio).[70] However, BAL provides only limited prognostic information in SSc-ILD.[71] BAL abnormalities persist after treatment with cyclophosphamide.[72] Therefore, the usefulness of BAL is questionable outside of clinical suspicion of infection or malignancy. BAL may be useful in demonstrating the abnormal presence of pulmonary accumulations of mineral or metallic particles in cases of suspected occupational exposure. It should be emphasized that, at present, there is no justification for systematically performing BAL at the presentation of ILD, or for repeating BAL to monitor lung involvement in scleroderma.

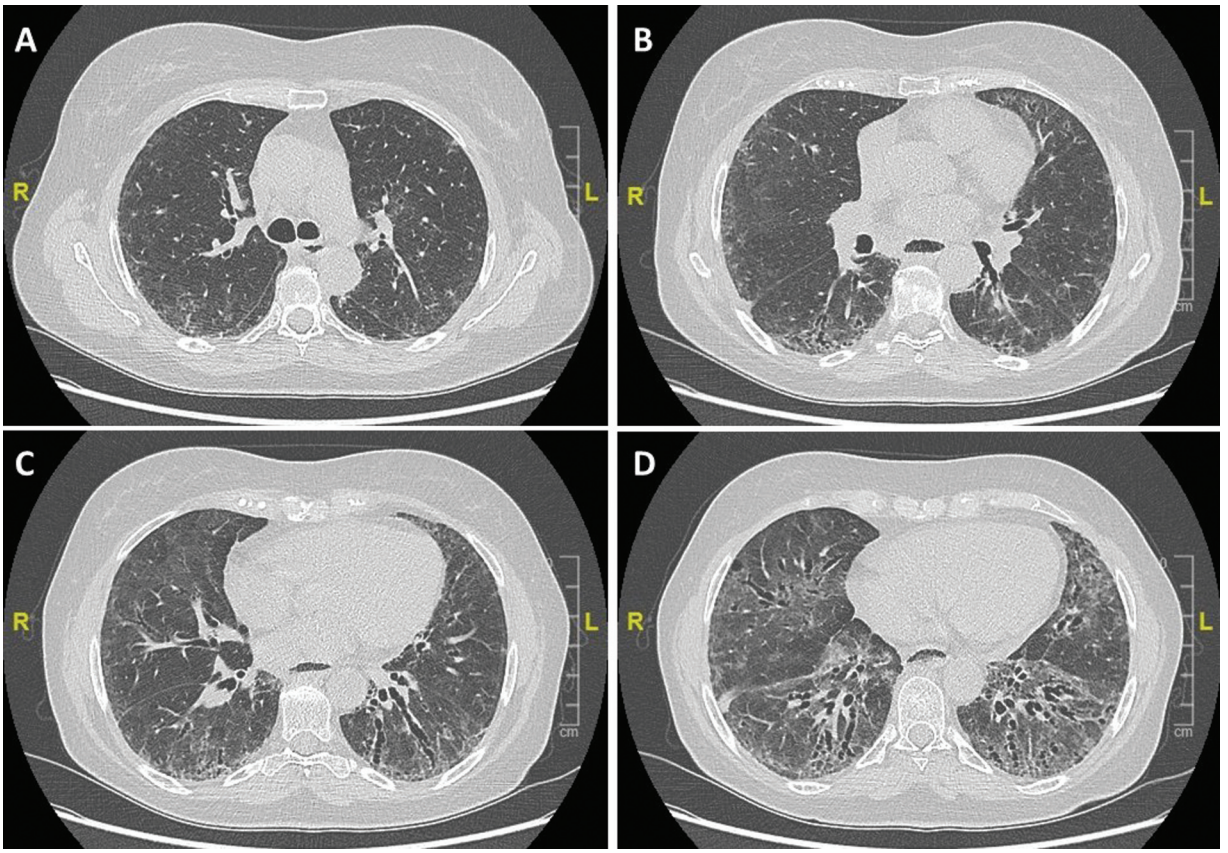

Fig. 2 Chest HRCT in a female patient with SSc-ILD demonstrating extensive peripheral reticular lesions and ground-glass opacities in areas associated with fibrotic lesions (bronchiectasis) in favor of a nonspecific interstitial pneumonia pattern. Note that esophageal dilatation is seen in the lower part of the lungs.

Histopathology

NSIP is the most common pathological pattern found in lung histology of patients with SSc,[73–75] although results from series may have been affected by selection biases. NSIP in SSc does not differ pathologically from idiopathic NSIP,[76] although a pattern of centrilobular fibrosis may be associated.[77] In a series of 80 surgical lung (open or thoracoscopic) biopsies performed in SSc at presentation, NSIP accounted for 77% of the cases, with fibrosing NSIP being present in three out of four cases, while cellular NSIP occurred in one out of four cases. In comparison, a histologic pattern of UIP was found only in six cases, end-stage lung in further six, and other lesion types in the remaining six.[74] Importantly, patient survival did not appear to be associated with the specific pathological pattern, but was rather related to the severity of the lung involvement at the time of diagnosis and to the progressive disease as assessed by a decrease in DLCO during serial examinations.[74] At the time of lung transplantation, however, UIP is the predominant histopathological pattern in SSc.[78] Overall, surgical lung biopsy should not be routinely performed in SSc patients, but can be useful in rare cases, such as an atypical HRCT pattern, and suspected differential diagnosis including malignancy. Experience of transbronchial lung cryobiopsy is limited in patients with SSc-ILD; whether it may inform treatment decision warrants further research.[79]

Serological Profile and Biomarkers

In the context of SSc, the involvement of antibodies in ILD represents a rapidly expanding field of study, highlighting the importance of immunological markers in the prognosis and risk stratification of patients. Recent research indicates that specific autoantibodies are closely associated with an increased risk of developing ILD in SSc. For example, anti-topoisomerase I (anti-Scl-70) antibodies have been strongly correlated with an increased prevalence and severity of ILD in SSc, offering prospects for the screening and monitoring of ILD in these patients.[6,11,12] In addition, the study of anti-centromere antibodies has demonstrated their usefulness in identifying patients less likely to develop severe ILD, suggesting a potential role in the prognosis of the disease. These findings highlight the diversity of clinical presentations of SSc and the need for personalized approaches to the management of ILD, based on patients' antibody profiles. However, it is important to note that these associations are neither automatic nor exclusive.

Interestingly, SSc patients with a persistent inflammatory phenotype, characterized by persistently elevated C-reactive protein levels ($\geq$5 mg/L), showed features of more severe ILD and had a six-fold increased risk of mortality within 5 years of the start of the study.[80,81] Repeated measurement of a biomarker, such as C-reactive protein, could improve not only risk stratification, but also monitoring of treatment response

and modification of treatment plans for patients with SSc.[80] Increased C-reactive protein level contributes to identifying patients with a high risk of ILD progression, especially if carrying anti-Scl70 antibodies, in whom initiation of immunosuppressive therapy may be warranted without waiting for disease progression.[1,80]

Screening and Diagnostic Approach

The poor prognosis of ILD in SSc makes systematic screening essential at disease onset. Chest HRCT is the most sensitive and specific method to diagnose ILD in SSc. In an evidenced-based consensus statement conducted through a modified Delphi process based on a systematic literature review analysis, a panel of Europe-based pulmonologists, rheumatologists, and internists with expertise in SSc-ILD recommended that patients with SSc should be screened for ILD using HRCT, particularly if they are showing one or more risk factors.[4] The same statement indicated that HRCT is the primary tool to diagnose ILD in patients with SSc. Another modified Delphi process completed by pulmonologists and rheumatologists mostly from North America, with expertise in the management of patients with SSc-ILD, recommended that all patients with SSc be screened for ILD by chest auscultation, spirometry with DLCO, HRCT, and/or autoantibody testing.[82] As individual items were separately voted for in this initiative, no screening or algorithm was provided.

Non-validated alternatives to HRCT for ILD screening in SSc include spirometry and/or DLCO, which lack sensitivity; magnetic resonance imaging and positron emission tomography scanning, which may be useful to detect early inflammatory changes but are not appropriate for broad, systematic screening of patients with SSc; single-photon emission CT, a promising technique that warrants further study; and thoracic ultrasound, which has not been validated for ILD screening and lacks specificity.[49] Another potential approach to help identify patients with ILD is nailfold videocapillaroscopy, which is routinely used to noninvasively detect microangiopathy patterns associated with SSc, and may also improve the detection of patients at high risk of ILD and heart/lung involvement.[83]

In addition to systematic screening for ILD, early identification of symptomatic ILD is warranted, as respiratory symptoms such as frequent cough or dyspnea could suggest the presence of ILD in patients with SSc,[4] and should trigger further examination including chest HRCT.

To ensure early identification of ILD and to provide baseline measurements for comparison with future assessments, the workup should include[4,5,82]:

- Complete clinical respiratory assessment, including systematic search for dry crackle (rales) at the basis of the lungs.
- HRCT, to be repeated if new respiratory symptoms or respiratory function deteriorates.
- Pulmonary function test including spirometry to assess FVC, and measurement of DLCO. The risk of developing lung damage is higher in the first few years of the course of SSc. Therefore, to ensure early detection but also to monitor progression of ILD, pulmonary function tests are required every 4 to 6 months for the first 3 to 5 years following a diagnosis of SSc.[84] In SSc patients without ILD or with stable or controlled ILD after the first 3 to 5 years, annual pulmonary function tests are useful to monitor both onset and progression of ILD.[85]
- 6-minute walk test with measurement of oxygen saturation and estimation of dyspnea using the Borg index.

As discussed earlier, BAL has no diagnostic value, but may be warranted when infection, alveolar hemorrhage, drug-induced ILD, or malignancy, is suspected. An etiological workup should be performed to avoid wrongly attributing ILD to SSc and, in particular, to rule out a possible differential diagnosis.

Clinical Development and Risk of Progression

Prognosis at Baseline

SSc-ILD is associated with early mortality, accounting for a large proportion of causes of death and making ILD the most common cause of SSc-related mortality.[2,7,8] In addition, it is important to note that prevalent cohorts underestimate mortality in SSc by not taking into account early deaths, particularly in men and people with diffuse disease. Indeed, in a recent cohort study of 1,070 patients with SSc, 140 deaths (13%) were recorded over a 3-year follow-up period, with a pooled of 4.06 standardized mortality ratio of 4.06 (95% CI: 3.39–4.85).[86]

Baseline and serial chest CT and pulmonary function tests account for most of the prognostic information in patients with SSc-ILD.[87] In the study by Goh et al,[71] both increasingly extensive disease on CT and baseline FVC were powerful predictors of mortality, with an optimal threshold of disease extent of 20%, and an optimal threshold of FVC at baseline of 70% of predicted value. A simple classification system was proposed, which divides patients into those with extensive disease ($>$30% disease extent on HRCT, or 10–30% disease extent on HRCT and FVC $<$70% of predicted) or limited disease (minimal disease extent on CT or, in indeterminate cases, FVC $\geq$70% expected). Extensive disease stage was a strong predictor of increased mortality (HR: 3.46, 95% CI: 2.19, 5.46).[29] This staging system has proven to be applicable to routine clinical practice, and was since then confirmed to be discriminatory of outcome in various series, confirming that the extent of disease on CT is associated with prognosis.[88–90] Many clinicians use this staging system to inform prognosis but also to guide treatment decisions, although it has not been formally validated to guide management.

There is no evidence that CT pattern or histology has a significant impact on disease progression or mortality in patients with SSc,[91] advanced age,[92,93] African American ethnicity, ever-smoking history,[92] presence of anti-topoisomerase-1 antibodies,[6,94] lowest SpO2 after 6-minute walking test,[95] and lower lung function.[93] Several biomarkers have also

been associated with a worse outcome,[87] although they have not translated into the clinic.

Monitoring Disease Progression

Performing pulmonary function tests regularly in the first 5 years following SSc diagnosis may be useful for detecting changes in lung function indicative of ILD.[87] Serial pulmonary function tests are the main tool to monitor disease progression, with FVC and DLCO being the most commonly used measures. An FVC decline $\geq$10% at 1 year and a DLCO decline $\geq$ 15% at 1 year are better predictors of mortality than FVC and DLCO at diagnosis.[71] These results were confirmed by a more recent study which showed a better prediction of mortality from the decline in FVC and DLCO over a 2-year follow-up this time, compared with initial FVC and DLCO.[96] Goh et al found that an optimal definition of disease progression was an FVC and DLCO composite, consisting of either an FVC decline from baseline >10% or an FVC decline of 5 to 9% in association with a DLCO decline of >15%.[97] Such composite definition accounts for the prognostic value of these variables as well as sensitivity to change and measurement variation.

Although impairment of DLCO is present very early in the course of disease, its measurement lacks accuracy and reproducibility, and suffers from significant inter-measurement variability. In addition to reflecting parenchymal lung disease, DLCO is affected by involvement of the pulmonary vasculature, and a decline in DLCO not paralleled by worsening in FVC should prompt to assess for pulmonary hypertension. Therefore, FVC is the preferred method to monitor progression of pulmonary fibrosis, in SSc-ILD as in idiopathic pulmonary fibrosis, both in clinical practice and as an endpoint in clinical trials. Measurement of FVC, however, has the caveat of being potentially affected by the involvement of the respiratory muscles or of the thoracic skin causing ventilatory restriction when present.

Although the frequency of pulmonary function tests is not standardized, clinicians commonly repeat PFTs at 3- to 6-month intervals during the first couple of years following the diagnosis of SSc-ILD, potentially increasing to 6- to 12-month intervals thereafter in the absence of observed progressive disease. Whether the frequency of serial pulmonary function tests can be individualized according to risk factors of progression (early disease, inflammatory biomarkers, anti-topoisomerase-1 antibody, etc.) warrants further study.

Currently, there is also no consensus with regard to the frequency of repeat CT in patients with SSc. Patients with SSs and normal chest HRCT at baseline who are at risk of ILD development may be prescribed repeat screening HRCT at intervals guided by risk of developing ILD. Most experienced clinicians would not repeat HRCT more than once a year or every other year for the first few years unless symptoms arose.[49] In subjects with SSc-ILD at risk of ILD progression, HRCT may be repeated for monitoring in patients with a significant decline in pulmonary function tests, 6-minute walking distance, and/or worsening symptoms.[4] Specifically, comparative HRCT may help decipher among various possible causes of worsening symptoms in SSc, including ILD, pulmonary hypertension, pulmonary embolism, emphysema, anemia, cardiac involvement, and deconditioning.[49] However, information provided by monitoring CT should be balanced with the risk of radiation exposure and cost of the procedure. Low-radiation protocols have been developed in recent years, especially applying iterative reconstruction methods, which may be suitable for regular monitoring while maintaining sufficient image quality to obtain the desired diagnostic information.[49]

Visual scoring of short-term changes of HRCT abnormalities is challenging. Nevertheless, participants in Scleroderma Lung Study (SLS) I or II who had an increase in the radiographic extent of ILD scores of $\geq$2% at 12 months or 24 months, respectively, had worse long-term survival than those with no or less extensive changes.[98] Computer-aided methods were developed for classifying ILD patterns, quantifying ILD extent, quantitating features of ground glass, lung fibrosis, and honeycomb cysts, and objectively assessing disease progression. The extent of ILD using the quantitative lung fibrosis (QLF) algorithm (quantitating lung fibrosis) can assess HRCT changes that are associated with lung function decline at 1 year.[55,99] CALIPER (computer-aided lung informatics for pathology evaluation and rating) quantitates specific ILD patterns and ILD changes.[100,101] These algorithms may help assess disease progression of SSc-ILD, although both are patented and not routinely available. Deep learning-based methods depict novel metrics of disease progression, such as lung shrinkage detected from elastic registration of chest CT,[68] or patterns of pulmonary vascular volume changes.[102] It is hoped that artificial and deep learning will soon provide algorithms and quantitative CT softwares, such as data-driven textural analysis,[103–105] to predict and assess disease progression based on HRCT performed using standard protocols, and hopefully routinely acquired, serial chest HRCTs.

Disease Trajectories

Progression of SSc-ILD is considered typically slow but can eventually lead to a considerable loss of lung function as it takes place over a long period of time. Rapidly progressive forms of SSc-ILD also exist.[106–108] Classically, SSc-ILD is considered to progress most rapidly early in the course of the disease, and may be more stable after 4 or 5 years following diagnosis. As most studies have focused on predicting the risk of mortality, there are in fact few studies describing the long-term natural course of disease including lung function decline. In a monocentric study of 171 patients with SSc-ILD, Guler et al described distinct patterns of physiological progression that remain relatively consistent during long-term follow-up.[109] Prognostic subgroups included short-term mortality associated with a high rate of decline in FVC and DLCO, medium-term mortality, and long-term survival, after adjustment for age, sex, and tobacco smoking history. These findings are relevant for how SSc-ILD should be monitored, as they suggest that prognostic subgroups exist among patients with SSc-ILD determining long-term mortality, rather the more traditional perception that the rate of progression of SSc-ILD plateaus after an initial period of more rapidly progression.

Some controversy exists as to whether a decline in lung function predicts subsequent decline in lung function in SSc-ILD. Guler et al found relative lack of association between change in FVC in the previous year and change in FVC in the subsequent year, although change in DLCO in the previous year was a statistically significant predictor of DLCO change in the subsequent year.[109] In a study of 234 patients with SSc-ILD, Scheidegger et al reported that ~40% had experience disease progression after a follow-up of 3 years.[110] In a study of 826 patients with SSc-ILD from the EUSTAR database, Hoffmann-Vold et al found that 58% of the patients had a pattern of lung function decline at 5 years, whereas only 8% showed rapid, continuously declining FVC.[111] The strongest predictive factors for FVC decline over 5 years were male sex, higher modified Rodnan skin score (mRSS), and reflux/dysphagia symptoms.[111] Most patients had both progressive and stable periods, suggesting that disease progression over one period may not predict subsequent disease progression. This interpretation must be tempered, however, by biases inherent to study design (selection bias, lead time bias), regression to the mean, and the impact of thresholds on categorical decline (e.g., FVC decline of 10.1% would correspond to disease progression while FVC decline of 9.9% would not). Nevertheless, these results stress the heterogeneity of the course of ILD in SSc, and highlight the need for close monitoring of all patients with SSc-ILD especially when the known risk factors for disease progression are present.

Importantly, early SSc-ILD consisting of ground-glass opacities at HRCT later progresses to NSIP pattern.[53] Although FVC and disease extent on CT help in assessing the risk of mortality, patients with SSc-ILD and subnormal normal lung volumes, and those with limited extent of ILD on CT, nevertheless have an increased risk of mortality as compared with SSc patients without ILD.[42] A dose–response relationship exists between ILD extent and standardized mortality ratios, even in groups with "mild" lung fibrosis and within normal-range FVC,[43] but in early SSc, progressive pulmonary fibrosis can occur in patients without CT abnormalities at baseline.[112] The importance of regular follow-up of patients with ILD even of limited extent should therefore not be underestimated to identify disease progression as early as possible and guide treatment indications. From the clinician's point of view, both disease severity and disease progression should be taken into account to guide management decisions.

Disease Progression

Several definitions were reported for the progression of SSc-ILD. Following the work of Goh et al,[97] OMERACT (Outcome Measures in Rheumatology) proposed a definition based on a relative decline of $\geq$10% in FVC, or a relative decline of 5 to 9% in FVC and a relative decline of $\geq$ 15% in DLCO.[113] The same definition was supported by an international panel of SSc-ILD experts from Europe and North America, who also stated that an increase in the extent of ILD on HRCT imaging if present would also be taken into account.[87] There was no agreement on what time period should be used to assess for lung function decline.

The INBUILD trial enrolled patients with fibrosing ILD that progressed despite conventional management over a period of up to 2 years prior to study enrollment, using a composite definition based on the following criteria:(1) a relative decline of $\geq$10% in FVC (% predicted), (2) a relative decline of 5 to <10% in FVC (% predicted) and worsening respiratory symptoms or increased extent of fibrosis on HRCT, or (3) worsening respiratory symptoms and increased extent of fibrosis on HRCT, independent of change in FVC (% predicted).[114] These criteria selected a population of patients who over the 52 weeks of the trial had a clinical course similar to idiopathic pulmonary fibrosis, irrespective of underlying ILD diagnosis or the fibrotic pattern on HRCT, as demonstrated by lung function decline in patients allocated to the placebo arm.[115]

The 2022 ATS/ERS/JRS/ALAT guideline defined progressive pulmonary fibrosis as the presence of at least two of the following three criteria occurring within the past year: (1) worsening of dyspnea or cough; (2) functional progression of the disease (>5% absolute decrease in FVC or >10% absolute decrease in DLCO [with no alternative explanation particularly pulmonary hypertension]); or (3) radiological evidence of disease progression. A strict definition of timelines for defining progressive pulmonary fibrosis was challenged,[116] however, as a time period of 1 year may not be appropriate in all cases. Accordingly, the latest ATS guideline on the treatment of SSc-ILD proposed to adapt the criteria to define progressive SSc-ILD and to eliminate the timeline for disease progression.[117] The guideline further suggested dividing the SSc-ILD population into three subgroups: initial diagnosis of SSc-ILD, stable SSc-ILD, and progressive SSc-ILD. Initial SSc-ILD refers to a new diagnosis of SSc-ILD before the start of treatment. Stable SSc-ILD is defined by the presence of ILD that does not meet the criteria for progressive SSc-ILD.[117]

Factors associated with a risk of rapid progression are presented in ►**Table 2**.[5,49,118] Other biomarkers may predict the progression of SSc-ILD, such as KL-6, CCL2, CCL18, CXCL4, or SP-D. However, with the notable exception of C-reactive protein,[80] they are not available in routine practice and are currently used only in the context of clinical research.[5,87,118–120]

Management of SSc-ILD

Treatment aims at improving symptoms, preserving quality of life and lung function, and on the longer term at preventing disease progression and ultimately improving survival. Several factors need to be taken into account in treatment decisions, including the available evidence from RCTs, international or local guidelines, the existence of extra-pulmonary manifestations in addition to ILD and their respective importance, severity of the lung disease, progressive disease, comorbidities and comedications, patient preferences, and others (►**Fig. 3**). Available information is best integrated in multidisciplinary discussion, with pulmonologists, rheumatologists, radiologists, and pathologists, with expertise in ILD, and the possible contribution of other specialists such as nurse specialist, physiotherapist, respiratory physiologist.[121]

Table 2 Factors associated with a greater risk of progression in patients with SSc-ILD (adapted from Khanna D, et al.[49])

Domains	Factors associated with greater risk of progression
Demographic	Male gender Advanced age Afro-American ethnic origin
Clinical	Diffuse cutaneous systemic sclerosis
Biological	Anti-Scl70/Topoisomerase I antibody Nucleolar pattern (especially including anti-Th/To and U3-RNP) Elevated acute phase reactants, including serum CRP levels Short telomere length
Functional	FVC < 70% at diagnosis DLCO < 55% at diagnosis
Imaging	Extent of ILD on HRCT (>20% of lung parenchyma for total lung involvement) Honeycombing

Abbreviations: CRP, C-reactive protein; DLCO, diffusion capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease.

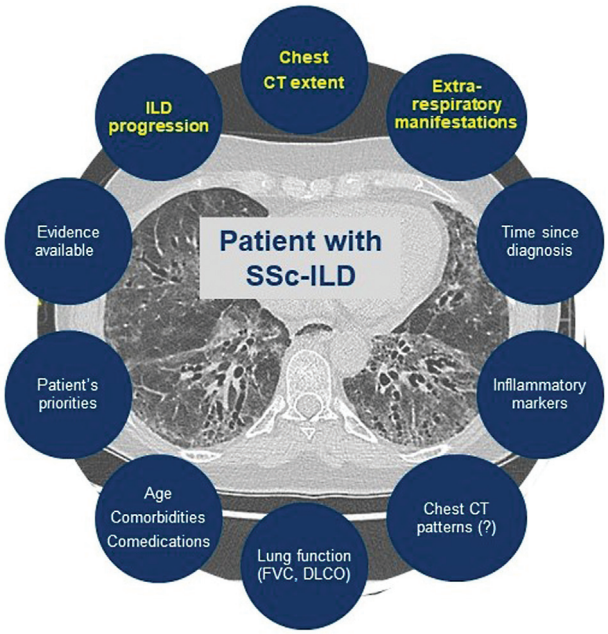

Fig. 3 Main factors to take into account for management decisions in patients with SSc-ILD. CT, computed tomography; CTD, connective tissue disease.

The following section and ►**Table 3** review the main data from RCTs in SSc-ILD.

Cyclophosphamide

Cyclophosphamide is a cytotoxic alkylating agent that has been shown to be effective in SSc-ILD in two RCTs.[40,122]

In the FAST study, 45 patients were randomized to receive 6 monthly infusions of cyclophosphamide (600 mg/m^2) followed by azathioprine treatment for 6 months combined with a low dose of prednisolone (20 mg/day on alternate days), or placebo, for 12 months.[122] Only 62% of the patients completed the first year of treatment. This trial did not demonstrate significant improvement in the primary endpoint (FVC); however, FVC improved at 12 months with cyclophosphamide, whereas it deteriorated on placebo, with a difference between the two groups of 4.2% of the predicted value (95% CI, −0.57 to 8.95). No improvements in DLCO (a co-primary endpoint) or secondary outcome measures (change in HRCT, dyspnea score) were identified. Findings from this study were limited, however, by a small sample size, and a population of patients with relatively preserved lung volumes and stable disease for the majority of them, which may have contributed to the failure to achieve statistical significance.

The SLS-I[40] was a multicenter RCT that compared treatment with oral cyclophosphamide (≤ 2 mg/kg/day) or placebo for a period of 12 months in 158 patients diagnosed with SSc-ILD within 7 years. Patients had to have exertional dyspnea, FVC between 45 and 85% of predicted value, DLCO ≥30% of predicted, and ground glass on chest CT of any extent or active alveolitis on BAL (defined as neutrophilia of ≥3%, eosinophilia of ≥2 percent, or both). Patients were followed up for a further 12 months after the end of the treatment period. The study demonstrated significant stability of FVC at 12 months in patients treated with cyclophosphamide compared with placebo, with a statistically significant but modest difference of 2.53% (95% CI: 0.28–4.79%).[105] In addition, there was clinical improvement (dyspnea and improved quality of life, reduction in skin thickening). However, with the exception of dyspnea, the efficacy observed at 1 year was lost 12 months after treatment was stopped.[123] This indicates the need for continued immunosuppression to maintain the benefit of cyclophosphamide, which, however, was outweighed by the known serious adverse effects of this compound.[123] Compared with placebo, there was an increased risk of events, particularly hematological (leukopenia [26 vs. 0%], neutropenia [9.6 vs. 0%], anemia [2.7 vs. 0%]), and infectious (pneumonia [6.8 vs. 1.4%]).[40]

In the SLS-II trial, 142 patients with SSc-ILD were randomized to receive intravenous cyclophosphamide for 12 months followed by placebo for 12 months, or mycophenolate mofetil (MMF) (target dose: 3 g/day) for 24 months,[124]

Table 3 Characteristics of the main trials evaluating different drugs in SSc-ILD

	Trials and references	Drugs assessed	Targeted population	Controlled group	*N* assigned arm	Outcome	Results
Cyclophosphamide	FAST[122]	CYC + CTC + AZA	SSc patients with early pulmonary fibrosis (as indicated by HRCT or thoracoscopic lung biopsy)	PCB + CTC + AZA	$n = 22$ CYC $n = 23$ PCB	FVC % of the predicted value and change in DLCO	No statistically significant difference between combination therapy with oral CTC, IV CYC, and oral AZA vs. PCB, but trend toward PFTs response with active therapy
	SLS I[40,123]	CYC	Limited or diffuse SSc, with evidence of active alveolitis on BAL fluid or any ground-glass opacity on thoracic HRCT, onset of the first non-Raynaud symptom within ≤ 7 y, FVC 45–85%, and exertional dyspnea	PCB	$n = 79$ CYC $n = 79$ PCB	FVC % of the predicted value at 12 mo	The mean absolute difference in adjusted 12-mo FVC% predicted between the CYC and PCB groups was 2.53% (95% IC, 0.28–4.79%), favoring CYC ($p < 0.03$). These improvements were not maintained at 24 mo in further analysis, except for a sustained improvement in dyspnea
MMF	SLS II[124]	MMF	Similar to SLS I	CYC	$n = 69$ MMF $n = 73$ CYC	FVC % of the predicted value over time from 3 to 24 mo	The adjusted % predicted FVC improved from baseline to 24 mo by 2.19 in the MMF group (95% CI: 0.53–3.84) and 2.88 in the CYC group (1.19–4.58) without significant difference ($p = 0.24$)
Rituximab	DESIRES[138]	RTX	SSc, with a mRSS of ≥ 10 and an expected survival of at least 6 mo	PCB	$n = 28$ RTX $n = 28$ PCB	Absolute change in mRSS 24 wk after initiation of study treatment	The absolute change in mRSS 24 wk after initiation of study treatment was lower in the RTX group than in the PCB group (difference −8.44 [95% CI: −11.00 to −5·88]; $p < 0·0001$). FVC stabilized with RTX vs. PCB in the SSc-ILD subgroup
	RECITAL[139]	RTX	Severe or progressive ILD related to SSc, idiopathic inflammatory myositis, or mixed connective tissue disease	CYC	$n = 51$ RTX $n = 50$ CYC	Rate of change in FVC at 24 wk compared with baseline	At 24 wk, FVC was improved in both the CYC group (unadjusted mean increase 99 mL [SD: 329]) and the RTX group (97 mL [234]). In the adjusted mixed-effects model, the difference in the primary endpoint at 24 wk was −40 mL (95% CI −153 to 74; $p = 0·49$) between the RTX group and the CYC group
	EVER-ILD[140]	RTX + MMF		PCB + MMF			

(*Continued*)

Table 3 (*Continued*)

	Trials and references	Drugs assessed	Targeted population	Controlled group	*N* assigned arm	Outcome	Results
			Patients with a NSIP pattern including 23 with SSc-ILD		$n = 63$ RTX $n = 59$ PCB	Change in % predicted FVC from baseline to 6 mo	The mean change from baseline to 6 mo in FVC (% predicted) was +1.60 (se 1.13) in the RTX + MMF group and −2.01 (se 1.17) in the PCB + MMF group (between-group difference 3.60, 95% CI: 0.41–6.80; $p = 0.0273$)
Tocilizumab	FaSScinate[133]	TCZ	Patients with dcSSc with or without ILD with active disease Disease duration < 5 y	PCB	$n = 43$ TCZ $n = 44$ PCB	FVC (milliliters) declined at weeks 24 and 48 (secondary endpoint) and % of patients experiencing worsening in FVC (%pred) in each arm	Smaller decrease in FVC for TCZ than for PCB from baseline to 24 wk (TCZ −34 mL vs. PCB −171 mL; least square mean difference 136 mL, 95% CI: 9–264; $p = 0.0368$) but from baseline to 48 wk no significant difference (TCZ −117 mL vs. PCB −237 mL; 120 mL, 95% CI −23 to 262; $p = 0.0990$). Fewer patients in the TCZ group than in the placebo group had worsening of FVC (%pred) at 24 wk ($p = 0.009$) or at 48 wk ($p = 0.037$)
	focuSSced[134]	TCZ	Patients with dcSSc with or without ILD With active disease Disease duration < 60 mo	PCB	$n = 105$ TCZ $n = 107$ PCB	Difference in distribution of change from baseline to week 48 in FVC% predicted (key secondary outcome)	Shift in the distribution of change from baseline in FVC (%pred) at week 48 favoring TCZ (van Elteren nominal, $p = 0.002$ vs. placebo). In patients with SSc-ILD at baseline, the LSM of FVC (% pred) change from baseline was −6.4 in the PCB group and 0.1 in the TCZ with LSM difference between treatment groups of 6.5 (95% CI: 3.4–9.5) $p < 0.0001$
Abatacept	STRATUS[182]	ABT	SSc-ILD with FVC 40–85% predicted, DLCO ≥ 30% predicted, stable MMF ≥ 2 mo, HRCT lung fibrosis ≥ 5%	PCB	$n = 14$ ABT $n = 10$ PCB	Annual rate of change in absolute FVC (12 mo)	Terminated prematurely due to slow enrollment
Nintedanib	SENSCIS[149]	NINT	Patients with diffuse or limited cutaneous subset SSc-ILD with CT showing fibrosis affecting at least 10% of the lungs FVC ≥40%	PCB	$n = 288$ NINT $n = 288$ PCB	Annual rate of decline in FVC (mL/y), assessed over 52 wk	The adjusted annual rate of change in FVC was −52.4 mL per year in the NINT group and −93.3 mL per year in the PCB group (difference, 41.0 mL per year; 95% CI: 2.9–79.0) ($p = 0.04$)

Table 3 (*Continued*)

	Trials and references	Drugs assessed	Targeted population	Controlled group	*N* assigned arm	Outcome	Results
	INBUILD[114]	NTB	Patients with progressive fibrosing lung disease affecting more than 10% of lung volume on HRCT including 39 with SSc-ILD	PCB	$n = 23$ NINT $n = 16$ PCB	Annual rate of decline in FVC over a 52-wk period	Positive trial in the overall and co-primary population, without heterogeneity of effect across subgroups. In the SSc subgroup population, adjusted difference in FVC decline of 120.7 mL at 52 wk (95% CI: −53.2, 294.6) in favor of NTB
Pirfenidone	RELIEF[164]	PFD	Patients with progressive fibrotic ILD due to connective tissue disease, fibrotic NSIP, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis	PCB	$n = 64$ PFD $n = 63$ PCB	Absolute change in FVC % predicted from baseline to week 48	The study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment. Significantly lower decline in FVC % predicted in the PFD group compared with placebo ($p = 0.043$)
	SLS III	PFD + MMF	SLS I	PCB + MMF	$n = 27$ PFD $n = 24$ PCB	Change from baseline in the mean FVC% predicted 18 mo	Recruitment was prematurely stopped due to COVID-19 and the impact of prior drug treatment on eligibility. A similar magnitude of improvement in FVC% over 18 mo in both arms (2.24% MMF + PLA vs. 2.09% MMF + PFD; $p = 0.93$) with a more rapid improvement in the MMF + PFD arm over 6 mo

Abbreviations: ABT, abituzumab; AZA, azathioprine; BAL, bronchoalveolar lavage; CYC, cyclophosphamide; dcSSc, diffuse cutaneous systemic sclerosis; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; NTB, nintedanib; NSIP, nonspecific interstitial pneumonia; PCB, placebo; PFD, pirfenidone; RTX, rituximab; SLS, scleroderma lung study; SSc, systemic sclerosis; TCZ, tocilizumab.

using inclusion criteria similar to those of SLS I. Although no difference in FVC was observed between groups, the study confirmed some improvement in FVC. Furthermore, several post hoc studies demonstrated a benefit of cyclophosphamide on dyspnea and cough-related quality of life, quantification of ILD on HRCT, and skin disease assessed by mRSS.[55,124–128] A significant improvement in skin thickness was also found with cyclophosphamide in an open-label randomized trial comparing cyclophosphamide and rituximab.[129]

Although these studies demonstrated a beneficial effect of cyclophosphamide in SSc-ILD, as well as some beneficial effect on the skin, treatment was also associated with serious adverse effects, particularly hematological effects and infections. The long-term cumulative toxicity of cyclophosphamide, including its association with bladder cancer and other malignant diseases and the risk of sterility, were not evaluated in these studies but are well identified. Overall, the benefit–risk ratio of cyclophosphamide may not be favorable in many patients. Cyclophosphamide may be used particularly in SSc-ILD patients with severe or rapidly progressive disease. The side-effects are managed with protective measures, using the intravenous route of administration (which leads to lower cumulative doses), and appropriate patient selection.

Mycophenolate Mofetil

MMF is an inosine monophosphate dehydrogenase inhibitor that impairs T and B cell proliferation and migration[130] and is commonly used to treat SSc-ILD, based on indirect evidence from the SLS-2 trial,[124,127,128] which compared oral cyclophosphamide for 12 months followed by placebo for 12 months, to MMF (target dose: 1,500 mg twice daily) for 24 months in 142 patients with SSc-ILD. The inclusion criteria were similar to those of SLS I, including an FVC comprised between 45 and 80% of predicted. Overall, 142 patients were randomly assigned to either MMF or cyclophosphamide, including 126 patients (MMF [$n = 63$] and cyclophosphamide [$n = 63$]) who were included in the primary analysis. The adjusted % predicted FVC improved from baseline to 24 months by 2.19 in both treatment arms (+2.19%; 95% CI: 0.53–3.84) of predicted value in the MMF group, and +2.88% (1.19–4.58) in the cyclophosphamide group [95% CI: −3.1 to 1.7], with no significant difference in FVC change between groups.[124] MMF was better tolerated than cyclophosphamide, with a lower frequency of cytopenias and of treatment discontinuation (35 vs. 42%). No difference was observed in dyspnea score, health-related quality of life assessed by SF-36, mRSS, or HRCT visual assessment.[127,128] No difference between groups was observed either in the QLF scores, which slightly improved at 24 months in both groups.[55]

In another, monocentric, placebo-controlled, RCT of 42 patients with SSc-ILD, MMF did not result in significant improvement in lung function, but was effective in reducing the skin tightness assessed by mRSS.[131] In this study, lung function was only minimally impaired at enrollment (FVC ≥ 70% predicted, mean FVC at enrollment of 80% of predicted [80–104%]). This study was underpowered, of short duration (6 months), enrolled patients with up to 40 years of duration of disease since the first non-Raynaud phenomenon, including some who experience very minimal disease progression in the placebo group, which may have contributed to the negative result. Interestingly, almost 30% of patients in the MMF group and 36% in the cyclophosphamide group had deterioration in FVC during the trial period, suggesting that non-responders to treatment may need therapeutic adaptations.

In addition, some supportive evidence of a benefit of MMF came from a post hoc, subgroup analysis of the SENSCIS trial,[132] in which patients were randomized to receive nintedanib or placebo. In this trial, 49% of the patients were receiving MMF at baseline. Nintedanib reduced the progression of SSc-ILD. FVC changes over 52 weeks were numerically lower in patients who were using MMF at baseline compared with those not using MMF, with no heterogeneity in the treatment effect of nintedanib.

Although SLS II did not compare MMF to placebo, and did not demonstrate a better efficacy of MMF at 24 months than cyclophosphamide for 1 year, it provided indirect evidence of the efficacy of MMF in SSc-ILD, and substantiated its value in treating SSc-ILD, with an additional potential benefit on the skin. Based on these results, and especially the better benefit: tolerability profile of MMF compared with cyclophosphamide with manageable side effects, MMF is now often considered a first-line treatment option for SSc-ILD, and is increasingly used.

Tocilizumab

Tocilizumab is a monoclonal antibody targeting the interleukin-6 (IL-6) receptor. High levels of IL-6 have been associated with skin fibrosis and with the development of SSc-ILD,[133] which provided a rationale for exploring the efficacy of this drug in SSc-ILD.

In the phase 2 faSScinate RCT,[133] 77 patients with progressive SSc were assigned to receive weekly subcutaneous tocilizumab 162 mg or placebo for 48 weeks. No significant difference was found between groups in the primary endpoint (mRSS at week 24). In an exploratory analysis, fewer patients in the tocilizumab group than in the placebo group had a decline in percent FVC at 48 weeks. Importantly, the study enrolled patients with SSc of 5 or fewer years of duration from first non-Raynaud manifestations, mRSS score of 15 to 40, clinical skin involvement proximal to the elbows, knees, or both, with or without face involvement, early progressive skin disease (recent onset of skin disease or worsening of mRSS), and high acute-phase reactants (C-reactive protein ≥10 mg/L, erythrocyte sedimentation rate ≥28 mm/h, or platelets ≥330 000/μL). These criteria probably enriched for patients at high risk for ILD,[133] although the study was not designed to enroll patients with progressive SSc-ILD. Lung function at baseline was preserved, with an FVC of 80 to 82% of predicted value, and a DLCO of 73 to 74% of predicted.

The phase 3, focuSSced RCT[134] had very comparable design and eligibility criteria to the faSScinate trial. In total, 210 patients (with mRSS of 10–30) were randomly assigned to receive weekly subcutaneous tocilizumab or placebo, stratified by IL-6 levels. Participants had normal to mild

impairment in lung function at baseline (mean FVC% predicted was 83.9 ± 15.0 in the placebo group and 80.3 ± 14.4 in the tocilizumab group, and % predicted DLCO was $76.8 \pm 18{\cdot}6$ and 74.4 ± 19.2, respectively); 65% of the participants had evidence of SSc-ILD on HRCT. No difference was found between groups in the skin fibrosis primary endpoint (mRSS at week 48). However, at week 48, the mean change from baseline in FVC% predicted was –4.6 in the placebo group and –0.4 in the tocilizumab group (difference: 4.2 [95% CI: 2.0–6.4], nominal $p = 0.0002$). Among SSc patients with ILD, the mean change from baseline in FVC% predicted was –6.4 in the placebo group and –0.1 in the tocilizumab group (difference: 6.5 [95% CI: 3.4–9.5], nominal $p < 0.0001$), corresponding to a difference between groups of 241 m (124–358) at week 48. Nine percent of patients with SSc-ILD had a decline in FVC of 10% or greater at week 48 in the active arm, compared with 25% in the placebo group. Differences between groups were also significant in favor of tocilizumab for the extent of fibrosis on HRCT measured by QLF.[134] Stabilization of FVC was maintained until the second year in the extension phase of the trial.[135] Safety was consistent with the safety profile of tocilizumab and complications of SSc,[134] and no new safety concerns emerged in the extension phase.[135] Supportive results were also observed in a real-life observational study[136] and from the open label extension studies of faSScinate and focused.[135,137]

Overall, these results led to the approval by the Food and Drug Administration of tocilizumab for the treatment of SSc-ILD. Tocilizumab is particularly used for SSc-ILD with early diffuse SSc and increased inflammatory markers or recent skin fibrosis progression.

Rituximab

Rituximab is a monoclonal antibody that binds to cell surface proteins found on B cells.[129] The key role of humoral immunity in the pathogenesis has prompted several trials to be conducted with this molecule.

In the DESIRES RCT,[138] 56 patients with SSc and a mRSS of 10 or greater were randomly assigned to receive intravenous rituximab ($375\ mg/m^2$) or placebo once per week for 4 weeks. The absolute change in mRSS 24 weeks after initiation of study treatment (the primary endpoint of the study) was lower in the rituximab group than in the placebo group. Adverse events were similar in both groups. In the subgroup of 89% of patients with SSc-ILD ($n = 48$), FVC was stable at week 24 in patients receiving rituximab, and decreased in the placebo group (difference between groups: 2.96% [95% CI: 0.08–5.84]; $p = 0.044$).[138] No difference in DLCO was observed between groups at week 24.

In another, open-label, randomized trial,[129] patients with SSc-ILD were randomly assigned to receive monthly pulses of intravenous cyclophosphamide $500\ mg/m^2$ or rituximab 1,000 mg at day 0 and at day 15. FVC % of predicted improved from 61.3 ± 11 to 67.5 ± 13 at 6 months in the rituximab group while it declined from 59.2 ± 13 to 58.1 ± 11 in the cyclophosphamide group ($p = 0.003$), corresponding to an improvement of 140 mL with rituximab versus no change with cyclophosphamide. An improvement was found on skin fibrosis measured by mRSS, and in the 6-minute walking distance, with rituximab but not with cyclophosphamide.

The RECITAL, phase IIb RCT[139] assessed the efficacy of rituximab versus cyclophosphamide in 101 patients with severe or progressive ILD related to SSc ($n = 37$), idiopathic inflammatory myositis, or mixed CTD over 24 weeks. An improvement in FVC at 24 months and clinically important improvements in patient-reported quality of life were reported in both groups, with no significant difference between the two treatment arms. Rituximab was not superior to cyclophosphamide; however, it was associated with fewer side effects.

The EVER-ILD trial[140] assessed the efficacy of rituximab in combination with MMF compared with rituximab and placebo in patients with a pattern of NSIP (defined on lung biopsy and/or on HRCT). Rituximab plus MMF was associated with benefits in FVC and progression-free survival compared with MMF plus placebo after 24 weeks of treatment (difference between groups: 3.60, 95% CI: 0.41–6.80; $p = 0.0273$). The safety profile of rituximab plus MMF was generally comparable to that of MMF plus placebo, however, with numerically more infections, especially viral, in the rituximab group. Out of 122 patients randomized, 23 had SSc-ILD, and no subgroup analysis by etiological diagnosis was reported.

Supportive evidence of the efficacy of rituximab in SSc-ILD also came from a small sample size trial[141] and observational studies.[142–144]

Collectively, these results indicate that patients with SSc-ILD benefit from rituximab treatment in terms of FVC, quality of life, and skin fibrosis, offering an effective treatment option for this group of patients at the expense of a manageable risk of infection.[138,140]

Glucocorticoids

As SSc-ILD is predominantly associated with a histological pattern of NSIP, it may in theory be potentially sensitive to glucocorticoids. However, systemic glucocorticoids should be used with caution in patients with SSc with or without SSc-ILD, as they have been associated with renal crisis. Indeed, the risk of developing renal crisis contraindicates the use of high doses of corticosteroids. Whenever possible, the daily dose should not exceed the equivalent of 15 mg per day of prednisone, with the exception of special situations (e.g., life-threatening intra-alveolar hemorrhage).[117,145,146]

Nintedanib

Nintedanib is a tyrosine kinase inhibitor targeting pathways involved in fibrogenesis. It has been recommended for the treatment of idiopathic pulmonary fibrosis and progressive pulmonary fibrosis[147] based on phase III trials.[114,148]

In the SENCSIS, phase III,[149] RCT, 576 subjects with SSc-ILD were randomized to receive nintedanib 150 mg orally twice daily or placebo for 52 weeks. Patients had to have SSc with an onset of the first non-Raynaud symptom within the past 7 years and a HRCT scan that showed fibrosis affecting at least 10% of the lungs. Dose reduction to 100 mg twice daily and treatment interruptions were allowed per protocol. Patients

could receive immunosuppressive treatment with MMF during the trial, which was the case for approximately half of the patients enrolled. In the primary end-point analysis evaluated at week 52, the change in FVC was −52.4 mL in the nintedanib group and −93.3 mL in the placebo group (difference, 41.0 mL per year; 95% CI, 2.9–79.0; $p = 0.04$), corresponding to a relative reduction in the rate of decline in FVC by more than half.[149,150] No treatment benefit was found for skin fibrosis (mRSS) or the dyspnea score, which changes were correlated with FVC changes.[151] The lowest decline in FVC was observed in patients randomized to receive nintedanib, who also were treated with MMF at baseline.[132] No difference in the treatment effect were found by subgroups by severity of lung involvement,[152] anti-topoisomerase-1 antibody status, mRSS, SSc subtype,[153] or sex.[154] A numerically greater effect was found in patients with early disease, elevated inflammatory markers, or extensive skin fibrosis at baseline.[155] Diarrhea was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group.[149,156] Continuation of nintedanib in the extension phase found a safety profile of nintedanib over longer term use consistent with that seen in the SENSCIS trial, and a change in FVC similar to that seen in patients who received nintedanib in SENSCIS.[157,158] Based on the results of the SENSCIS trial, nintedanib has marketing authorization for the treatment of SSc-ILD in the United States and in most regions of the world.

Patients with SSc-ILD and progressive pulmonary fibrosis despite management were also eligible to enter the INBUILD, phase III, RCT.[114] This study, hypothesizing a shared pathophysiological mechanism in different types of progressive pulmonary fibrosis independent of the underlying etiology, compared nintedanib to placebo. Among 663 participants, a subgroup of 39 patients had SSc-ILD. The trial demonstrated a beneficial effect of nintedanib to prevent FVC decline in progressive pulmonary fibrosis.[43] No significant difference in treatment efficacy was found across underlying etiological subgroups,[159] although the study was neither designed nor powered to demonstrate treatment efficacy in specific etiologies. Nintedanib is approved for the treatment of progressive pulmonary fibrosis in most regions of the world. As most immunosuppressive therapies were prohibited in the INBUILD trial, it is not known whether the combination of nintedanib and immunosuppressive therapy might be beneficial in patients with progressive pulmonary fibrosis. However, the treatment effect of nintedanib was not influenced by concomitant treatment in subjects who used prohibited or restrictive therapies in INBUILD.[160]

Pirfenidone

Pirfenidone is an antifibrotic immunosuppressant approved for the treatment of idiopathic pulmonary fibrosis[147] based on phase III RCTs.[161,162] Several RCTs also support the efficacy of pirfenidone in patients with progressive pulmonary fibrosis[163] including the RELIEF trial with only eight patients with SSc-ILD,[164] and a RCT in rheumatoid arthritis-associated ILD.[165]

The efficacy and safety of the combination of pirfenidone and MMF was evaluated in the SLS III trial (NCT03221257). The study, not yet published at the time of this writing, was underpowered as recruitment was prematurely halted, and results were reported as negative in congresses. The LOTUSS trial had previously showed an acceptable safety profile of pirfenidone in patients with SSc-ILD, unaffected by the concomitant use of MMF.[166] Evidence of the potential benefit of pirfenidone in this indication warrants further assessment in future, larger trials.

Hematopoietic Stem Cell Autograft

Three RCTs (ASSIST, ASTIS, SCOT) have evaluated the efficacy of high doses of cyclophosphamide followed by bone marrow autograft compared with more conventional doses of cyclophosphamide in patients with recent SSc.[167–169] In all three published studies, this procedure improved the medium-term prognosis but was accompanied by early increased mortality. In the ASTIS study, which had the largest number of participants ($n = 156$), 86% of patients had pulmonary involvement and 83% had interstitial abnormalities on CT scan (mean FVC 86% of predicted, mean DLCO of 58%). At 2 years, the FVC was improved in the autograft group while it declined in the control group. There was no difference in the progression of DLCO.[168] Therapeutic intensification with hematopoietic stem cell autograft can be considered in some well-selected patients with a rapidly progressive form of SSc, provided that respiratory function is not too impaired (FVC > 60% with a DLCO > 40%) and should be performed in expert centers accredited for these practices.

Treatment of Gastroesophageal Reflux

Although the causal and direction of the relationship between fibrosing ILD and gastro-esophageal reflux disease is still under debate in SSc, intense gastro-esophageal reflux often heralds impaired lung function in SSc, and is associated with the degree of fibrosis detected by CT scan.[170] Therefore, treatment of gastro-esophageal reflux disease when present is recommended in SSc-ILD patients.[171]

Non-Drug Therapy

Patients must, of course, completely and permanently quit smoking. Respiratory reeducation and rehabilitation are indicated according to the degree of respiratory insufficiency. Any malnutrition must be corrected. Ambulatory supplemental oxygen therapy may be used in patients with exercise-induced oxygen desaturation <80%, or exercise-induced oxygen desaturation <85 to 89% associated with significant exertional dyspnea or exercise limitation that improves with oxygen.[172] Patients should be offered *influenza*, pneumococcal, and COVID19 vaccinations.

Lung Transplantation

Lung transplantation should be considered for carefully selected SSc-ILD patients who have no contraindications and have not responded to specific therapies.[173] Retrospective series suggest that the overall survival after lung transplantation is comparable in patients with SSc-ILD and those with other indications for transplantation.[174] Nevertheless, lung transplantation proves to be an option

for only a small proportion of patients with SSc-ILD, due to multiple contraindications caused in particular by active systemic disease, severe parietal thoracic involvement, and increased inhalation risk caused by esophageal dysmotility (infections, progression to constrictive bronchiolitis). Particularities of lung transplantation for SSc-ILD are reviewed elsewhere.[175,176]

Principles Guiding Treatment Decisions

Clinical practice guidelines concerning the therapeutic approach for patients with SSc-ILD are mainly based on consensus intended to serve as a basis for informed and shared decision-making.[82,113,117,177] An official clinical practice guideline of the American Thoracic Society was approved in May 2023 based on a systematic review of the literature and using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[117] For the treatment of patients with SSc-ILD, the committee (1) recommended the use of MMF; (2) recommended further research into the safety and efficacy of pirfenidone and the combination of pirfenidone plus MMF; and (3) suggested the use of cyclophosphamide, rituximab, tocilizumab, nintedanib, and the combination of nintedanib plus MMF (►**Table 4**).[123] This guideline, however, does not provide a detailed guidance on a treatment algorithm or decision tree, with especially criteria to select between recommended and suggested treatment options in the individual patients, or guide about the optimal timing of treatment initiation. Guidelines by the ACR, and by a joint effort of the European Respiratory Society and the European League Against Rheumatism, are in preparation at the time of this writing. However, the process of guideline is limited by the evidence available. Several consensus and expert opinions were published[82,177] in an endeavor to address this gap.

In practice, treatment decisions should be based on a multidisciplinary meeting,[121] with the goal of integrating into the treatment decision, most if not all components of the discussion in a patient with SSc-ILD, including the following: existence and severity of extrapulmonary manifestations, time since SSc diagnosis, severity of ILD (extent of fibrosis on HRCT, lung function impairment), observed disease progression, risk of ILD progression, inflammatory biomarkers, pattern on chest HRCT, age, comorbidities, comedications, and patient' expectations and preferences.

Identifying subgroups of patients with SSc-ILD that may benefit the most of each treatment option available would be an invaluable guidance for clinicians. Precision medicine, however, is still in its infancy in SSc-ILD. For example, although some predictors of ILD progression were identified, predicting the outcome remains challenging. There are patients in whom the disease may be relatively stable and who could develop side-effects from the drugs without any associated benefits. On the other hand, early initiation of treatment in the appropriate clinical setting could halt the progression of fibrosis. Progression of ILD does not always begets further progression in SSc.[111] Nevertheless, the

Table 4 Recommendations for specific drugs in SSc-ILD as per American Thoracic Society (ATS) guideline[117]

Drug	ATS guideline	Comments by these authors
Mycophenolate	Recommended	• Commonly used as a first-line treatment after consideration of the side-effect profile
Cyclophosphamide	Suggested	• May be used particularly in patients with severe or rapidly progressive disease
Tocilizumab	Suggested	• Particularly used for SSc-ILD with early diffuse SSc and increased inflammatory markers or recent skin fibrosis progression
Rituximab	Suggested	• May particularly be used as a second-line immunosuppressive therapy, balancing the benefit with the risk of infection
Nintedanib	Suggested	• Approved in patients with SSc-ILD • Approved in patients with progressive pulmonary fibrosis including SSc-ILD
Mycophenolate + nintedanib	Suggested	• May be used at presentation (upfront combination) in patients with severe ILD, at risk of severe ILD, or with severe multiorgan disease. • May be used during follow-up (sequential combination) in patients with ILD progressing despite immunosuppressive therapy
Pirfenidone	Recommendation for further research	• Insufficient evidence available ; off-label use may be considered in progressive pulmonary fibrosis when nintedanib is contra-indicated or not tolerated
Pirfenidone + mycophenolate	Recommendation for further research	• Insufficient evidence available
Mycophenolate + rituximab	Not assessed	• May be used in patients with SSc-ILD and a pattern of fibrotic nonspecific interstitial pneumonia, balancing the benefit with the risk of infection

extent of disease on chest HRCT, the severity of disease, the likelihood of its progression, and the observed decline in serial measurements of FVC are currently the best available tools to appreciate the risk of a poor outcome in SSc-ILD,[48,97] and will determine the course of treatment.

In a modified Delphi process completed by pulmonologists and rheumatologists, there was agreement that patients with SSc-ILD and the following characteristics should be offered treatment[82]:

- FVC <80% and any degree of ILD or symptoms.
- 20% of total lung involvement on HRCT.
- >10% of total lung involvement with abnormal pulmonary function tests.
- High-risk of ILD progression (early diffuse cutaneous SSc) with evidence of mild ILD (< 10%).
- Worsening HRCT with symptoms or declining pulmonary function tests.
- Treatment may also be considered in patients with exertional desaturation on SpO_2.

Although very few studies have compared existing drugs head-to-head, it is often assumed that there is a predilection for efficacy depending on the stage of the disease, with immunomodulatory therapies probably being more effective in the early inflammatory stages and antifibrotic therapies in the later stages of fibrosis progressing despite immunomodulation. First-line immunosuppressive treatments can be represented by MMF, tocilizumab, rituximab, or cyclophosphamide (►**Fig. 4**). The choice of medication should be discussed in the multidisciplinary meeting, clearly acknowledging the therapeutic objective, which generally is to stabilize FVC. Nintedanib is approved in most regions of the world, while tocilizumab is approved in the United States and rituximab is approved in Japan for the treatment of SSc-ILD. If cyclophosphamide is used, it should be continued for 6 to 12 months and then followed by maintenance immunosuppression preferably using MMF and possibly azathioprine. In the event of disease progression despite treatment or of drug intolerance, cases should be discussed again at a multidisciplinary meeting to select a second-line treatment.

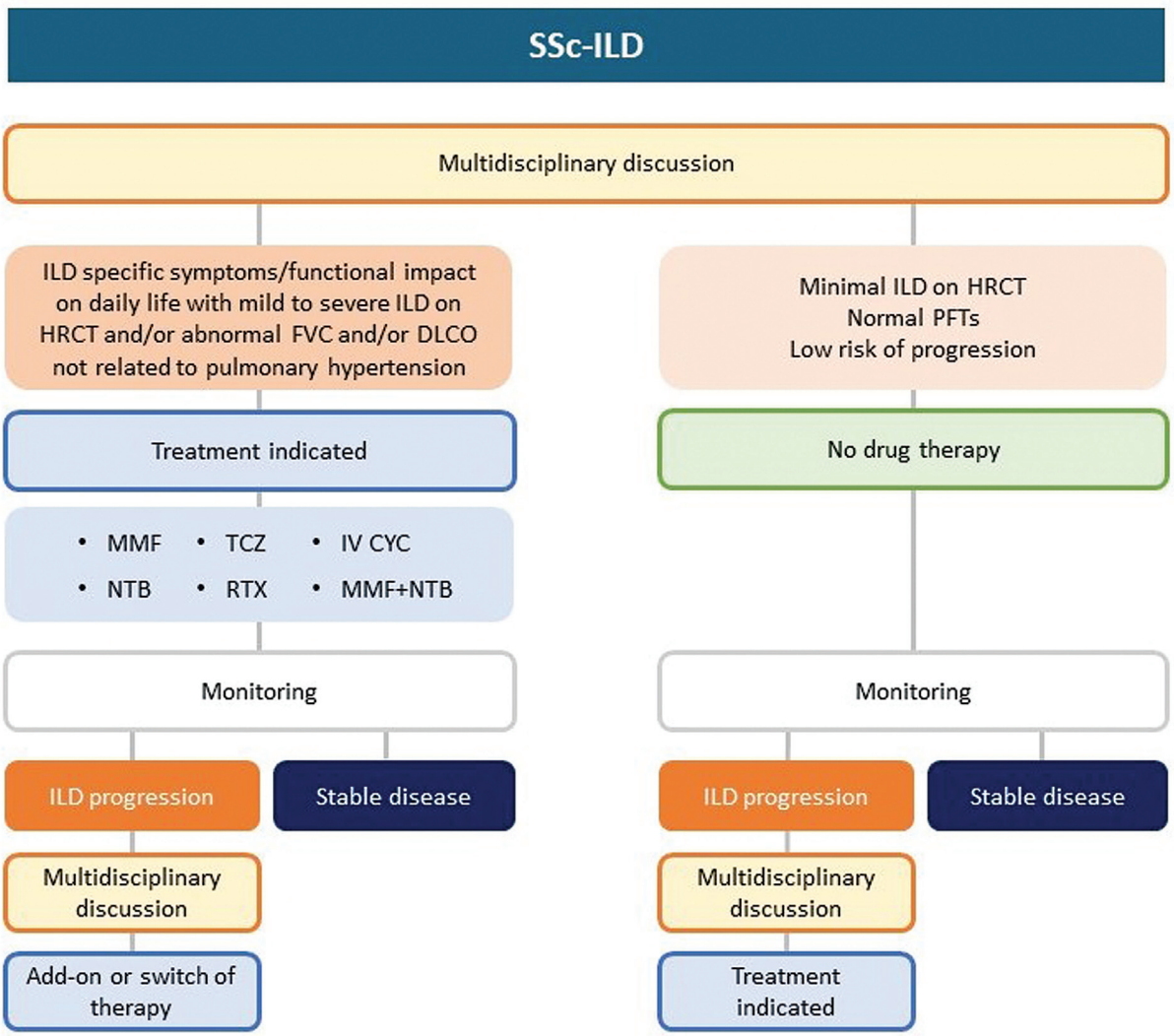

Fig. 4 Simplified management algorithm of SSc-ILD. ILD, interstitial lung disease; IV CYC, intravenous cyclophosphamide; MMF, mycophenolate mofetil; NTB, nintedanib; RTX, rituximab; TCZ, tocilizumab; SSc, systemic sclerosis.

Nintedanib can be used a first-line therapy based on the SENSCIS trial,[149] or as second-line therapy especially in case of progressive pulmonary fibrosis,[114] and can be used alone or in combination with an immunosuppressant. When initiating nintedanib in SSc-ILD, a benefit of maintaining prolonged therapy with immunosuppressants in combination with nintedanib is less likely in the absence of previous response to immunosuppressants, and in case of recurrent infections.[178]

Upfront combination therapy is generally reserved for patients with severe ILD. High-dose glucocorticoids (> 15 mg per day of prednisone) should be avoided. Overall, treatment when indicated should be continued for at least 2 years. Hematopoietic stem cell transplantation is currently used for a small minority of patients with SSc-ILD, and has yet to be widely viewed as standard therapy in this indication.

Perspectives

Since immunomodulatory and antifibrotic therapies play an important role in the treatment of SSc-ILD, there is significant potential for combining immunomodulatory and antifibrotic therapies. Several ongoing trials are exploring combination therapy, and examining the sequence of initiation of each therapy will be necessary. Several novel agents are also being evaluated. Romilkimab, an anti-IL-4 and anti-IL-13 antibody,[179] has shown promising results in animal models and is currently in phase II RCT in the treatment of diffuse SSc (NCT02921971). Janus kinase inhibitors may have both antifibrotic and anti-inflammatory actions and are currently being investigated for their potential role in the treatment of SSc-ILD.[180] Belimumab, a monoclonal antibody binding to BLyS, is another promising treatment option.[181] Many studies are currently recruiting (clinicaltrials.gov). In addition, omics may soon provide biomarkers to address the unmet need for reliable and accessible predictive markers of progression and to take the path toward truly personalized medicine. The Scleroderma Research Foundation is preparing an international platform to conduct adaptative trials.

Conclusion

SSc is a complex and heterogeneous disease in which ILD is a major determinant of morbidity and mortality. After decades of treatment nihilism, several positive clinical trials have recently demonstrated the benefit of several effective therapeutic options in SSc-ILD. Discussions at a dedicated multidisciplinary consultation meeting should take place to gauge the most appropriate management, be it for treatment initiation, second-line therapy, further treatment choices, and non-pharmacological approaches. Research must continue to optimize the management of SSc-ILD, to better guide indications based on patient subgroups and precision medicine, and to discover novel effective and well-tolerated compounds. However, we must not forget that the treatment armamentarium is already rich of several effective options in SSc-ILD, which should prompt clinicians to actively treat SSc-ILD, for the benefit of the long-term preservation of the lung function and of the quality of life of our patients.

Conflict of Interest
None declared.

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