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PERSPECTIVES

Interstitial Lung Disease in Systemic Sclerosis: Focus on Early Detection and Intervention

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Abstract: Systemic sclerosis (SSc) is a progressive and often devastating disease characterized by autoimmune dysfunction, vasculopathy, and fibrosis. Interstitial lung disease (ILD) is identified in the majority of patients with SSc and is the leading cause of SSc-related mortality. Although clinical manifestations and ILD severity vary among patients, lung function typically declines to the greatest extent during the first 3–4 years after disease onset. We aim to provide an overview of SSc-associated ILD (SSc-ILD) with a focus on current and emerging tools for early diagnosis of ILD and current and novel treatments under investigation. Early detection of ILD provides the opportunity for early therapeutic intervention, which could improve patient outcomes. Thoracic high-resolution computed tomography is the most effective method of identifying ILD in patients with SSc; it enables detection of mild lung abnormalities and plays an important role in monitoring disease progression. Cyclophosphamide and mycophenolate mofetil are the most commonly prescribed treatments for SSc-ILD. Recently, nintedanib (an antifibrotic) was approved by the Food and Drug Administration for patients with SSc-ILD; it is indicated for slowing the rate of decline in pulmonary function. However, there is a need for additional effective and well-tolerated disease-modifying therapy. Ongoing studies are evaluating other antifibrotics and novel agents. We envision that early detection of lung involvement, combined with the emergence and integration of novel therapies, will lead to improved outcomes in patients with SSc-ILD.

Keywords: systemic sclerosis, interstitial lung diseases, early diagnosis, disease progression, treatment outcome

Plain Language Summary

Systemic sclerosis (SSc) is a rare condition characterized by immunologic abnormalities, organ fibrosis and vasculopathy. Interstitial lung disease (ILD), also called pulmonary fibrosis, is a common manifestation of SSc. ILD in SSc is often associated with a decline in lung function within the first several years of lung disease onset. Effective screening to improve early diagnosis of patients with SSc with associated ILD (SSc-ILD) is of paramount importance. We analyzed the SSc-ILD medical literature to look at available and emerging tools for the early diagnosis of ILD, current treatments, and novel agents under study. Several methods are available to diagnose ILD, including high-resolution computed tomography, the "gold standard" method for detecting SSc-ILD, and lung function tests. Cyclophosphamide and mycophenolate are recommended for the treatment of SSc-ILD based on data from the Scleroderma Lung Studies I and II. In addition, the FDA recently approved nintedanib to slow the decline of lung function in patients with progressive fibrotic SSc-ILD. There remains a need to identify additional, more effective therapies for SSc-ILD. We hope that early diagnosis of lung involvement and the development of safe and more effective medicines will lead to improved outcomes in SSc-ILD.

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Introduction

Systemic sclerosis (SSc) is a clinically heterogeneous disease characterized by a complex interplay between autoimmunity, vasculopathy, and fibrosis. This condition affects multiple organ systems, including the skin, gastrointestinal tract, lungs, kidneys, and heart.[1–3] The most common pulmonary manifestations of SSc, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), are the leading causes of death and account for up to 60% of the SSc-associated mortality.[4,5] In a meta-analysis, patients with SSc with associated ILD (SSc-ILD) were found to have a mortality risk nearly three times greater than SSc patients without ILD.[6]

When examined using high-resolution computed tomography (HRCT), ILD in patients with SSc is typically characterized by bilateral, lower-lobe predominant reticulations, ground-glass opacities, and in some cases, honeycombing.[7] The initial clinical presentation of SSc-ILD, however, varies, which can make diagnosis challenging. Patients with mild ILD can be asymptomatic in the early stages of disease and, therefore, may not undergo pulmonary function testing or diagnostic radiology until they experience symptoms such as dyspnea on exertion and an increasingly persistent cough. Despite recent improvements in the overall survival rates of patients with SSc, current therapies do not curtail disease-related inflammation or fibrosis consistently.[8–10] Clinical trials have demonstrated that immunosuppressant therapy can provide modest benefits in patients with SSc-ILD, and some patients experience ILD progression despite receiving such treatment.[11]

Administration of treatment early in the course of SSc-ILD may lead to improved clinical outcomes.[12] This was demonstrated in a retrospective study comparing the use of cyclophosphamide (CYC) with other drugs and no treatment in patients with SSc-ILD.[13] Irrespective of the drug used, the factor that predicted significant improvement in lung function was the initiation of treatment at an early stage in the disease process.[13] In line with this, rigorous screening programs to facilitate early diagnosis of SSc-ILD and, hopefully, early initiation of treatment are of paramount importance.[14]

In this review, we aim to provide an overview of SSc-ILD with a focus on current and emerging tools for early diagnosis of ILD, as well as novel treatments currently under investigation. Relevant articles were identified by screening the literature using the PubMed search engine, with various combinations of the following search terms: "systemic sclerosis" OR "scleroderma"; "interstitial lung disease"; "pathology"; "epidemiology"; "treatment" OR "therapy"; and "detection" OR "diagnosis". The contents of the retrieved articles were reviewed to identify those of relevance. We were particularly interested in literature that discussed early detection and interventions that were published within the last 10 years; however, strict limits on time from publication were not imposed. We also searched clinicaltrials.gov to identify relevant clinical trials on SSc-ILD.

Epidemiology and Clinical Outcomes of SSc-ILD

For the majority (70–90%) of patients with SSc who develop ILD, ILD is observed within the first 3 years of SSc diagnosis; 40–75% of the patients with SSc have reduced pulmonary function.[15,16] SSc-ILD tends to occur with increased severity and/or increased risk of progression in patients with Scl-70 (anti-topoisomerase I) antibodies,[5,17] male sex,[18] and African–American ethnicity.[19] SSc-ILD is most often associated with a histological pattern of nonspecific interstitial pneumonia, while usual interstitial pneumonia and other histologic patterns are less commonly observed.[20–22] Differences in histological patterns do not appear to have prognostic significance in SSc-ILD.[20]

When evaluating SSc-ILD, a variety of parameters should be considered as relevant to the patient's prognosis. The presence of Scl-70 antibodies is a key risk factor for disease severity and mortality.[5,17,23] Diffusing capacity of the lung for carbon monoxide (DLco) at baseline has been shown to be an independent predictor of mortality in SSc-ILD including in early SSc-ILD, while the extent of disease on baseline HRCT independently predicts ILD progression, as well as mortality.[24] Patients with cardiac involvement are more likely to have worse lung function.[19] Increased cutaneous sclerosis is associated with decreased lung function,[19,25] and the extent of skin disease appears to be an independent predictor of mortality.[26] Decline in forced vital capacity (FVC) and DLco over 2 years, and increased age are also independent predictors of mortality.[26]

Considering the heterogeneity of SSc-ILD, the potential absence of symptoms in early or mild disease, and the potential impact of ILD on outcomes in patients with SSc, it is prudent to consider the above parameters when assessing and monitoring newly diagnosed patients. Patients may be diagnosed early and more efficiently through multidisciplinary evaluation and collaboration; this is expected to help optimize care and lead to improved clinical outcomes.

Current Diagnostic Tools for ILD in SSc

The most frequently used methods to diagnose ILD in patients with SSc are HRCT and pulmonary function tests (PFTs).[27,28] HRCT is considered the "gold standard" method for diagnosing SSc-ILD, as well as other types of ILD.[29–31] Despite the established utility of PFTs in assessing the progression of ILD, these tests should not be used in isolation to screen for, or diagnose, SSc-ILD.[32] PFT results suggesting restricted lung function can be caused by SSc without ILD due to severe skin involvement, while results outside the normal range may not be apparent in patients with early ILD. These points are discussed in more detail below.

High-Resolution Computed Tomography

For the diagnosis of SSc-ILD, HRCT is more sensitive than conventional chest CT or PFTs and allows recognition of mild abnormalities.[28,33,34] The high sensitivity of HRCT can help identify mild or early interstitial abnormalities that are of unknown clinical significance,[34] which should prompt heightened surveillance for signs of progression. HRCT is well suited to detecting mild or early SSc-ILD; a scan of a patient with mild ILD compared with a patient with severe ILD is presented in Figure 1. As a non-invasive diagnostic tool, HRCT is used not only to detect ILD but also to predict ILD progression and decline in pulmonary function. In one study, 68% of the patients with SSc with areas of ground-glass opacities on their initial HRCT scan showed progressive lung fibrosis in a second scan that was conducted 2–5 years later.[35] This suggests that ground-glass opacities may precede lung fibrosis in SSc and that early intervention with immunosuppressive therapy should be considered.[35] HRCT can not only be used to detect ILD, predict the development of fibrosis, ILD progression and decline in pulmonary function,[36] but it can also be used to identify patients with SSc with low risk of developing ILD. Of 108 patients with SSc and no signs of lung fibrosis at baseline, none exhibited fibrosis upon follow-up HRCT assessment a mean of 3.1 years later.[36]

As alluded to earlier, baseline HRCT findings can be used to predict the likelihood of future progression, decline in FVC, or response to therapy,[36–38] and serial HRCT scans can be performed to check whether a patient has developed ILD or to monitor the progression of existing disease. HRCT also enables the detection of increased esophageal diameter, which has been associated with, and is an important predictor of, severe ILD and low DLco in patients with SSc.[34,39,40]

Radiation exposure is considered a potential limiting factor in the use of HRCT.[41] Recent findings highlight that the required HRCT slice number can be reduced, thereby limiting the radiation dose to the patient without affecting the assessment of lung fibrosis (severity or extent) in comparison to standard protocols.[42,43] This approach may be most useful in patients with established ILD, in whom HRCT may be used regularly to monitor progression. Nevertheless, it has been reported that sequential reduced 9-slice HRCT could reliably detect mild ILD[42] and discriminate lung fibrosis at a threshold of 20% with high sensitivity and specificity.[43] It may, therefore, be useful in detecting early disease progression in patients with SSc. However, further validation in additional cohorts of patients with SSc is required.

Quantitative imaging is emerging as a powerful tool for measuring the extent of lung fibrosis and for assessing disease progression more objectively than visual assessment.[44,45] In this method, computer-generated algorithms are applied to quantify the extent of features such as fibrosis, ground-glass opacities, and honeycombing, in a uniform and standard manner. Currently, quantitative imaging is being used primarily in SSc-ILD clinical trials, but may become established in daily clinical practice in due course.[44–46] Semi-quantitative imaging may also be used for diagnosis and quantification of lung involvement in SSc-ILD; however, this method does not eliminate subjectivity or variability from the assessor.[47,48]

Pulmonary Function Tests

FVC and DLco are important pulmonary function parameters for assessing lung involvement in SSc-ILD.[27] A recent systematic review of 219 SSc-ILD studies reported that FVC% predicted was the primary endpoint in 70.4% of the studies, and DLco was the primary endpoint in 11.3% of the studies.[29] Despite official American Thoracic Society guidelines which define ILD by a reduction of total lung capacity, this parameter remains rarely used as an outcome measure in SSc-ILD studies.[29]

Data from the Pittsburgh Scleroderma Databank demonstrated that the greatest declines in FVC often occur early, within the first 3 years of SSc onset, even in asymptomatic patients.[3,15] This was supported by the results of the Scleroderma Lung Study (SLS) I study. In SLS I, patients with SSc-ILD (n=77) who were randomly assigned to receive placebo had a 4.2% decline in

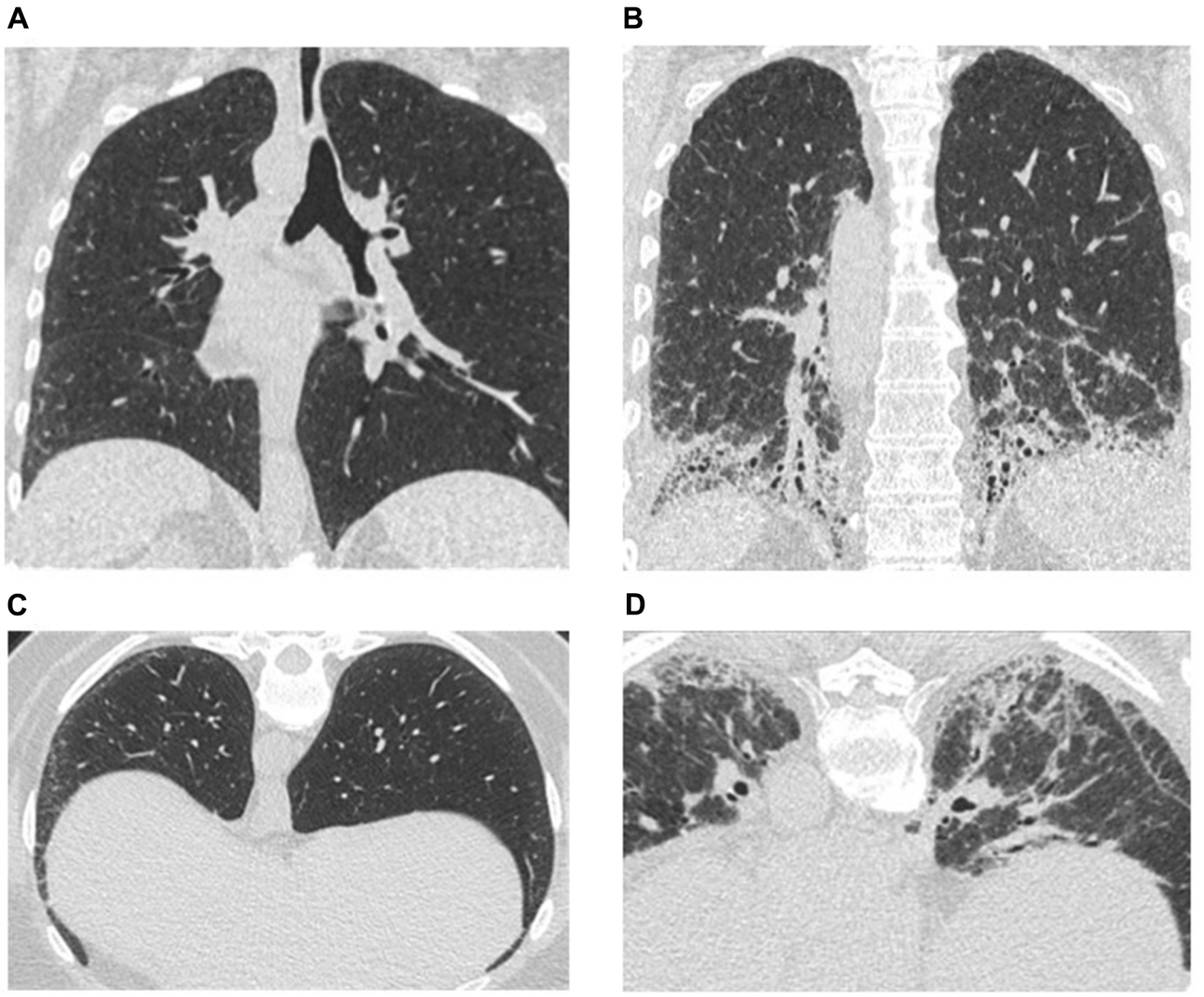

Figure 1 HRCT scans of lungs from patients with SSc-ILD of different severities.
Notes: Patient with mild severity: coronal view (**A**) and axial view (**C**); patient with severe disease: coronal view (**B**) and axial view (**D**). Both patients participated in the SLS II trial.
Abbreviations: HRCT, high-resolution computed tomography; SLS, Scleroderma Lung Study; SSc-ILD, systemic sclerosis with associated interstitial lung disease.

unadjusted FVC% predicted and an 8.2% decline in DLco % predicted over 12 months. The unadjusted decline in FVC% predicted and DLco% predicted were similar regardless of the disease duration (0–7 years) group, although an association between the extent of fibrosis (assessed via HRCT) at baseline and decline in FVC was most evident during the first 2 years after disease onset.[37]

FVC% or DLco% predicted values >80% are considered to be "normal" in patients without respiratory symptoms, but the threshold for "normal" varies between individual patients, potentially affecting interpretation of test results. In our experience and in line with the literature, a decline from baseline of 5–10% in FVC and 10–15% in DLco in a patient with SSc-ILD should be further evaluated, as it may be indicative of disease progression, even if absolute values remain above the 80% threshold.[32] Goh et al showed that a decline of ≥10% in FVC, or a decline of 5–9% in FVC together with a decline of ≥15% in DLco, was associated with a higher risk of subsequent mortality in patients with SSc-ILD.[49] This finding was attributed to disease progression in patients with extensive lung fibrosis. To illustrate this point, a patient with early SSc-ILD with an FVC of 90% would usually be considered normal. However, if this patient had an FVC of 110% a year earlier, the value of 90% represents a significant decline from their baseline, and, potentially, disease progression. It should be noted that the rate of decline in pulmonary function from baseline during the

first 12 months has been shown to have strong prognostic significance.

The clinical course of FVC decline in SSc is highly variable between patients, with the possibility of stability or improvement even in patients with low baseline FVC. Man et al identified the following groups of patients within SSc, based on baseline values and changes over the subsequent 72 months in FVC: (1) very low – slow decline (5.5% of the overall population of SSc patients); (2) very low – improve (13.8%); (3) low – fast decline (9.5%); low – stable (19.7%); (4) low-normal – improve (31.1%); (5) normal – improve (16.1%); and normal – stable (4.3%).[50] Patients with longer disease duration (>4 years) are less likely to experience a future decline in lung function compared with those who have early stage disease.[37]

Values for both FVC and DLco can be influenced by SSc disease processes other than ILD, and this should be a consideration during ILD assessment.[29] For example, a disproportionate decline in DLco relative to FVC may be related to the development of PAH.[51] FVC correlates poorly with the quantitative extent of fibrosis, while DLco has been shown to be the best predictor of HRCT-measured ILD.[52] The reliability of lung function as a predictor of SSc-ILD remains controversial. In a recent study involving 256 patients with SSc, among patients with radiographic ILD (n=188; 71%), 59 patients (31%) had a normal FVC (≥80% predicted). Of the 256 patients, 151 had accurate DLco measurements available; among these patients, 65 (43%) had a DLco ≥60% predicted.[33] These data emphasize limitations of PFTs and show that normal FVC and DLco measurements in patients with SSc do not exclude the presence of ILD or obviate the need to pursue HRCT imaging to definitively assess for ILD. Due to the variability arising from technical factors, diurnal or seasonal changes, and patient-related factors, PFTs alone are insufficient for determining the true extent of ILD and changes in PFT parameters do not mirror changes in the extent of radiographic fibrosis consistently.[53]

Combined Data from HRCT and PFTs

Considering the aforementioned limitations of HRCT and PFTs, combined use of these tests can provide more informative and reliable prognostic information than either component used alone.[54,55] We suggest that, in addition to assessing and quantifying dyspnea and cough, and performing PFTs in patients with newly diagnosed SSc, HRCT should be used to assess the presence of ILD. Depending on the clinical scenario, appropriate follow-up investigations might include DLco for PAH evolution or serial FVC, DLco, and HRCT assessments in patients with established ILD. In order to increase the likelihood of diagnosing ILD at an early stage, yearly PFTs with a low threshold are recommended in patients with SSc and no known ILD. HRCT should be pursued if there is a decline in FVC and/or DLco, or a change in the clinical scenario (e.g., increased dyspnea or audible crackles on chest auscultation).

Other Diagnostic Tools

Lung Ultrasound and Other Imaging Modalities

One drawback of HRCT is radiation exposure,[41] and this casts concern over the frequent use of this method to monitor for SSc-ILD disease progression. The past few years have seen extensive evaluation of lung ultrasound (LUS) as a non-invasive and non-ionizing imaging method for detecting ILD.[56] Discrete vertical hyperechoic reverberation artifacts arising from the pleural line and extending to the bottom of the screen without fading when the lung parenchyma air content is decreased or when the interstitial space is expanded, known as B-lines, have been observed in 51% of the patients with SSc.[57] Several studies have reported a significant linear correlation between the number of B-lines and HRCT score.[58–60] Pleural irregularity (PI; loss of normal hyperechoic linear pleural contouring) represents another potential LUS assessment criterion. A recent study reported significantly higher PI scores in patients with SSc with ILD versus without ILD, and in patients with extensive versus limited disease. In addition, the PI scores correlated with the Wells scores and with DLco measurements.[61] Thus, the PI score could be valuable in diagnosing, classifying, and assessing SSc-ILD.

LUS may also represent a useful tool for the detection of ILD at an early stage in patients with SSc.[62] In a recent study, 58 patients with SSc were evaluated for signs of ILD with HRCT and then LUS. Using HRCT, evidence of ILD was confirmed in 88% of the patients with SSc and in 41% of the patients with early stage SSc. When subsequently analyzed with LUS, there was a significant difference in the number of B-lines in patients with or without evidence of ILD on HRCT (57±53 vs 9±9; $p<0.0001$), with a concordance rate of 83%.[62]

Overall, LUS seems to be an attractive and promising technique, with the potential to be integrated with HRCT and PFTs in the screening and evaluation of ILD in

patients with SSc. However, at this stage, LUS remains a relatively experimental and unproven technique for ILD diagnosis. Validation and protocol standardization across institutions are needed before LUS can be implemented in routine clinical practice.

Further imaging modalities with potential application in early SSc-ILD include magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).[63] Such modalities have been used to obtain diagnostic information with regard to disease activity and treatment response in cardiac disease, neurodegenerative disease, and oncology, and are being investigated more frequently in pulmonary diseases including SSc-ILD.[63] The use of MRI to image pulmonary fibrosis in SSc-ILD has been investigated. For instance, the capacity of MRI to determine the presence and degree of ILD was assessed retrospectively in 18 patients with SSc who underwent MRI and HRCT of the chest within a 12-month period. MRI could detect ILD with high sensitivity and specificity in patients with greater than 0.5% parenchymal involvement.[63,64] However, in comparison with HRCT, MRI was found to be less sensitive and under-measured disease extent.[64] MRI has been investigated in terms of its capacity to detect early functional changes with treatment in various diseases; however, further research is needed to confirm if MRI could be used to detect early changes in SSc-ILD.

Molecular probes can be combined with various imaging modalities, such as MRI, SPECT, or PET to help visualize and quantify the expression of specific molecular targets. For instance, probes have been designed to target molecular components involved in the onset of inflammation following epithelial injury or the development of pulmonary fibrosis.[65] Several molecular probes have been utilized in animal models of pulmonary fibrosis or in humans with pulmonary fibrosis including SSc-ILD; further research and development in this area may lay foundations for early and more personalized precise diagnostic and treatment approaches.[63,65] At present, however, these methods are investigational in relation to the diagnosis and assessment of SSc-ILD and not commonly used currently in clinical practice.[63,66]

Bronchoalveolar Lavage

Currently, bronchoalveolar lavage (BAL) is most often performed when there is suspicion of an underlying infection. It is seldom used for diagnosis or screening of SSc-ILD due to inconclusive study outcomes,[67] as well as being an invasive procedure with potential complications. In a follow-up study from SLS I, evaluation of BAL inflammation did not improve prediction of disease progression or treatment response, in comparison with physiologic and HRCT findings.[68] However, in a later study, BAL was used in conjunction with comprehensive clinical information and HRCT findings, and this approach provided useful information for the diagnostic evaluation of patients with suspected ILD.[69] Overall, the role of BAL as a tool for early diagnosis of ILD in patients with SSc is controversial and not recommended.

Surgical Lung Biopsy

Obtaining lung tissue samples is an invasive procedure that requires the use of anesthesia and carries the potential risk of significant complications, including acute exacerbation of ILD, prolonged air leak, and respiratory failure.[70–72] Given the availability of the methods described earlier and the unclear implications of defining histologic subsets in SSc-ILD, lung biopsy is not clinically necessary in most patients.[20,73,74] However, it can be diagnostically useful in certain circumstances, such as when there are contradictions between clinical and radiological findings.[75]

Serum Biomarkers

Although techniques such as HRCT and PFTs can be used to detect early development or progression of SSc-ILD, it is necessary to find additional reliable and easily obtained markers of disease progression. Biomarkers may have a role in this respect since they can be readily obtained, are informative, and can be monitored over time.[76] Elevated serum levels of the glycoprotein Krebs von den Lungen-6 (KL-6) at first visit have been associated with lung involvement in patients with SSc.[77] Elevated serum KL-6 has been linked to the degree of inflammation and fibrosis, and future decline in lung function.[78–83] Thus, KL-6 is emerging as a promising biomarker for the diagnosis of SSc-ILD, with potential for predicting lung involvement and disease progression. The detection of high KL-6 levels at baseline could help to identify patients in need of therapy or more frequent clinical monitoring.[78,81,84]

High levels of the cytokines, chemokine (C-C motif) ligand 2[85] and CCL18,[86] are predictive of ILD progression[82,83] and poor survival in patients with early SSc-ILD.[82] However, a recent study highlighted that, although CCL18 levels are higher in patients with SSc-ILD, they do not predict progression of ILD based on FVC decline.[81] Serum levels of surfactant protein D (SP-D) are also elevated in patients with SSc-

ILD,[83] and longitudinal measurement of SP-D levels may help to monitor fibrosis. However, there is some uncertainty regarding the interpretation of SP-D results and validation is required.[77] Several other biomarkers, including interleukin-6[87] and CXC chemokine ligand 4,[88,89] may also be important in SSc-ILD. High levels of certain serum biomarkers could potentially serve to prompt physicians to undertake further pulmonary imaging and PFTs. For most biomarkers, the available evidence is insufficient to justify utilizing them in clinical practice; however, further research may shed light on the most important biomarkers for ILD screening in patients with SSc. The key strengths and limitations of each technique discussed in this section are summarized in Table 1.

Monitoring and Predicting the Progression of ILD in Patients with SSc-ILD

Considering the potentially progressive fibrosing phenotype of SSc-ILD and the risk of rapid deterioration particularly evident in the first 3 years of disease onset, effective and early disease monitoring is of utmost importance.[14] In addition to this, monitoring treatment response is important. Disease progression and response to treatment are usually assessed through the evolution of respiratory symptoms, exercise tolerance, HRCT findings, and PFTs. In SLS I, patients with any cough at baseline displayed increased ILD severity.[90] Treatment of SSc-ILD patients with CYC and mycophenolate (MMF)[91] was shown to produce significant reductions in cough,[92] along with improvements in measures of ILD severity over 2 years.[91]

Not only is it important to detect and monitor SSc-ILD, it is essential to identify those who are at high risk of disease progression at an early stage. Recently, studies have been undertaken to investigate the possibility of using predictive models for this purpose.[50,93–95] Ryerson et al showed that the modified du Bois index (parameters: age, respiratory-related hospitalization in the past 6 months, and predicted baseline and 24-week change in FVC) was slightly superior to the composite physiologic index, ILD-gender, age, physiology index, and the du Bois index in predicting 1-year mortality in SSc-ILD.[94] Additionally, the FVC and 6 min walk test distance (6MWT) were identified as independent predictors of mortality.[94] The 6MWT is frequently used as a measure of exercise tolerance in patients with SSc-ILD.[96] However, although it is a straightforward and non-invasive assessment of exercise capacity, its usefulness and accuracy remain unclear in patients with SSc-ILD due to potential concomitant neuromuscular effects that can introduce bias.[96]

Despite recommendations to perform these assessments (as well as 6MWT) at regular intervals in patients with idiopathic pulmonary fibrosis (IPF),[97] there are no formal guidelines for monitoring progression in SSc-ILD. Most clinicians would perform PFTs every 3–6 months,[30] whereas opinions on the optimal interval between HRCT assessments are variable. Table 2 shows our suggestions for monitoring patients with SSc-ILD, including those with early disease.

Current Treatments for SSc-ILD

Due to the complexity and heterogeneous nature of SSc-ILD, treatment approaches should be tailored to the individual, with consideration of disease stage and organ-specific complications.[98] While early treatment of ILD in SSc is of high importance to reduce the rate of lung deterioration and mortality,[13] not every patient with SSc-ILD requires treatment for their ILD — treatment is often reserved for patients with progressive disease, ILD-related clinical impairment, or those patients at high risk for ILD progression. Table 3 provides a summary of treatments currently being investigated for the treatment of SSc-ILD, and Figure 2 presents a diagrammatic summary of the mechanism of action of these drugs.

Immunosuppressive Therapy

CYC and MMF are the most broadly prescribed therapies for SSc-ILD. A retrospective study from the European Scleroderma Trials and Research group involving over 3000 patients with SSc-ILD recently reported that non-selective immunosuppressive therapy was prescribed to 71% (2681/3778) of patients.[99] Also, a survey from the Scleroderma Clinical Trial Consortium and the Canadian Scleroderma Research group (n=170) revealed that 69% of the experts surveyed would use CYC, MMF, or rituximab (RTX) for induction therapy, and MMF for maintenance therapy.[100] However, CYC and MMF are not consistently disease-modifying for all patients, as some patients experience ILD progression despite treatment with these agents.

Cyclophosphamide

In the early 1990s, CYC was found to improve pulmonary function in patients with SSc-ILD when administrated

Table 1 Diagnostic Tests for ILD: Summary of Available Methods, and Their Main Strengths and Limitations

Diagnostic Test	Use in ILD	Key Strengths	Key Limitations
HRCT	Detailed cross-sectional imaging of the lung parenchyma	• Non-invasive[145] • Enables early detection, monitoring, assessment of temporal progression, and response to treatment[36–38] • Enables assessment of esophageal diameter[39,40,57] • Possible to reduce slice number and, therefore, radiation dose[42,43] • Can be combined with computer-generated algorithms to allow quantitative imaging[44,45,146] • High sensitivity, specificity, and accuracy compared with chest X-ray[147]	• Exposure to ionizing radiation[41–43] • Insensitive for certain changes, particular airways, and pulmonary vascular disease[31] • Sometimes too sensitive: clinical relevance with respect to early interstitial changes is uncertain[148]
Chest CT	Two-dimensional imaging of the lungs	• Widely available[149] • Economical[149] • Simple[150] • Observations can be suggestive of specific ILD entities[151]	• Exposure to ionizing radiation[152] • Limited spatial resolution[153] • Lower sensitivity compared with HRCT[147] • Lower specificity compared with HRCT[147] • Two-dimensional rather than three-dimensional imaging[147] • Provides only a crude estimate of disease severity[53]
PFTs (e.g., spirometry, diffusion capacity)	Determination of lung function, including lung capacity, airflow obstruction, and gas exchange	• Enables detection of changes in pulmonary function even when patients are asymptomatic[15,27] • Reflects disease severity more accurately than chest X-ray[53] • Useful in monitoring for disease progression and response to treatment[15,37] • Results can be considered in combination with other data to increase reliability[54,55] • Independent predictor of mortality[94]	• Dependent on patient effort[147] • Normal results can be observed in ILD patients[33] • Abnormalities on PFTs are often non-specific with regard to etiology[29] • Variations between individual patients are a major constraint in disease staging[53] • Variations may be caused by technical factors[53]
LUS	Ultrasonographic characterization of the lung	• Non-invasive[154] • Enables imaging of the surface of the lungs[155] • No ionizing radiation[41,154] • Detection of fibrosis is possible, which may correlate with observations using HRCT[58–60] • Characteristic changes are observed in certain instances (e.g., B-lines when lung parenchyma air content is decreased or when the interstitial space is expanded)[57] • Bedside procedure[155] • Easy to learn[155] • Inexpensive[154]	• Quality of results is dependent on operator experience[154] • Not standardized for the evaluation and examination of patients with ILD[156]

MRI	Magnetic imaging of the lungs based on the oscillation of protons relative to an applied magnetic field	• Non-invasive[157] • No ionizing radiation[158] • High spatial resolution[159] • Can be paired with specific molecular probes/tracers[63] • Can acquire both structural and functional information following a single examination[157,160,161] • Can be used to assess motion and perfusion of the thoracic organs[162] • Recent development (e.g., use of oxygen-enhanced ^{1}H MRI; MRI with noble or hyperpolarized gases) mean that the scan results in the lung can be enhanced[163]	• Expensive[164,165] • Strong magnetic field can exert strong forces on objects and devices that have ferromagnetic components, unless they are designed or programmed to be resistant to external magnetic influences[166,167] • Signal-to-noise ratio can be an issue in the lung[66] • Relatively loud[168] • Can be stressful for those with claustrophobia[168,169] • Scan times can be long and uncomfortable[168] • Can underestimate ILD extent compared with HRCT[64] • Imaging of the lungs can be challenging without the use of advanced equipment or inhaled contrast agents[170] • Not standardized for the evaluation and examination of patients with ILD[162]
PET/PET-CT	Nuclear (gamma radiation) functional imaging of specific metabolic processes in the lung with the use of positron-emitting radiotracers	• Provides physiological information through functional imaging[171] • Can be used to study various specific metabolic processes depending on the radiotracer employed[63] • Can be combined with CT and other anatomical imaging methods permitting both metabolic, functional, and structural imaging[172] • Can be used to detect early signs of ILD based on specific biochemical changes[63,173] • Sensitive to specific metabolic changes[174,175] • Non-invasive apart from administration of the radiotracer[176] • Can be used for the quantitative assessment of active ILD in patient with SSc-ILD[177]	• Expensive[164] • Involves and is reliant on the administration of a radiotracer which, following the emission of a positron and an annihilation event, results in the emission of ionizing radiation[171] • Inconvenient and long scan times[178] • Can require an on-site cyclotron[66] • Not standardized and not commonly used for the evaluation and examination of patients with ILD; studies are still at the investigational stage[66]
SPECT/ SPECT-CT	Nuclear imaging scan of biochemical processes in the lung using radiotracers; the scanning system is integrated with CT	• Provides physiological information through functional imaging[179] • Can be used to study various specific metabolic processes, including those involved in early ILD in SSc, depending on the radiotracer used[180] • Can be combined with CTand other anatomical imaging methods to help facilitate anatomical localization of SPECT images; enables accurate and rapid attenuation correction of SPECT studies.[181] • Non-invasive apart from administration of the radiotracer[182]	• Involves and is reliant on administration of a radiotracer[179] • Ionizing radiation[183] • Regular availability of radio isotopes is required[65] • Scan times can be long and inconvenient[184] • Spatial resolution is highly dependent on various factors and can be limited[179] • Not standardized and not commonly used for the evaluation and examination of patients with ILD; studies are still at the investigational stage

(*Continued*)

Table 1 (Continued).

Diagnostic Test	Use in ILD	Key Strengths	Key Limitations
BAL	Characterization of recovered cellular and non-cellular components from the epithelial surface of the alveoli and terminal bronchioles	• Useful for the diagnosis of intrapulmonary infections[69] • Can support an ILD diagnosis[69] • Can be completed as an outpatient procedure[185]	• Invasive (though minimally)[186] • Typically non-specific for ILD, limiting diagnostic potential[67,69,185,187] • Only the surfaces of internal pulmonary structures are assessed, with collection of non-adherent cells and fluid lining the bronchial and alveolar epithelium[69,188]
Surgical lung biopsy	Tissue sampling for characterization of the lung parenchyma	• Can be useful in making a confident diagnosis[189] • Beneficial when there is clinical-radiological discordance[75]	• Invasive[70] • Potential for sampling error if only a single biopsy is taken[70,190] • Requires the use of anesthesia (usually general)[71] • Mortality risk is elevated in certain patient groups (e.g., elderly patients with comorbidities, patients with pulmonary hypertension)[72]
6MWT	Exercise tolerance	• Non-invasive[191] • Simple in concept[191] • 6MWT distance is an independent predictor of mortality[94]	• Pain may act as a limitation, potentially preventing patients from reaching a dyspnea limitation[192] • Accuracy and specificity remain unclear due to various influencing factors such as patient neuromuscular and psychological state, pharmacological effects of medication, test conducts, and technician experience; all can introduce bias[96] • Finger-measured oxygen saturation results may be affected by Raynaud's phenomenon[193] • Lacks organ specificity[194]
Serum biomarker screening	Characterization of serum biomarkers	• Readily obtained and non-invasive; suitable for serial monitoring[195] • Could help to guide clinical decisions[196]	• More research required to enable use of serum biomarkers in clinical practice for SSc-ILD[195]

Abbreviations: 6MWT, 6-min walk test; BAL, bronchoalveolar lavage; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LUS, lung ultrasound; MRI, magnetic resonance imaging; PET, positron emission tomography; PET-CT, positron emission tomography with X-ray CT; PFT, pulmonary function test; SPECT, single-photon emission computed tomography, SPECT-CT, single-photon emission computed tomography with X-ray CT; SSc, systemic sclerosis.

Table 2 Monitoring the Progression of SSc-ILD in Different Clinical Scenarios: Suggested Frequencies for Assessment[a]

Clinical Scenario	TESTS			
	History and Physical	HRCT	PFTs	6MWT
New diagnosis of SSc-ILD in early SSc (<5 years)	Every 3 months	Every 12 months unless clinical scenario changes	Every 3–4 months	Every 3–6 months
New diagnosis of SSc-ILD in established SSc (>5 years)	Every 3 months	Every 12 months	Every 3–6 months	Every 3–6 months
Patient with SSc-ILD who is receiving treatment for ILD	Every 3 months	Every 6–12 months, at discretion of treating physician	Every 3–4 months	Every 3–6 months
Patient with SSc-ILD who has completed a course of treatment for ILD	Every 3–6 months	As needed based on discretion of treating physician	Every 6–12 months	Every 6–12 months
Patient with SSc-ILD and concurrent pulmonary hypertension	Every 3 months	As needed based on discretion of treating physician	Every 3–6 months	Every 3–6 months
Patient with SSc-ILD and concurrent muscle disease	Every 3 months	Every 12 months unless clinical scenario changes	Every 3–4 months; considered along with respiratory muscle pressure testing	Every 3 months

Notes: [a]Table derived from author recommendations. Data from these studies.[37,49,197,198]
Abbreviations: 6MWT, 6-min walk test; HRCT, high-resolution computed tomography; PFT, pulmonary function test; SSc-ILD, systemic sclerosis with interstitial lung disease.

Table 3 Current and Potential Future Therapeutic Agents: Supporting Evidence and Ongoing Studies

Treatment/Drug Name	Category	Available Clinical Evidence in SSc-ILD	Ongoing Studies
Cyclophosphamide	Immunosuppressant	26,44,90,103,104	• NCT01570764
Mycophenolate mofetil	Immunosuppressant	10,106,108,109	• NCT03221257
Azathioprine	Immunosuppressant	113–115	–
Pirfenidone	Antifibrotic agent	126,127	• NCT03221257
Nintedanib	Antifibrotic agent	112	• NCT02597933 • NCT03313180 • NCT03675581
Imatinib	Antifibrotic agent	128–130	–
Dasatinib	Antifibrotic agent	131	–
Nilotinib	Antifibrotic agent	132	–
Rituximab	Other (monoclonal antibody)	119	• NCT01862926
Dabigatran	Other (direct thrombin inhibitor)	133	–

Abbreviations: SSc-ILD, systemic sclerosis-related interstitial lung disease.

with low-dose prednisone.[101] It was subsequently shown that CYC alone improved lung function and survival outcomes.[102] A retrospective study provided evidence supporting the role of CYC in SSc-ILD, particularly for patients with early SSc-ILD (<4 years), compared with high-dose prednisolone, immunosuppressive other than

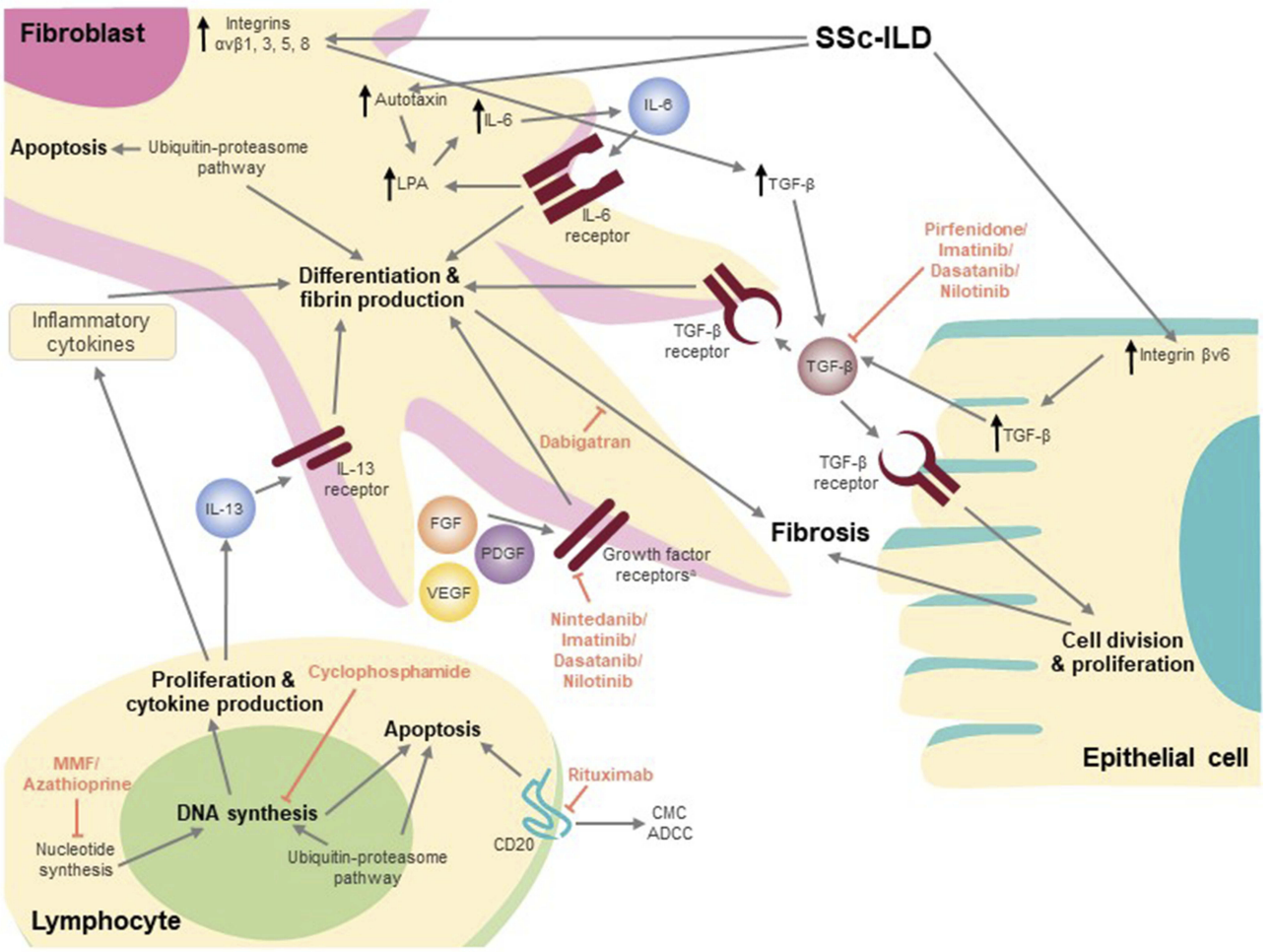

Figure 2 Key pathogenic pathways involved in SSc-ILD and purported targets of existing and potential therapeutic agents.

Notes: Khanna D, Tashkin DP, Denton CP, et al, Ongoing clinical trials and treatment options for patients with systemic sclerosis–associated interstitial lung disease, Rheumatology 2019; 58 (4): 567–579, doi:10.1093/rheumatology/key151. Reprinted by permission of Oxford University Press on behalf of the British Society for Rheumatology. © The Author(s) 2018. All rights reserved. For permissions, please email: journals.permissions@oup.com.[7] [a]Multiple growth factor receptors.

Abbreviations: ADCC, antibody-dependent cell-mediated toxicity; CD, cluster of differentiation; CMC, complement-mediated cytotoxicity; DNA, deoxyribonucleic acid; FGF, fibroblast growth factor; IL, interleukin; LPA, lysophosphatidic acid; MMF, mycophenolate mofetil; PDGF, platelet-derived growth factor; SSc-ILD, systemic sclerosis with associated interstitial lung disease; TGF, tumor growth factor; VEGF, vascular endothelial growth factor.

CYC, D-penicillamine, and no drug. The CYC-treated group showed significantly more improvement in FVC than the other groups.[13] The randomized, controlled trial SLS I provided robust evidence of CYC efficacy compared with placebo; after 12 months of CYC therapy, modest but significant improvements were reported in FVC decline, total lung capacity, dyspnea, skin thickening, and health-related quality of life.[90] Follow-up data from the SLS I study showed that the beneficial effects of 12 months of CYC therapy persisted for a few months after cessation of therapy, although there was no difference in FVC between the two study groups at 24 months post-treatment.[103] Quantitative analysis based on HRCT findings from SLS I showed decreased quantitative lung fibrosis scores in the CYC group compared with placebo at 12 months.[44]

Subsequent studies of CYC in SSc-ILD have yielded conflicting results. Nannini et al conducted a systematic review and meta-analysis of randomized, controlled trials and prospective observational studies in patients with SSc-ILD.[104] The meta-analysis showed that CYC treatment does not result in clinically significant improvement of pulmonary function.[104]

Despite the conflicting efficacy data, CYC remains the most widely used treatment for SSc-ILD in the world.[99] However, CYC therapy is associated with toxicities, including an increased risk of leukopenia and neutropenia.[90,105] Consequently, CYC is unsuitable for use in some patients. Additionally, a recent study found that 1 year of treatment with CYC did not improve long-term survival compared with placebo in patients who participated in SLS I.[26]

Mycophenolate Mofetil

MMF has been suggested as an alternative to CYC and was shown to stabilize lung function in patients with SSc-ILD in a retrospective study.[106] Additionally, a pilot study assessed the safety and efficacy of anti-thymocyte globulin given for 5 days, followed by MMF for 12 months, in patients with recent-onset diffuse SSc. It was shown that systemic disease was stabilized as measured by various assessments including FVC and that MMF was well tolerated.[107] In a prospective, observational 1-year study of 14 SSc-ILD patients treated with MMF, six patients reported at least a 10% improvement in their FVC and five had stable pulmonary function.[108] In SLS II, 2 years of treatment with MMF was compared with 1 year of treatment with CYC followed by 1 year of placebo in patients with SSc-ILD. The two treatments produced similar improvements in FVC% predicted at 24 months; MMF and CYC treatment led to an overall improvement in the FVC% predicted with an absolute change from baseline in FVC% predicted of 3.3%±1.1 and 3.0%±1.2, respectively. However, MMF showed a more favorable safety and tolerability profile.[10] A recent analysis of data from the SLS I and SLS II studies was performed to compare MMF with placebo, with adjustments for disease severity. Patients treated with MMF showed a significant improvement in FVC% predicted, DLco% predicted, and dyspnea compared with the placebo group.[109] Together, these data support the continued use of MMF to treat SSc-ILD.

Nintedanib

Nintedanib is a tyrosine kinase inhibitor (TKI) that acts on the platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor receptor signaling pathways. As a result, it inhibits cytokine-induced activation of fibroblasts and has demonstrated potent antifibrotic effects in mouse models of SSc.[110] Recently, nintedanib became the first Food and Drug Administration-approved treatment for SSc-ILD; it is indicated for slowing the rate of decline in pulmonary function in patients with SSc-ILD[111] based on the results of the phase III, randomized, double-blind, placebo-controlled Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial (NCT02597933).[112] In the SENSCIS trial, a broad population of patients with SSc-ILD were selected, including those with limited and diffuse cutaneous SSc, those receiving mycophenolate at a stable dose for 6 months at baseline, and those with several lung function impairments. In the primary endpoint analysis, there was significant difference in the adjusted annual rate of change in FVC between nintedanib and placebo (difference 41.0 mL/year; 95% confidence interval [CI] 2.9–79.0; p=0.04) over a 1-year period in the total study population. The differences in change from baseline in the modified Rodnan skin score (mRSS) and total score on the St George's Respiratory Questionnaire were not significant. Adverse events (AEs) were similar between the nintedanib and placebo groups. In line with the known safety profile of nintedanib in IPF, diarrhea was the most common AE. Among nintedanib-treated patients who experienced diarrhea AE, diarrhea events which were at worst mild or moderate in severity were reported in 49.5% and 45% of the patients, respectively.[112] An open-label extension trial to assess whether there is sustained efficacy with nintedanib, as well as its long-term safety (NCT03313180), is ongoing.

Azathioprine

A retrospective case series study suggested that azathioprine (AZA) given in combination with low-dose prednisone may play a role in stabilizing pulmonary function in patients with SSc.[113] A recent case study reported that AZA combined with prednisone improved pulmonary function.[114] However, no significant improvements in FVC and DLco were observed compared with placebo in patients with SSc-ILD who received CYC and low-dose prednisolone followed by oral AZA in a randomized, controlled trial.[115] In an open-label prospective study conducted in 13 patients with early diffuse SSc (nine of whom had lung involvement), patients who completed a year of treatment with low-dose intravenous pulse CYC received 1 year of treatment with AZA (50 mg/day for the first 20 days and 100 mg/day thereafter).[116] The results showed that the improvement following a year of CYC therapy was maintained by AZA treatment; no outcome measures deteriorated, including FVC and DLco. This study, therefore, may suggest a role of AZA in maintaining the improvement induced by low-dose pulse CYC in early diffuse SSc; however, these findings require confirmation in controlled studies.[116] Therefore, the clinical value of AZA in SSc-ILD remains unclear and, to the best of our knowledge, this drug is not currently being investigated further in SSc-ILD.

Adjunctive Therapies

The primary aim of treatment for SSc-ILD is to optimize patients' quality of life as early as possible. Pharmacologic

therapy is the primary focus, but adjunctive supportive measures can lessen the symptom burden.[117] The primary adjunctive measures to consider in the care of patients with SSc-ILD are similar to those used for other types of ILD. These include smoking cessation, appropriate vaccinations, supplemental oxygen (if oxygen saturation is below 89% at rest or upon exertion), and pulmonary rehabilitation. Additionally, the association between gastroesophageal reflux disease (GERD) and ILD necessitates appropriate management of GERD in patients with SSc-ILD.[117]

Other Potential Future Therapeutic Agents

Several treatments are being investigated in SSc-ILD. This review focuses on treatment options for SSc-ILD with the most published evidence supporting their use in this condition. Additional agents under investigation for SSc-ILD that are not included here are bortezomib and abatacept.

Rituximab

RTX is a CD20-targeting chimeric monoclonal antibody that causes rapid B-cell depletion and immunosuppression. It is licensed for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis.[118] In a 1-year, proof-of-principle study in SSc-ILD, a 10% increase in FVC% predicted versus baseline was observed with RTX compared with a 5% decrease in the control group (p=0.002).[119] A retrospective analysis of data from the European League Against Rheumatism Scleroderma Trials and Research Group database showed that over a mean follow-up period of 2 years, RTX use was associated with an acceptable safety profile, and significant improvement was observed in skin fibrosis, but not in lung function.[120] RTX is currently being compared with CYC in a randomized, controlled trial, as a first-line treatment in patients with SSc-ILD and other connective tissue diseases with associated ILDs.[121]

Antifibrotic Agents

Antifibrotic agents slow lung function decline in IPF and were approved for the treatment of this lung disease in 2014.[122] Due to the clinical and mechanistic parallels between IPF and SSc-ILD, including lung parenchymal injury, transforming growth factor (TGF)-β-mediated fibroblast activation, and myofibroblast accumulation,[123] antifibrotics are being studied as potential treatment options in SSc-ILD. The exact mechanism of action of the antifibrotic agent pirfenidone is currently under investigation and is not yet fully understood, but it has been shown to reduce TGF-β-stimulated fibrosis.[124,125] A small study of five patients with SSc-ILD reported improved FVC upon treatment with pirfenidone at doses ranging from 1200 to 1800 mg/day.[126] Subsequently, in the randomized, open-label, phase II Safety and Tolerability of Pirfenidone in Patients With Systemic Sclerosis−Related Interstitial Lung Disease (LOTUSS) study (NCT01933334), pirfenidone showed an acceptable safety and tolerability profile.[127] The ongoing SLS III trial (NCT03221257) will compare pirfenidone plus MMF versus placebo plus MMF in patients with SSc-ILD.

TKIs other than nintedanib are also being assessed in SSc-ILD. Imatinib was first investigated in a phase I/IIa, open-label, pilot study (NCT00512902) in patients with SSc-ILD and showed trends towards improvement in FVC and DLco over 1 year.[128] However, treatment-related toxicities were observed with the 600 mg/day dose.[128] A subsequent phase IIa study assessed imatinib 400 mg/day in patients with diffuse cutaneous SSc, 53% of whom had SSc-ILD; most patients tolerated the treatment, and sustained FVC improvements were observed.[129] Conversely, in a small phase I/II study (NCT00506831) conducted in seven patients with SSc, imatinib 300 mg/day produced no improvement in pulmonary function. A subsequent phase II pilot study reported that imatinib 200 mg/day stabilized lung function and improved HRCT scan patterns in patients with SSc-ILD who were unresponsive to CYC (NCT00573326).[130]

Dasatinib and nilotinib are examples of second-generation TKIs; these compounds block several receptor and non-receptor kinases, many of which have been shown to be activated in SSc. In a single-arm, open-label, phase IIa study of dasatinib in SSc-ILD (NCT00764309), the safety profile was acceptable.[131] No significant changes at Day 169 versus baseline were observed in mRSS or PFTs, but comparison with a historical, placebo-treated control group indicated that dasatinib may have reduced the rate of deterioration of lung fibrosis. An open-label pilot study of nilotinib was, therefore, performed in patients with SSc, three (30%) of whom had ILD. Nilotinib was well tolerated, and the principal safety finding was mild QTc-prolongation. The study showed significant improvements in skin parameters in response to nilotinib, but these findings should not be considered as definitive because of the open-label study design and the small number of patients included.[132] Further investigations are warranted.

Dabigatran

The thrombin inhibitor dabigatran directly prevents fibrin formation and, therefore, could have therapeutic potential in fibrosing ILD. Preliminary data from a phase I, open-label clinical trial (NCT02426229), which investigated the safety and efficacy of dabigatran in patients with SSc-ILD, suggested that individuals with high baseline plasma/BAL fluid thrombin activity were more likely to benefit from dabigatran.[133]

Tocilizumab

Tocilizumab is a monoclonal antibody that targets interleukin-6, a cytokine that has been implicated in the pathogenesis of SSc. Two major placebo-controlled studies have investigated the safety and efficacy of tocilizumab in patients with SSc. These studies were focused on patients with an early, active progressive diffuse cutaneous SSc (progression defined by increase in mRSS), but not specifically those diagnosed with associated ILD, as in the SLS and SENSCIS trials; nevertheless, both tocilizumab trials included lung function assessment. In the phase II Safety And Efficacy Of Subcutaneous Tocilizumab In Adults with SSc (faSScinate) trial, the percentage of patients with SSc showing a decline in FVC at 48 weeks was significantly lower in the tocilizumab group than in the placebo group (p=0.0373).[134] This benefit was maintained in a 48-week, open-label extension of the study. Tocilizumab treatment was associated with benefits in skin fibrosis, lung fibrosis, and physical function in patients with SSc; however, it was also associated with increased risk of serious infections. Taken together, the results of the faSScinate trial and its associated open-label extension period may indicate a role for tocilizumab for the treatment of patients with progressive SSc who have few treatment options.[135] The phase III Efficacy and Safety of Tocilizumab in Participants With SSc (focuSSced) trial reported a 167 mL (95% CI 83–250 mL) difference in favor of tocilizumab versus placebo in the mean change from baseline in FVC at Week 48.[136] The primary endpoints in the focuSSced and faSScinate clinical trials, which were change in mRSS at 48 and 24 weeks, respectively, were not met.

Additional Therapeutic Options

Stem Cell Transplantation

For over 2 decades, hematopoietic stem cell transplantation (HSCT) has been used in the treatment of autoimmune disorders that are refractory to conventional immunosuppressive therapy.[137] HSCT has been studied in three randomized, controlled trials in patients with SSc; a summary of each of these studies is provided in Table 4. There is evidence that HSCT may prevent organ deterioration and improve skin thickening, pulmonary function, and long-term survival in patients with SSc.[137] In addition, follow-up assessment of participants in the Scleroderma: Cyclophosphamide or Transplantation trial (summarized in Table 4) showed that HSCT results in significant correction of molecular signatures associated with SSc.[138] However, HSCT has been associated with treatment-related mortality in the early, post-transplant period, and some patients who demonstrate an initial response may subsequently experience progression of SSc-related symptoms. Overall, HSCT is likely to be beneficial in patients with early, diffuse skin disease who are at risk of rapid progression, although candidates need to be selected carefully, with particular consideration of cardiac disease.[139]

Lung Transplantation

Lung transplantation represents a life-saving option for selected patients with progressive SSc-ILD who are at risk of respiratory failure.[140] Short- and intermediate-term survival rates after lung transplantation appear similar in carefully selected patients with SSc-ILD compared with PAH and other connective tissue disease-ILDs.[141–143] A retrospective, single-center study also showed that outcomes were similar in patients with or without SSc who underwent lung transplant; and that esophageal dysfunction – present in 60% of the patients with SSc – only rarely precluded or affected the listing of the outcome of lung transplantation.[144] Overall, patients with advanced and refractory SSc-ILD may be candidates for lung transplantation, although careful consideration of age and comorbidities (e.g., esophageal dysfunction) is essential.[141]

Conclusion

As ILD is the leading cause of death in SSc, screening for its presence is essential – even in the absence of symptoms. HRCT is the most effective means of identifying ILD in patients with SSc, as it enables the detection of mild lung abnormalities; it can also play an important role in monitoring disease progression. Early detection of ILD provides the opportunity for early therapeutic intervention, which could improve patient outcomes. Due to multi-organ involvement and the complex nature of SSc-ILD, interdisciplinary engagement is key to provide optimal

Table 4 Randomized Controlled Trials of HSCT in SSc-ILD

Trial Name (Study Identification Number) and Design	Patient Characteristics (Selection Criteria)	No. of Patients	Primary Outcome Measure	Efficacy Outcomes	Safety Outcomes
ASSIST (NCT01445821)[199] Design • Open-label, randomized, phase II trial Control treatment • Intravenous CYC (1000 mg/m^2, once per month for 6 months)	• <60 years old • Diffuse SSc • mRSS >14 • Internal organ involvement OR • Restricted skin involvement (mRSS <14) • Coexistent pulmonary involvement • Disease duration ≤4 years	19	Decrease in mRSS (>25% for those with initial mRSS >14) or 10% increase in FVC at 12 months	• 10/10 patients treated with HSCT demonstrated improvement per the primary outcome measure versus 0/9 patients in the control group (p=0.00001) • At 12 months, FVC had increased by 15% in the HSCT group versus the control group in which FVC had declined by 9% (p=0.006) • At 12 months, the mRSS had decreased by almost 50% in the HSCT group versus the control group in which mRSS had increased by almost 25% • At 12 months, SF-36 scores showed that patients undergoing HSCT perceived that their general health status had significantly improved versus the control group who considered their health status to have significantly worsened	• 12-month, treatment-related mortality was 0% in both the transplant group and the control group

ASTIS (ISRCTN54371254)[200] Design • Open-label, randomized, phase III trial Control treatment • Intravenous CYC (750 mg/m^2, once per month for 12 months)	• 18–65 years old • Diffuse cutaneous SSc • mRSS ≥15 • Disease duration ≤4 years • Internal organ involvement (heart, lungs, or kidneys)	156	Event-free survival (time from randomization until the occurrence of death due to any cause or the development of persistent, major organ failure)	• In the first 12 months, there were 13 events (16.5%) in the HSCT group, including eight treatment-related deaths, versus eight events (10.4%; no treatment-related deaths) in the control group (RR 1.59; 95% CI 0.7–4.4) • HSCT was associated with better long-term event-free survival: during median follow-up of 5.8 years, 22 events occurred in the HSCT group (19 deaths and three irreversible organ failures) versus 31 events in the control group (23 deaths and eight irreversible organ failures) • Time-varying hazard ratios for event-free survival were 0.35 (95% CI 0.16–0.74) at 2 years and 0.34 (0.16–0.74) at 4 years • After 2 years, mean changes from baseline in the following parameters were significantly better with HSCT versus CYC: mRSS, FVC, total lung capacity, physical component of the SF-36, and EQ-5D index-based utility score	• Treatment-related mortality was 10.1% in the HSCT group compared with 0% in the control group (p=0.007) • The incidence of Grade 3–4 AEs was 62.9% in the HSCT group and 37.0% in the control group (p=0.002) • Viral infections occurred in 27.8% of patients undergoing HSCT and 1.3% of those treated with control (p<0.001) • After 2 years, mean change from baseline in creatinine clearance was significantly worse with HSCT versus control treatment (p=0.02)

(*Continued*)

Table 4 (Continued).

Trial Name (Study Identification Number) and Design	Patient Characteristics (Selection Criteria)	No. of Patients	Primary Outcome Measure	Efficacy Outcomes	Safety Outcomes
SCOT (NCT00114530)[201] Design • Open-label, randomized, phase II trial Control treatment • Intravenous CYC (initial dose of 500 mg/m^2 followed by 750 mg/m^2 once per month for 11 months)	• 18–69 years old • SSc • Disease duration ≤5 years • Internal organ involvement (lungs or kidneys)	75	GRCS at 54 months (derived from a hierarchy of disease features)	• At 54 months, the GRCS was superior for patients receiving HSCT versus the control group (67% of pairwise comparisons favored HSCT and 33% favored control treatment; p=0.01) • Event-free survival rate at 54 months was 79% with HSCT versus 50% with control treatment (p=0.02) • HSCT was superior to control with respect to mRSS and quality of life assessments (HAQ-DI score; physical component of the SF-36) • Post-hoc GRCS analyses controlling for between-group imbalances at baseline favored HSCT over control treatment	• Treatment-related mortality at 54 months was 3% in the HSCT group versus 0% in the control group • The percentage of patients with serious AEs was 74% with HSCT versus 51% with control treatment; the corresponding rates per person-year were 0.38 and 0.52, respectively • In the HSCT group, 96% of serious AEs occurred during the first 26 months versus 71% in the control group • Rates per person-year of infections of any grade were 0.75 in the HSCT group versus 0.79 in the control group; corresponding rates of Grade ≥3 infections were 0.21 and 0.13, respectively

Abbreviations: AE, adverse event; ASSIST, Autologous Stem Cell Systemic Sclerosis Immune Suppression trial; ASTIS, Autologous Stem Cell Transplantation International Scleroderma trial; CI, confidence interval; CYC, cyclophosphamide; EQ-5D, European Quality of Life Five Dimension Five Level Scale Questionnaire; FVC, forced vital capacity; GRCS, global rank composite score; HAQ-DI, Health Assessment Questionnaire Disability Index; HSCT, hematopoietic stem cell therapy; mRSS, modified Rodnan skin score; RR, response rate; SF-36, 36-Item Short Form Health Survey; SCOT, Scleroderma: Cyclophosphamide or Transplantation trial; SSc-ILD, systemic sclerosis-related interstitial lung disease.

care to patients. Currently, immunosuppressive treatment with CYC or MMF is most commonly prescribed for SSc-ILD. However, these drugs may not provide consistent and sustained disease-modifying effects, and may not improve long-term survival; toxicity is also a concern (particularly with CYC). New therapies for SSc-ILD are urgently needed, and ongoing studies are evaluating antifibrotics and other novel agents.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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