Arthritis & Rheumatology
Vol. 74, No. 1, January 2022, pp 13–27
DOI 10.1002/art.41933

American College of Rheumatology
Empowering Rheumatology Professionals

REVIEW

Systemic Sclerosis–Associated Interstitial Lung Disease: How to Incorporate Two Food and Drug Administration–Approved Therapies in Clinical Practice

Dinesh Khanna,[1] Alain Lescoat,[2] David Roofeh,[1] Elana J. Bernstein,[3] Ella A. Kazerooni,[1] Michael D. Roth,[4] Fernando Martinez,[5] Kevin R. Flaherty,[1] and Christopher P. Denton[6]

Systemic sclerosis (SSc; scleroderma) has the highest individual mortality of all rheumatic diseases, and interstitial lung disease (ILD) is among the leading causes of SSc-related death. Two drugs are now approved by the US Food and Drug Administration (FDA) and indicated for slowing the rate of decline in pulmonary function in patients with SSc-associated ILD (SSc-ILD): nintedanib (a tyrosine kinase inhibitor) and tocilizumab (the first biologic agent targeting the interleukin-6 pathway in SSc). In addition, 2 generic drugs with cytotoxic and immunoregulatory activity, mycophenolate mofetil and cyclophosphamide, have shown comparable efficacy in a phase II trial but are not FDA-approved for SSc-ILD. In light of the heterogeneity of the disease, the optimal therapeutic strategy for the management of SSc-ILD is still to be determined. The objectives of this review are 2-fold: 1) review the body of research focused on the diagnosis and treatment of SSc-ILD; and 2) propose a practical approach for diagnosis, stratification, management, and therapeutic decision-making in this clinical context. This review presents a practical classification of SSc patients in terms of disease severity (subclinical versus clinical ILD) and associated risk of progression (low versus high risk). The pharmacologic and nonpharmacologic options for first- and second-line therapy, as well as potential combination approaches, are discussed in light of the recent approval of tocilizumab for SSc-ILD.

Introduction

Systemic sclerosis (SSc; scleroderma) is a heterogeneous chronic autoimmune disease characterized by vascular damage, inflammation, and fibrosis of the skin and internal organs (1). SSc is the rheumatic disease with the highest individual mortality and has a detrimental impact on quality of life (1,2). Two main subsets of SSc are described based on the distribution of skin involvement: limited cutaneous SSc (lcSSc), characterized by distal skin thickening, and diffuse cutaneous SSc (dcSSc), with widespread distal and proximal cutaneous changes (3,4). SSc is also characterized by the detection of specific and often mutually exclusive serum autoantibodies (5). A composite classification of SSc patients based on the combination of degree of skin involvement and antibody subtype is now considered more helpful in predicting the disease course, since scleroderma-specific antibodies are predictive of internal organ involvement (6). Patients who develop progressive SSc-associated interstitial lung disease (SSc-ILD) are more likely to be positive for the anti–topoisomerase I antibody (anti–Scl-70 antibody) and antinuclear antibody with

Dr. Khanna's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grants K24-AR-063120 and R01-AR-070470). Dr. Lescoat's work was supported by the French network of the University Hospitals, Hôpitaux Universitaire du Grand Ouest (grant AAP JCM2020), and a CORECT Visiting grant from Rennes University Hospital. Dr. Roofeh's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant T32-AR-007080). Dr. Bernstein's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K23-AR-075112).

[1]Dinesh Khanna, MD, MSc, David Roofeh, MD, Ella A. Kazerooni, MD, MS, Kevin R. Flaherty, MD, MS: University of Michigan, Ann Arbor; [2]Alain Lescoat, MD, PhD: University of Michigan, Ann Arbor, and University of Rennes 1, Centre Hospitalier Universitaire Rennes, INSERM, École des Hautes Études en Santé Publique, and Institut de Recherche en Santé, Environnement et Travail, Rennes, France; [3]Elana J. Bernstein, MD, MSc: Columbia University Irving Medical Center, New York, New York; [4]Michael D. Roth, MD: University of California, Los Angeles; [5]Fernando Martinez, MD, MS: New York University and Cornell University, New York, New York; [6]Christopher P. Denton, MD, PhD: University College London, London, UK.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.41933&file=art41933-sup-0001-Disclosureform.pdf.

Address correspondence to Dinesh Khanna, MD, MSc, University of Michigan Scleroderma Program, Division of Rheumatology, Department of Internal Medicine, Suite 7C27 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109. Email: khannad@med.umich.edu.

Submitted for publication April 30, 2021; accepted in revised form July 22, 2021.

nucleolar pattern (notably including anti-PM/Scl-75, anti-PM/Scl-100, anti-Th/To, anti–U3 RNP/fibrillarin, anti–RNA polymerase I, or anti–NOR-90 antibodies), regardless of cutaneous subset (6–9).

ILD is among the leading causes of SSc-related death (10). The prevalence of SSc-ILD varies depending on the assessment method (radiography or high-resolution computed tomography [HRCT]), the screening strategy (systematic HRCT versus selection of patients based on the results of pulmonary function tests [PFTs]), the targeted populations (dcSSc versus lcSSc), and differences in geographic location or expertise of the medical center (11,12). In national observational registries and international cohorts, ~65% of SSc patients have or will develop ILD in the course of their disease (11–14).

The high mortality related to SSc-ILD has led to recent randomized controlled trials (RCTs) forging substantial progress in the management of this manifestation (15). Conventional immunomodulatory agents such as cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are evidence-based treatments typically implemented in clinical practice (16,17). More recently, well-conducted phase III RCTs have led to US Food and Drug Administration (FDA) approval of 2 targeted therapies for SSc-ILD (18–22). Nintedanib is a tyrosine kinase inhibitor; in 2019 it became the first medication approved to slow the rate of decline in pulmonary function in patients with SSc-ILD, based on the results of the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial (ClinicalTrials.gov identifier: NCT02597933) (18,19). Tocilizumab is a monoclonal antibody targeting the interleukin-6 (IL-6) receptor; in 2021 it became the first biologic medication approved for the same indication, based on the results of the Safety and Efficacy of Subcutaneous Tocilizumab in Adults With Systemic Sclerosis (faSScinate) trial (ClinicalTrials.gov identifier: NCT01532869) and the Study of the Efficacy and Safety of Tocilizumab in Participants With Systemic Sclerosis (focuSSced) (ClinicalTrials.gov identifier: NCT02453256) (20–22).

Despite these recent FDA approvals, the optimal therapeutic strategy for the management of SSc-ILD is yet to be determined, especially given the heterogeneity of the disease (23). The objectives of this review are 2-fold: 1) to review the body of research focused on diagnosis and treatment of SSc-ILD and 2) to propose a practical approach for diagnosis, stratification, management, and therapeutic decision-making in this clinical context. The management strategy proposed in this review reflects the authors' opinions, experience, and clinical practice.

Pathogenic considerations and rationale for available therapeutic options in SSc-ILD

The pathogenesis of SSc-ILD is not fully understood but includes a triad of pathogenic events: endothelial dysfunction, early inflammatory features, and excessive deposition of extracellular matrix (ECM) components produced by activated myofibroblasts (9,24). ECM deposits induce an increased stiffness of lung tissue with reduction in pulmonary compliance and volumes. These pathogenic events can lead to a restrictive ventilatory defect captured by spirometry alongside impairment in gas exchange; some patients may remain asymptomatic despite evidence of disease on HRCT, whereas the consequences of severe and advancing disease include dyspnea and death.

The direct inhibition of myofibroblast activation or the targeting of other cellular subsets participating in the production of key mediators responsible for myofibroblast activation provide the rationale for candidate drugs in SSc-ILD. Early inciting factors include epithelial and endothelial damage that may be promoted by aberrant innate and adaptive immunity that can produce profibrotic and proinflammatory mediators, inducing myofibroblast activation. Through the production of IL-13 and IL-4, Th2 lymphocytes have a direct impact on fibroblasts and can induce the activation of profibrotic macrophages (M2 macrophages) that notably produce high levels of transforming growth factor β, platelet-derived growth factor (PDGF), and factors from the fibroblast growth factor (FGF) family favoring myofibroblast activation (25–27). The tyrosine kinase inhibitor, nintedanib, inhibits the receptors of vascular endothelial growth factor (VEGF), PDGF, and the FGF family, with subsequent antifibrotic effects (28).

Acute-phase reactants, and specifically IL-6, play an important role in the pathogenesis of SSc-ILD. IL-6 is produced by B cells, proinflammatory macrophages (M1 macrophages), and myofibroblasts (29,30). In vitro studies suggest that IL-6 can favor the expression of IL-4 and IL-13 receptors, with a subsequent increase in profibrotic M2 macrophage polarization (31). The inhibition of the IL-6 receptor by tocilizumab can directly impact myofibroblast activation and M2 macrophage polarization, with potential antifibrotic effects (29,32). Through their impact on the proliferation of fibroblasts, B cells, and T helper lymphocytes, conventional immunomodulatory agents such as MMF, an inhibitor of de novo synthesis of guanosine nucleotides, or the alkylating agent CYC can also have antifibrotic effects (33,34).

Key parameters for the diagnosis, screening, and assessment of SSc-ILD

HRCT is the reference standard for early diagnosis of SSc-ILD (12,35,36). In the majority of patients (70–80%), SSc-ILD is characterized by a pattern of nonspecific interstitial pneumonia that includes parenchymal changes classically located in bi-basal and posterior regions of the lungs, and defined by the presence of reticular abnormalities with peribronchovascular extension and subpleural sparing with absence of honeycombing and frequent ground-glass attenuations (13,37,38) (Figure 1A). Ground-glass opacity in early SSc may represent either inflammation or fibrosis that is below the resolution of the HRCT technique at the level of intralobular septa and interstitium surrounding alveoli. Early radiologic–pathologic correlation studies using HRCT have demonstrated that bronchiectasis or bronchiolectasis within areas

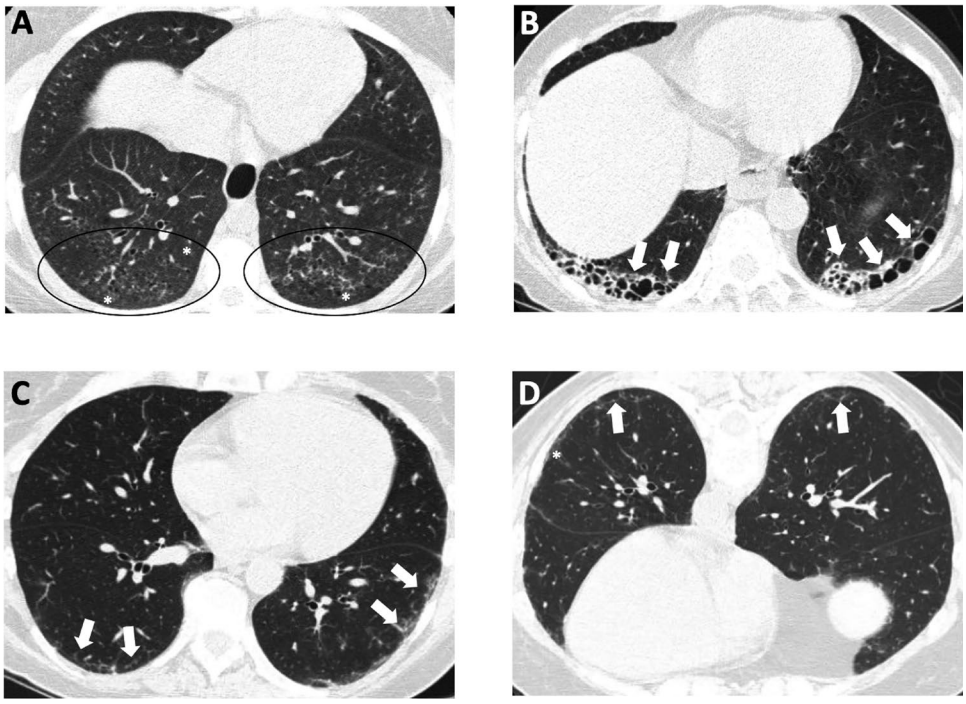


Figure 1. High-resolution computed tomography images of the lungs of 3 different patients with systemic sclerosis (SSc)–related interstitial lung disease (ILD). **A**, Nonspecific interstitial pneumonitis (NSIP) with a lower lobe subpleural predominant distribution of primarily ground-glass opacity (**asterisks** and encircled areas). **B**, Definite usual interstitial pneumonitis with subpleural lower lobe honeycombing (**arrows**). **C** and **D**, Mild ILD on the supine image (**arrows**) (**C**), which could be interpreted as dependent atelectasis; however, it persists on the prone image (**D**), confirming the presence of ILD. The pattern of septal thickening (**arrows**) and ground-glass opacity (**asterisk**) without bronchiectasis is most consistent with NSIP in a patient with SSc.

of ground glass are strong indicators of fibrosis, whereas ground glass without bronchiectasis is strong evidence of inflammation (39). The presence of traction bronchiectasis with minimal ground-glass opacifications is thus more specifically consistent with fibrotic nonspecific interstitial pneumonia. Approximately 10% of patients with SSc-ILD have an HRCT pattern of usual interstitial pneumonia (UIP) defined by subpleural and basal predominant lesions including honeycombing (mandatory criterion) with or without peripheral traction bronchiectasis or bronchiolectasis (Figure 1B).

In patients with connective tissue disease–associated ILD (CTD-ILD), especially rheumatoid arthritis–associated ILD, UIP is predictive of a worse prognosis compared to nonspecific interstitial pneumonia; the specific prognostic value of HRCT patterns in SSc-ILD is more controversial (40). Patient survival in SSc-ILD does not differ between nonspecific interstitial pneumonia and UIP according to the histopathologic patterns on lung biopsy (41). Considering the sensitivity and specificity of HRCT for SSc-ILD and the lack of predictive value of histopathologic patterns in SSc-ILD, lung biopsy is not recommended for the diagnosis and assessment of SSc-ILD. A prone HRCT acquisition is recommended to rule out early ILD, as the predominant bi-basal and posterior localization of HRCT findings in SSc-ILD may produce false-positives due to position-induced changes (i.e., atelectasis) (Figures 1C and D) (42). Quantitative HRCT allows precise quantification of SSc-ILD lung involvement (the sum of lung involvement with ground-glass opacities, fibrotic reticulations, and honeycombing) and of fibrotic changes (quantification of lung fibrosis, or fibrotic reticulations alone) (43,44). The extent of lung involvement has been demonstrated to have prognostic value; accurately assessing the degree of lung involvement provides a valuable tool for stratifying disease severity and risk of progression (45,46).

Spirometry and gas exchange are the reference standard measurements for the assessment of lung physiology. The impact of SSc-ILD on forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DL_{CO}) is a marker of disease severity. In terms of screening and diagnosis, SSc-ILD may initially have only mild or no impact on PFT parameters; normal values of FVC, TLC, and DL_{CO} do not rule out early SSc-ILD (12). In a US multicenter study of patients with early dcSSc, FVC percent predicted (FVC%) <80% had a sensitivity of 63% and a negative predictive value (NPV) of 61% for the detection of SSc-ILD. The combination of FVC% <80% or DL_{CO}% <80% had a sensitivity and NPV of 85% and 70%, respectively, demonstrating that PFTs alone are an inadequate screening tool for the diagnosis of SSc-ILD (12). A European study also demonstrated similar results and highlighted that among patients with normal FVC% but with SSc-ILD on HRCT, 50% had extensive ILD (>20% of parenchymal involvement) (47). In addition, FVC%

in healthy volunteers ranges from 80% to 120%, which can mean that a clinically meaningful decline may be missed in a patient who has declines within the "normal" range of FVC%, e.g., from 110% to 80%. Therefore, it is now accepted that both PFT and HRCT should be performed for initial screening and diagnosis of SSc-ILD (35).

We recommend performing HRCT and PFT for baseline ILD screening in all patients with early SSc (early relates to the onset of their symptoms that are specific for SSc), regardless of cutaneous or autoantibody subtype (36). Every patient with a new diagnosis of SSc-ILD based on HRCT should have initial full PFTs (i.e., spirometry, lung volumes, and DLco) for baseline reference and a 6-minute walk test to assess the impact on gas exchange and exercise capacity. Although the 6-minute walk test can be influenced by different organ involvement in SSc, such as pulmonary vascular disease and cardiac involvement, for example, we use the 6-minute walk test in clinical practice to document baseline distance and oxygen saturation and repeat it annually (or more frequently for new or worsening of symptoms) to assess for decline in both of these parameters (48,49). Clinical scales such as the modified Medical Research Council dyspnea scale or the New York Heart Association functional classification of dyspnea are simple to incorporate in clinical practice and can provide important information to assess for SSc-ILD progression (50,51).

Definitions, risk factors for, and monitoring of the progression of SSc-ILD

There are different definitions for the progression of SSc-ILD. Outcome Measures in Rheumatology (OMERACT) has proposed the definition of "clinically meaningful progression" of CTD-ILD based on the evolution of PFT parameters; this definition can be applied to SSc-ILD. OMERACT defines progression as a ≥10% relative decline in FVC% or a 5% to <10% relative decline in FVC% *and* ≥15% relative decline in DLco%. The Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (INBUILD) trial, which focused on fibrotic ILD, has also proposed a composite definition of "progressive fibrosing ILD" as an inclusion criterion, which was notably applied to patients with SSc-ILD (19). In that trial, one of the following criteria was required to fulfill the definition of progression within the prior 24 months: a) ≥10% relative decline in FVC%, or b) 5% to <10% relative decline in FVC% *and* worsening of respiratory symptoms or an increased extent of fibrosis on HRCT, or c) worsening of respiratory symptoms *and* an increased extent of fibrosis on HRCT, regardless of the evolution of FVC%.

The results of the focuSSced trial demonstrate that early treatment should be considered in patients with SSc-ILD at high risk of progression, regardless of the actual progression rate and/or before decline of lung function or progression is identified through close monitoring (21). This approach constitutes a paradigm shift in the field of SSc-ILD and emphasizes the need for reliable and accessible predictive markers of SSc-ILD progression. The predictive value of such markers in observational studies and RCTs varies according to the targeted populations and the definition of SSc-ILD progression (36,52) (Table 1). Serum markers used in clinical practice, such as anti–topoisomerase I antibodies and elevated C-reactive protein (CRP) values, are associated with SSc-ILD progression (53,54). Other biomarkers, such as KL-6, CCL2, CCL18, CXCL4, or surfactant protein D, may be predictive of the progression of SSc-ILD but are not available in routine practice and are currently used in the context of exploratory clinical research (36,52,55,56). Negative anticentromere antibody and a history of smoking may also constitute risk factors for progressive ILD, although the data are less consistent (6,57).

Table 1. Parameters available in clinical practice and associated with progressive SSc-ILD*

Demographic and clinical parameters
Advanced age
Male sex
African American ethnicity
dcSSc
Findings on pulmonary function tests
Low baseline FVC%†
Low baseline DLco%†
HRCT findings
Extent of ILD on HRCT (cutoff value >20% of lung parenchyma for total lung involvement)
Serum markers
Anti–Scl-70/topoisomerase I antibody
Nucleolar pattern (especially including anti-Th/To and anti–U3 RNP)
Elevated acute-phase reactant levels, including serum CRP levels greater than the ULN

* SSc-ILD = systemic sclerosis–related interstitial lung disease; dcSSc = diffuse cutaneous SSc; FVC% = forced vital capacity percent predicted; DLco% = diffusing capacity for carbon monoxide percent predicted; HRCT = high-resolution computed tomography; CRP = C-reactive protein; ULN = upper limit of normal.
† Cutoff values vary across studies.

The heterogeneous rates of disease progression and treatment response underscore the need for close monitoring of patients with SSc-ILD after initial diagnosis or treatment initiation (35,58). The majority of patients who will develop severe SSc-ILD will do so in the first 5 years after the onset of the disease, although late progression may also occur (52). After initial diagnosis of SSc-ILD with baseline HRCT and PFT, follow-up of all SSc-ILD patients should include PFT (FVC and DLco) at least every 6 months for the first 3–5 years from the onset of the first non–Raynaud's phenomenon manifestation (Table 1) in order to monitor for progression (36,52). Although substantial progress has been made in HRCT techniques, allowing high-quality HRCT with low-dose radiation (typically 1.5–2.5 mSv), the systematic follow-up and monitoring of all SSc-ILD patients with sequential chest HRCT is not currently recommended (35,36). In cases of worsening symptoms or clinically meaningful progression (as defined in the INBUILD trial), a follow-up HRCT can be considered to assess for progressive ILD. Other causes of progressive symptoms such as pulmonary

vascular disease or cardiac involvement should also be considered due to the multifactorial nature of SSc-associated manifestations. In SSc patients without ILD or with stable or controlled ILD after the first 3–5 years, annual PFTs are useful to monitor for both the onset and progression of SSc-ILD and to screen for SSc-associated pulmonary arterial hypertension (PAH) (7,59).

Classification of SSc-ILD and subgroups of patients according to initial severity and risk of progression

SSc-ILD trajectories are divided into 2 large subsets, depending on the initial clinical presentation. Subclinical ILD is defined by the presence of ILD *with* minimal extent on HRCT (usually 5–10% based on visual or computer quantification) *and* no ILD-related clinical symptoms (such as dyspnea and cough) *and* normal initial PFT (including FVC *and* DL_{CO}) or no clinically meaningful decline in PFT, if serial PFTs are available. With the institution of HRCT for screening and diagnosis of SSc-ILD, this subgroup is likely to increase over time. Clinicians also need to use their judgment to assess if symptoms such as cough are related to ILD or to other causes such as silent gastric aspiration or upper airway cough syndrome.

The remaining patients with ILD are classified as having clinical ILD (which comprises the majority of current cases of SSc-ILD due to a lack of universal screening in SSc patients); they are classified by the presence of mild to severe ILD on HRCT *and* one or more of the following features: abnormal initial PFT (including FVC *and/or* DL_{CO}) *and/or* clinically meaningful decline in PFT parameters (including FVC *and/or* DL_{CO}). Clinical ILD is associated with ILD-related symptoms or impact of ILD on daily life.

Within these subsets, patients can be further divided into those with a low risk of progressive ILD (no elevated acute-phase reactants, positive for anticentromere antibody) and high risk of progressive ILD (Table 1). The subgroup of patients with subclinical ILD at high risk of progression (as shown in the focuSSced trial), as well as all patients with clinical ILD, would benefit from early therapeutic intervention for SSc-ILD. Close monitoring (at least every 6 months) is also necessary in patients with subclinical ILD with low risk of progression in order to confirm stability.

Clinical evidence for the management of SSc-ILD based on phase II and III trials

The main therapeutic agents for the treatment of SSc-ILD have immunomodulatory properties, antifibrotic properties, or both (23). The results of the main phase II and III RCTs and their targeted populations are detailed in Table 2.

The Scleroderma Lung Study I (SLS I) evaluated the effects of oral CYC versus placebo in SSc-ILD. SLS I demonstrated that the mean absolute difference in adjusted 12-month FVC% was 2.53% favoring CYC ($P < 0.03$) (16). CYC also improved dyspnea and quality of life compared to placebo. SLS I is a pivotal study that demonstrated for the first time that SSc-ILD is responsive to immunosuppressive treatment in a clinical trial setting. The Scleroderma Lung Study II (SLS II) demonstrated that treatment of SSc-ILD with MMF for 2 years or CYC for 1 year was associated with statistically significant improvement in FVC% in both arms at 24 months, without a between-arm difference ($P = 0.24$) (17). Significant favorable transitions from ground-glass and/or lung fibrosis HRCT patterns to a normal pattern were observed in both arms of SLS II (44,60). MMF and CYC also improved the modified Rodnan skin thickness score (MRSS) course over 24 months in participants with dcSSc (61). In SLS II, MMF was associated with less toxicity and was better tolerated than CYC. For these reasons, MMF is now considered the standard of care as first-line therapy for SSc-ILD (62).

The SENSCIS trial, a phase III RCT, evaluated the efficacy of nintedanib compared to placebo for patients with SSc-ILD. Patients receiving a stable dose of MMF or methotrexate for at least 6 months prior to randomization were permitted to enroll. The intergroup difference in the annual rate of change in FVC was 41.0 ml per year (95% confidence interval [95% CI] 2.9, 79.0) in favor of nintedanib ($P = 0.04$) (18). The treatment effect of nintedanib on the annual rate of change in FVC was numerically, but not significantly, lower in participants who were taking MMF at baseline than in those not taking MMF (difference between nintedanib and placebo 26.3 ml per year [95% CI –27.9, 80.6] and 55.4 ml per year [95% CI 2.3, 108.5] in the group taking MMF and the group not taking MMF, respectively). In addition, there were marked geographic differences in the background use of MMF. In North America, where the majority of patients were receiving MMF, the difference between treatment arms was even smaller, at 10.3 ml per year (95% CI –27.9, 80.6), but still in favor of nintedanib. As a result, the SENSCIS data suggest a possible additive or synergistic effect from combining MMF and nintedanib, but the details of such a combination require further clarification (63).

The phase II faSScinate and phase III focuSSced trials evaluated the safety and efficacy of tocilizumab in patients with early active dcSSc (20,21). The primary end point was the difference in mean change in MRSS from baseline to week 24 and to week 48 in faSScinate and focuSSced, respectively. Despite a numerical difference in the change in MRSS in favor of tocilizumab, neither trial reached statistical significance at $P < 0.05$ for their primary end points. However, the key secondary end point showed statistically significant and clinically meaningful differences in the change in FVC% from baseline to week 48 in favor of tocilizumab. In faSScinate, patients treated with tocilizumab had a smaller decrease in FVC from baseline to 24 weeks (least squares mean difference 136 ml [95% CI 9, 264]; $P = 0.04$ in favor of tocilizumab) with a numerical effect in favor of tocilizumab also observed at week 48 (least squares mean difference 120 ml [95% CI –23, 262]; $P = 0.099$ in favor of tocilizumab) (20). At both time points,

Table 2. Inclusion criteria, targeted population, and main results of key phase II and III trials including SSc-ILD patients*

Trial name (ref.)	Drug tested	Targeted population (main criteria)	Control group	Background therapy	Total no./no. in active treatment group/no. in control group	% with SSc-ILD in active treatment group/% with SSc-ILD in control group	Pulmonary outcome measure used for efficacy	Main results for the pulmonary outcome measure used
SLS I (16)	CYC	dcSSc or lcSSc; SSc-ILD defined by active alveolitis or GGO on CT; disease duration <7 years; FVC% 45–85%; exertional dyspnea grade ≥2†	Placebo	Potentially disease-modifying medications excluded; prednisone >10 mg/day excluded	158/79/79	100/100	FVC% at 12 months adjusted for baseline FVC	Mean absolute difference in adjusted 12-month FVC 2.53% (95% CI 0.28, 4.79), favoring CYC ($P < 0.03$)
SLS II (17)	MMF	dcSSc or lcSSc; SSc-ILD defined by GGO on CT (with or without reticulation); disease duration <7 years; FVC% 45–80%; exertional dyspnea grade ≥2†	CYC	Potentially disease-modifying medications excluded; prednisone >10 mg/day excluded	142/69/73	100/100	Course of FVC% from 3 to 24 months	Course of FVC% did not differ significantly between the 2 treatment groups ($P = 0.24$); adjusted FVC% improved from baseline to 24 months by 2.19% in the MMF group (95% CI 0.53, 3.84) and 2.88% in the CYC group (95% CI 1.19, 4.58)
SENSCIS (18)	NINT	dcSSc or lcSSc; SSc-ILD with CT showing fibrosis affecting ≥10% of the lungs; FVC% ≥40%	Placebo	Allowed prednisone (up to 10 mg per day) or MMF/MTX at a stable dose for ≥6 months before randomization	580/288/288‡	100/100	Annual rate of decline in FVC (ml/year), assessed over a 52-week period	Adjusted annual rate of change in FVC −52.4 ml per year in the NINT group and −93.3 ml per year in the placebo group (difference 41.0 ml per year [95% CI 2.9, 79.0]; $P = 0.04$)
faSScinate (20)	TCZ	dcSSc with or without ILD; active disease§; disease duration <5 years	Placebo	No background immunomodulatory therapies allowed	87/43/44	NA	Decline in FVC (ml) at weeks 24 and 48 (secondary outcome); % of patients experiencing worsening of FVC% in each arm	Smaller decrease in FVC for TCZ than for placebo from baseline to 24 weeks (TCZ −34 ml vs. placebo −171 ml; LSM difference 136 ml [95% CI 9, 264]; $P = 0.0368$) but no significant difference from baseline to 48 weeks (TCZ −117 ml vs. placebo −237 ml; LSM difference 120 ml [95% CI −23, 262]; $P = 0.0990$); fewer patients in the TCZ group than in the placebo group had worsening of FVC% at 24 weeks ($P = 0.009$) or at 48 weeks ($P = 0.037$)

(Continued)

Table 2. *(Cont'd)*

Trial name (ref.)	Drug tested	Targeted population (main criteria)	Control group	Background therapy	Total no./no. in active treatment group/no. in control group	% with SSc-ILD in active treatment group/% with SSc-ILD in control group	Pulmonary outcome measure used for efficacy	Main results for the pulmonary outcome measure used
focuSSced (21)	TCZ	dcSSc with or without ILD; active disease§; disease duration <60 months	Placebo	No background immunomodulatory therapies allowed	212/105/107	67/65	Difference in distribution of change from baseline to week 48 in FVC% (key secondary outcome)	Shift in the distribution of change in FVC% from baseline to week 48 favoring TCZ (van Elteren nominal P = 0.002 versus placebo); in patients with SSc-ILD at baseline the LSM of change from baseline in FVC% was −6.4 in the placebo group and 0.1 in the TCZ group (LSM difference between groups 6.5 [95% CI 3.4, 9.5]; P < 0.0001)

* SSc-ILD = systemic sclerosis–associated interstitial lung disease; SLS I = Scleroderma Lung Study I; CYC = cyclophosphamide; dcSSc = diffuse cutaneous SSc; lcSSc = limited cutaneous SSc; GGO = ground-glass opacities; CT = computed tomography; FVC% = forced vital capacity percent predicted; 95% CI = 95% confidence interval; MMF = mycophenolate mofetil; SENSCIS = Safety and Efficacy of Nintedanib in Systemic Sclerosis; NINT = nintedanib; MTX = methotrexate; faSScinate = Safety and Efficacy of Subcutaneous Tocilizumab in Adults With Systemic Sclerosis; TCZ = tocilizumab; NA = not available; LSM = least squares mean; focuSSced = Study of the Efficacy and Safety of Tocilizumab in Participants With Systemic Sclerosis.
† On the Magnitude of Task component of the Mahler Baseline Dyspnea Index.
‡ An additional 3 patients were randomized despite noneligibility, and 1 patient withdrew from the study.
§ Defined as an increase of ≥3 on the modified Rodnan skin thickness score (MRSS) at screening compared to the last visit within the previous 1–6 months or new-onset SSc diagnosed within 1 year before screening, involvement of 1 new body area with an increase in MRSS of ≥2 or 2 new body areas with increase in MRSS of ≥1, documentation of worsening of skin thickening in the previous 6 months, or ≥1 tendon friction rub plus fulfillment of ≥1 laboratory criterion (C-reactive protein ≥10.0 mg/liter, erythrocyte sedimentation rate ≥28 mm/hour, or platelet count ≥330,000/μl).

fewer patients in the tocilizumab group than in the placebo group had worsening of FVC%.

In the focuSSced trial, 68 patients in each arm had SSc-ILD on HRCT (representing 67% and 65% of the patients in the tocilizumab and placebo arms, respectively). In these patients, risk factors for SSc-ILD progression were similar in the tocilizumab and placebo arms, including disease duration (mean ± SD 23 ± 17.2 months versus 22.6 ± 16.6 months), proportion positive for antitopoisomerase antibodies (68.7% versus 68.8%), CRP levels (mean ± SD 11.2 ± 17.4 versus 8.0 ± 13.1 mg/liter), baseline FVC% (mean ± SD 77.7 ± 13.9 versus 81.5 ± 14.9), and baseline quantitative ILD (mean ± SD 20.5 ± 12.8% versus 16.8 ± 8.8%) in the tocilizumab and placebo arms, respectively (22). In the focuSSced trial, the least squares mean difference in FVC% in patients with SSc-ILD showed a change from baseline of –6.4% for placebo and +0.1 for tocilizumab (least squares mean difference between groups 6.5% [95% CI 3.4, 9.5]; $P < 0.0001$) (21). Post hoc analysis showed that early SSc-ILD was not synonymous with minimal ILD on HRCT, as 41% of the patients had total lung involvement of >10% to 20%, and 36% had total lung involvement of >20%, determined using a computer-generated algorithm. These data highlighted that the stabilization of lung function in the tocilizumab arm was consistent across all severity groups of SSc-ILD, demonstrating that the effects of tocilizumab were observed in all subgroups (22).

Other targeted biologics such as rituximab (anti-CD20 antibody) and abatacept (CTLA-4Ig fusion protein) have shown some beneficial effects on FVC in patients with SSc-ILD (64). In a phase II trial, abatacept showed a nonsignificant reduction in FVC decline at 12 months (least squares mean FVC% 2.79% [95%CI –0.69, 6.27], favoring abatacept compared to placebo) (64). A similar trend was observed in the open-label extension at month 18 (65). In an open-label trial comparing rituximab to CYC, mean ± SD FVC% improved from 61.30 ± 11.28% at baseline to 67.52 ± 13.59% at 6 months in the rituximab arm, but declined from 59.25 ± 12.96% to 58.06 ± 11.23% in the CYC arm, with a mean difference in FVC% at 6 months of 9.46 (95% CI 3.01, 15.90) ($P = 0.003$) (66). A recent Japanese phase II trial evaluating the impact of rituximab on skin involvement also showed promising results with regard to FVC progression, as the change in FVC% from baseline to week 24 was 0.09% in the rituximab group compared to –2.87% in the placebo group (difference 2.96% [95% CI 0.08, 5.84]; $P = 0.04$ favoring rituximab) (67).

The phase II Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial has demonstrated the efficacy of myeloablative chemotherapy with radiation and hematopoietic stem cell transplantation (HSCT) to improve survival in a population of patients with severe SSc. Among the included patients, 100% in the transplantation group and 95% in the CYC control group had SSc-ILD (68). In this RCT, 36% of the patients in the HSCT arm had an improvement in FVC of ≥10% compared to 23% of the patients in the CYC arm. The proportion of the patients with a decrease in FVC of ≥10% was lower in the HSCT arm than in the CYC arm (17% versus 41%, respectively). Observational before-and-after HSCT studies also suggest an improvement in the extent of ILD on HRCT, although the small sample size precludes firm conclusions (69).

Lung transplant could be considered for patients with SSc-ILD, especially when other available treatments have failed (70,71). Referral for lung transplant should notably be considered in cases of progressive FVC and DL_{CO} decline despite a combination of immunosuppressive and antifibrotic therapies, worsening symptoms such as dyspnea on exertion (without any other identifiable cause), and/or increasing oxygen requirement (72). In carefully selected patients with mild-to-moderate extrapulmonary manifestations related to SSc, lung transplant for SSc-ILD has shown similar outcomes as in other fibrotic lung diseases or in PAH (73).

Points to consider when interpreting the RCTs of nintedanib and tocilizumab in SSc-ILD

When interpreting the results of SENSCIS and focuSSced, it is important to underscore that the study populations were different in these trials (early active dcSSc in focuSSced, and progressive ILD regardless of the cutaneous subset in SENSCIS), with potential impact on the natural progression rate in the placebo arms. Moreover, background therapies were allowed in SENSCIS, which could have contributed to limiting the decline in FVC in both arms and could have impacted the results regarding extrapulmonary manifestations. The expected decline in FVC after age 25 years in the general population is 25–30 ml/year, which is another point to consider in interpreting the decline in FVC in these phase III trials, notably in the placebo arms (74). In SENSCIS, the decline in FVC in the placebo arm was 93.3 ml (119.3 ml in patients not taking MMF in the placebo group), a 3- to 4-fold greater decline compared to the healthy population (18,63). In focuSSced, the placebo arm showed an absolute decline in FVC of 255 ml, which corresponds to a 10-fold greater decline compared to the healthy population, highlighting that the patients included in the study were at high risk of severe decline (21).

This difference in rate of FVC decline between the 2 trials can be explained by the natural history of SSc-ILD and the underlying pathogenic mechanisms. In focuSSced, the patients included had early dcSSc, with more prominent inflammatory immune features that were captured at a very early phase, without significant SSc-ILD during the screening phase prior to randomization and baseline HRCT (75). These patients were rarely included in previously designed SSc-ILD studies because significant and/or progressive clinical ILD was a required inclusion criterion. Thus, the early treatment of this specific population of patients with inflammatory SSc at high risk of progression may represent a window of opportunity to prevent the decline in pulmonary function in SSc-ILD. The patients included in the SENSCIS trial had clinical ILD, so that we can hypothesize that fibrotic pathways were more established,

with a more predictable decline in FVC that was similar to what was expected based on previous SSc-ILD studies (16,17). Both tocilizumab and nintedanib, nonetheless, showed biologic effects that can be considered disease-modifying in SSc-ILD.

A proposed strategy for the management of SSc-ILD

All patients with SSc-ILD deemed appropriate for pharmacologic treatment should be initiated on immunomodulatory treatment, as the pathogenesis of early ILD includes immune dysfunction and inflammation resulting in fibrosis (Figure 2). Our treatment decision algorithm for SSc-ILD is provided in Figures 2 and 3. The first step in the treatment decision algorithm is the classification of the patient along the dimension of disease severity (subsets of subclinical ILD or clinical ILD), based on ILD-specific symptoms and clinical impact, extent of ILD on HRCT, and functional impact based on FVC and/or DLco (58,70). All patients with clinical ILD should be considered for immunomodulatory treatment (15,35). If a patient has subclinical ILD, further stratification regarding risk of progressive disease determines if a given patient is a candidate for pharmacologic treatment. Treatment options may be further stratified based on the severity or activity of the extrapulmonary manifestations of SSc.

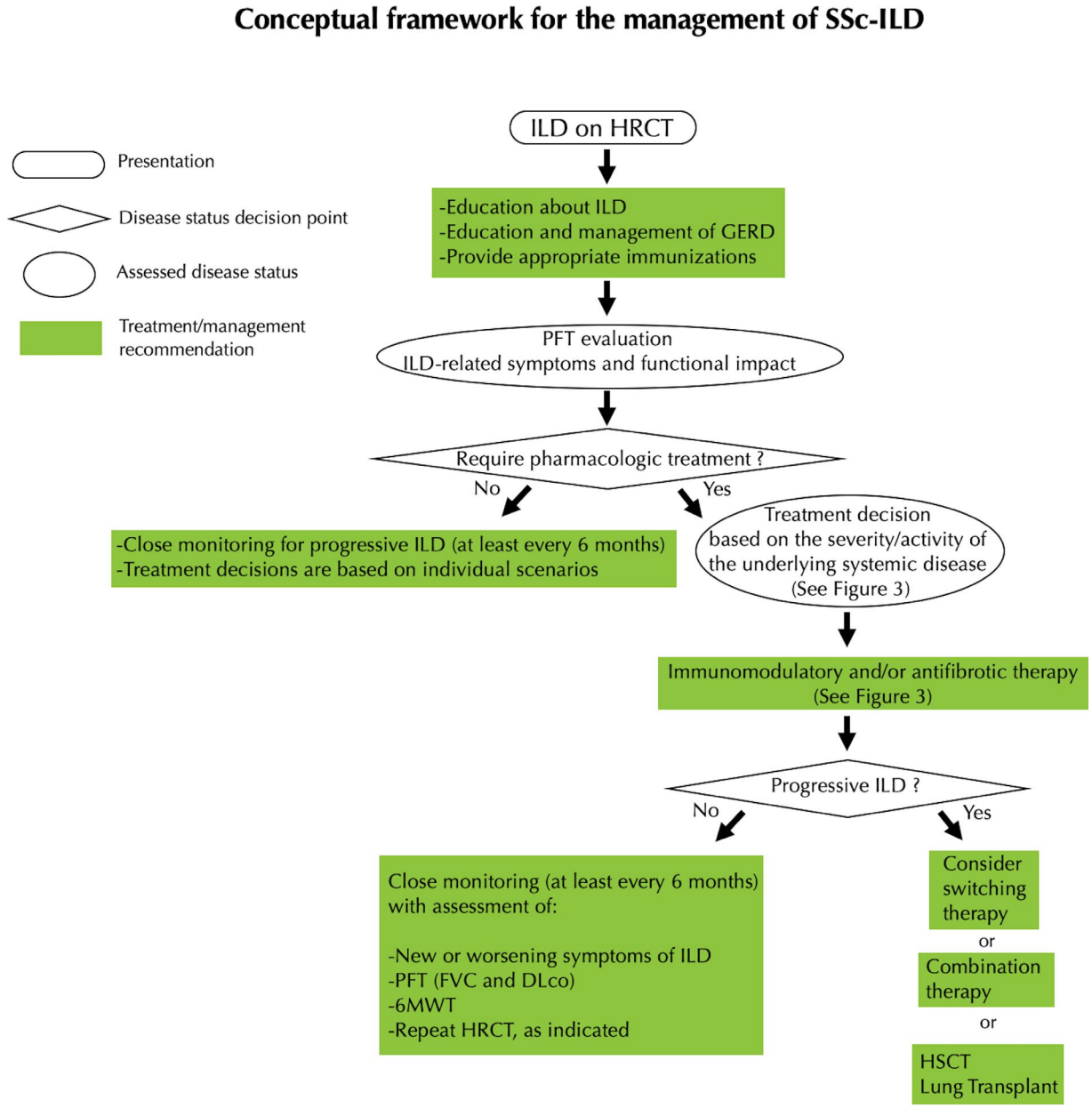
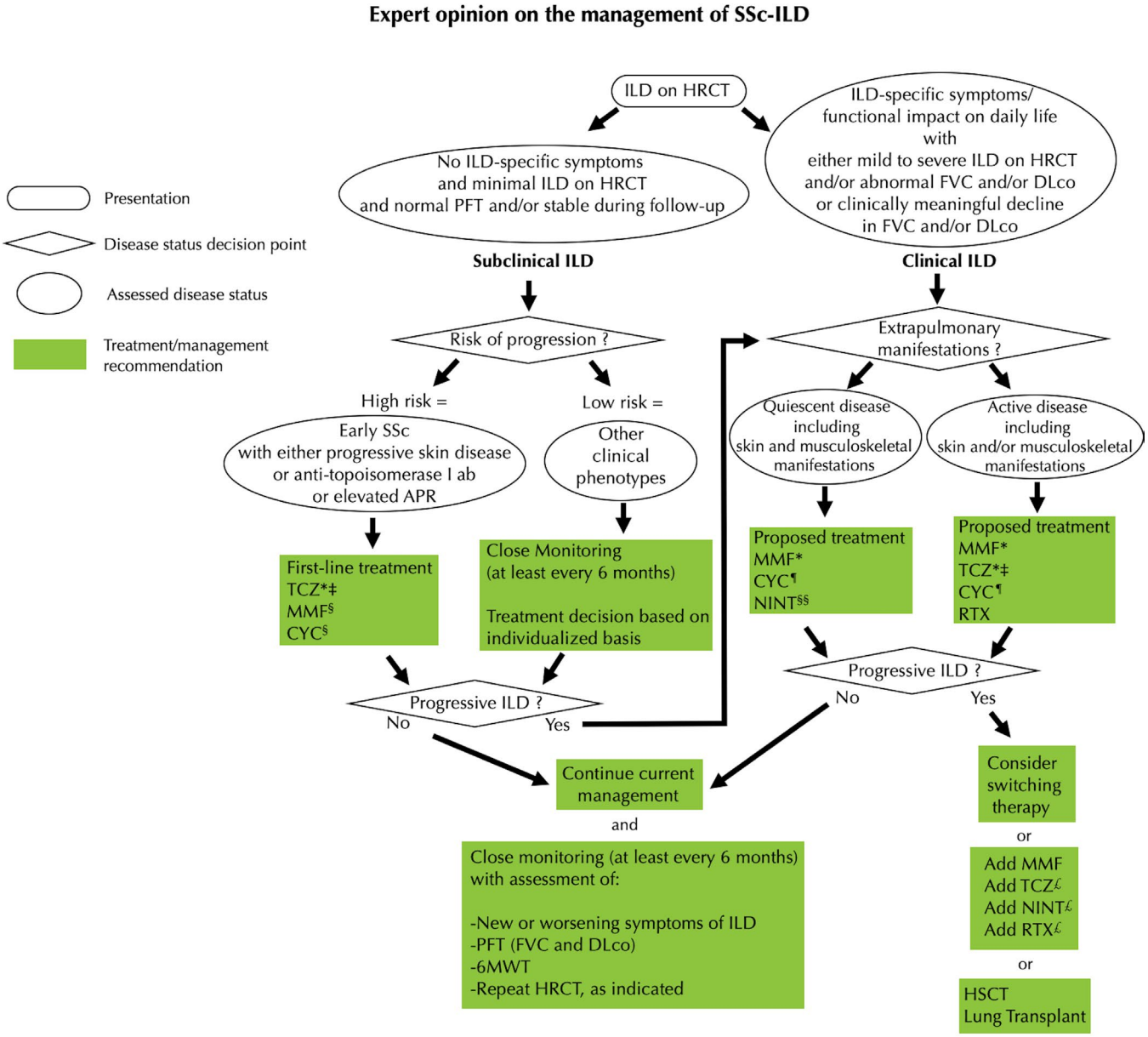


Figure 2. Conceptual framework for the management of systemic sclerosis–associated interstitial lung disease (SSc-ILD). HRCT = high-resolution computed tomography; GERD = gastroesophageal reflux disease; PFT = pulmonary function test; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; 6MWT = 6-minute walk test; HSCT = hematopoietic stem cell transplantation.



*Initial preference.
‡TCZ has only been evaluated in early active dcSSc, no specific data available in early lcSSc.
§ Based on expert opinion and extrapolation of the data from SLS 1 and SLS II.
§§ Although nintedanib was shown to be superior to placebo in a Phase 3 trial, there were no beneficial effects on skin, musculoskeletal and quality of life.
¶ Although CYC has two RCTs in SSc-ILD, the toxicity precludes us for advocating it as first line treatment.
£No data supporting combined therapy of two biologic DMARDs or Tyrosine kinase inhibitor with biologic DMARDs.

Figure 3. Expert opinion on the management of systemic sclerosis–associated interstitial lung disease (SSc-ILD). HRCT = high-resolution computed tomography; PFT = pulmonary function test; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; ab = antibody; APR = acute-phase reactants; TCZ = tocilizumab; MMF = mycophenolate mofetil; CYC = cyclophosphamide; NINT = nintedanib; RTX = rituximab; 6MWT = 6-minute walk test; HSCT = hematopoietic stem cell transplantation; dcSSc = diffuse cutaneous SSc ; lcSSc = limited cutaneous SSc; SLS I = Scleroderma Lung Study I; RCTs = randomized controlled trials; DMARDs = disease-modifying antirheumatic drugs.

Nonpharmacologic measures. All patients should be educated about ILD, symptom monitoring, and nonpharmacologic management. Nonpharmacologic treatments include receipt of appropriate vaccinations such as influenza, pneumococcal, and COVID vaccines; pulmonary rehabilitation; and oxygen therapy if indicated. Pulmonary rehabilitation should be offered to those patients with SSc-ILD in whom dyspnea and other aspects of ILD are limiting functional capacity (76). Oxygen therapy should be considered in cases of hypoxemia (SpO_2 <88%). The 6-minute walk test is useful to evaluate

cardiopulmonary exercise desaturation that would require oxygen therapy.

Patients should be educated about silent aspiration; optimal care of gastroesophageal reflux disease should be undertaken with early initiation of proton-pump inhibitors. Any inhalation of recreational drugs such as tobacco, marijuana, vaping, and other products should be discontinued. Recent studies have highlighted the importance of fostering a good nutritional status to maintain respiratory function in chronic respiratory disorders, especially in patients with gastrointestinal symptoms (77–79). Annual screening for immunosuppressant-induced nonmelanoma skin cancers is also recommended.

Pharmacologic treatment. Data emerging from the recent RCTs of tocilizumab suggest that early treatment with immunomodulatory agents should be considered for patients with subclinical ILD with a high risk of progression (i.e., early SSc with progressive skin disease, or antitopoisomerase antibody, or elevated acute-phase reactants). Tocilizumab may be proposed as initial treatment based on phase II and III trials; patients should be advised to administer the weekly subcutaneous injections in parts of the body spared from or minimally involved with skin thickening, typically the upper, outer/posterior region of the arm (21,80). MMF and CYC remain alternative options, although they lack RCT data in the context of subclinical ILD. In patients with subclinical ILD and a low risk of progression, close monitoring of PFT every 6 months in early SSc is needed, and case-by-case treatment decisions may be considered.

As mentioned above, all patients with clinical ILD should be considered for immunomodulatory treatment (15,35). In the case of quiescent skin and musculoskeletal manifestations, MMF is the preferred initial treatment from the authors' perspective, with CYC and nintedanib as other acceptable first-line options that might be considered. In the case of active disease including skin and/or musculoskeletal manifestations, tocilizumab, CYC, or MMF should be introduced, considering their effects on extrapulmonary manifestations in focuSSced, SLS I, and SLS II, respectively. Rituximab may also be an option, although we usually reserve it for second-line treatment given the absence of randomized double-blind controlled trials for this drug in SSc-ILD (Figure 3). Upfront combination of nintedanib with MMF in patients with active extrapulmonary and rapidly progressive disease is also acceptable first-line therapy (such patients may also be candidates for autologous HSCT). We do not recommend nintedanib alone as first-line therapy in patients with SSc-ILD with active extrapulmonary disease, given the absence of impact on these manifestations in SENSCIS (63).

After treatment initiation, clinical monitoring of FVC and DL_{CO} at least every 6 months is recommended, although in those with progressive ILD, we may consider monitoring FVC and DL_{CO} every 4 months until stabilization is documented (58). In the case of stabilization, first-line treatment should be continued. In the case of worsening respiratory symptoms, other diagnoses, such as cardiac involvement or pulmonary vascular disease, should be explored. If worsening parenchymal disease is suspected, a repeat HRCT should be performed to confirm progression of ILD. In the event of advancing disease despite first-line therapy, a second-line therapeutic strategy should be employed.

Three main options are proposed as second-line therapeutic strategies (Figure 3): 1) switching to another treatment, 2) considering combination of an immunomodulatory agent with an antifibrotic agent or combining 2 immunomodulatory agents (e.g., MMF and tocilizumab, or MMF and rituximab; although there are no data supporting the efficacy and/or safety of these combination therapies), and 3) considering HSCT. Lung transplant is usually reserved for those with progressive ILD despite trials of different therapies and requires referral to a lung transplant center.

Long-term management. The follow-up of patients from SLS I, SLS II, and the CYC arm of SCOT has suggested that the benefit of immunomodulation was not maintained after discontinuation of the immunomodulatory agent (68,81,82). Although the optimal duration of treatment has not been determined to date, we would recommend at least 5 years of treatment, although many patients need longer-term treatment. This duration should take into account the initial severity of ILD, the evaluation and stabilization of ILD-related symptoms, the extrapulmonary manifestations of SSc, and the risk of ILD progression/relapse once the treatment is stopped. In our practice, ~20–30% of patients experience relapse of skin and/or lung involvement once immunomodulatory therapy is discontinued. To date, there are no clinical data to support dose adjustments, such as decreased MMF dosage, after stabilization of the disease. Lower dosage may limit the risk of long-term side effects, including risk of malignancy, but such adjustments should be based on individual patient preferences and should take into account the initial severity and subsequent impact of progression in case of relapse. As an example, a patient with moderate ILD and FVC% of 70% may have adequate pulmonary reserve to consider dose down-titration but someone with an FVC% of 40% who requires supplemental O_2 therapy would likely not be an appropriate candidate for medication down-titration.

In the case of stabilization on treatment, and/or after treatment discontinuation, PFT should continue to be performed at least every 6 months in all SSc patients for 1–2 years. After this period of close monitoring, all patients should undergo annual PFT, as late progression may occur despite long-term stabilization. Screening for other visceral manifestations, especially PAH, should also be continued according to published screening algorithms (59).

Perspectives on the early introduction of combination therapies and new combinations

Recent RCTs in PAH have demonstrated that substantial progress could be obtained through an early combination of existing drugs (83,84). The combination of biologic disease-modifying

antirheumatic drugs (bDMARDs) with conventional DMARDs (cDMARDs) is widely used and recommended for the treatment of extrapulmonary manifestations in other CTDs, such as rheumatoid arthritis. The complex and overlapping pathobiology involved in SSc-ILD, which involves inflammation, fibrosis, and vascular changes, also supports the potential for combination therapies, as does the finding that a diverse range of drugs has clinical utility. As such, there are many reasons to consider combination therapy as a viable approach for treating SSc-ILD.

The combination of MMF and nintedanib demonstrated a reasonable safety profile in SENSCIS, although the benefit of the combination of the 2 active drugs compared to monotherapy alone could not be fully demonstrated in that trial (63). In the focuSSced trial, patients taking cDMARDs were excluded, precluding any conclusion regarding the safety or efficacy of tocilizumab in combination with MMF or methotrexate (21). Nonetheless, with their differing mechanisms of action, MMF and tocilizumab may have complementary effects (85). However, we need additional data to assess for tradeoffs between the efficacy and safety of this combination. The efficacy and safety of the combination of a biologic such as tocilizumab with a tyrosine kinase inhibitor such as nintedanib is still to be determined. This combination may be especially relevant considering the anti-inflammatory properties of tocilizumab and the potential more specific antifibrotic effects of nintedanib through PDGF and FGF receptor inhibition, as well as its potential impact on vasculopathy through VEGF receptor inhibition (28). The ongoing SLS III (ClinicalTrials.gov identifier: NCT03221257) is investigating the impact of pirfenidone, another antifibrotic agent indicated for the treatment of idiopathic pulmonary fibrosis, as an upfront combination treatment with MMF versus placebo and MMF in patients with SSc-ILD (86).

Conclusions

The current review provides a state-of-the-art practical overview of the management of SSc-ILD. As therapeutic options expand, expert perspective remains an important source of treatment guidance. The recent addition of 2 FDA-approved medications for SSc-ILD has broadened the cache of available treatments; management should be determined by stratifying patients in terms of disease severity, risk of progression, and activity of extrapulmonary disease. Patients with subclinical ILD and a high risk of progression should be provided therapy to prevent lung function loss; tocilizumab has demonstrated benefit in those with a high risk of progression. As shown in the focuSSced trial, early ILD is not necessarily mild ILD. Tocilizumab is effective in attenuating lung function loss along a wide spectrum of lung involvement on HRCT, suggesting it can be utilized in clinical ILD with a spectrum of degree of underlying lung involvement. Nintedanib can be considered as first-line therapy in SSc-ILD but preferentially in those with limited extrapulmonary disease (a rare scenario in early SSc) or as part of upfront combination therapy for progressive SSc-ILD in patients who are candidates for HSCT.

Immunosuppressive therapy with MMF should also be considered as a primary treatment approach for clinical ILD and particularly in those with other active manifestations. In this setting, MMF has the potential to improve pulmonary function over time in the majority of patients and is similarly active with respect to improvements over time in skin disease, dyspnea, and health-related quality of life (87). Current immunomodulatory and antifibrotic interventions attenuate the impact of SSc-ILD but have yet to demonstrate a long-lasting benefit on how patients feel, function, or survive. Further questions of upfront or sequential combination therapy with immunosuppressives and antifibrotics, or addition of bDMARDs, as done in other rheumatic diseases, remain areas of further research.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis [review]. Lancet 2017; 390:1685–99.
2. Frantz C, Avouac J, Distler O, Amrouche F, Godard D, Kennedy AT, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: a large international survey. Semin Arthritis Rheum 2016;46:115–23.
3. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.
4. LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis [review]. J Rheumatol 2001;28:1573–6.
5. Domsic RT, Medsger TA. Autoantibodies and their role in scleroderma clinical care. Curr Treatm Opt Rheumatol 2016;2:239–51.
6. Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol 2020;72:465–76.
7. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340–9.
8. Chan EK, Damoiseaux J, Carballo OG, Conrad K, de Melo Cruvinel W, Francescantonio PL, et al. Report of the first international consensus on standardized nomenclature of antinuclear antibody HEp-2 cell patterns 2014–2015 [review]. Front Immunol 2015;6:412.
9. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. Am J Respir Crit Care Med 2020;201:650–60.
10. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–905.
11. Meyer OC, Fertig N, Lucas M, Somogyi N, Medsger TA. Disease subsets, antinuclear antibody profile, and clinical features in 127 French and 247 US adult patients with systemic sclerosis. J Rheumatol 2007;34:104–9.
12. Bernstein EJ, Jaafar S, Assassi S, Domsic RT, Frech TM, Gordon JK, et al. Performance characteristics of pulmonary function tests

for the detection of interstitial lung disease in adults with early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol 2020;72:1892–6.

13. Hoffmann-Vold AM, Molberg Ø, Midtvedt Ø, Garen T, Gran JT. Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis. J Rheumatol 2013;40:1127–33.
14. Dougherty DH, Kwakkenbos L, Carrier ME, Salazar G, Assassi S, Baron M, et al. The Scleroderma Patient-Centered Intervention Network Cohort: baseline clinical features and comparison with other large scleroderma cohorts. Rheumatology (Oxford) 2018;57:1623–31.
15. Roofeh D, Distler O, Allanore Y, Denton CP, Khanna D. Treatment of systemic sclerosis–associated interstitial lung disease: lessons from clinical trials. J Scleroderma Relat Disord 2020;5:61–71.
16. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
17. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.
18. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis–associated interstitial lung disease. N Engl J Med 2019;380:2518–28.
19. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SL, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27.
20. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–40.
21. Khanna D, Lin CJ, Furst DE, Goldin J, Kim G, Kuwana M, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2020;8:963–74.
22. Roofeh D, Lin CJ, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab prevents progression of early systemic sclerosis–associated interstitial lung disease. Arthritis Rheumatol 2021;73:1301–10.
23. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Distler O. Assessment of recent evidence for the management of patients with systemic sclerosis-associated interstitial lung disease: a systematic review. ERJ Open Res 2021;7:00235–2020.
24. Volkmann ER, Varga J. Emerging targets of disease-modifying therapy for systemic sclerosis [review]. Nat Rev Rheumatol 2019;15:208–24.
25. Lescoat A, Ballerie A, Augagneur Y, Morzadec C, Vernhet L, Fardel O, et al. Distinct properties of human M-CSF and GM-CSF monocyte-derived macrophages to simulate pathological lung conditions in vitro: application to systemic and inflammatory disorders with pulmonary involvement. Int J Mol Sci 2018;19:894.
26. Lescoat A, Ballerie A, Jouneau S, Fardel O, Vernhet L, Jego P, et al. M1/M2 polarisation state of M-CSF blood-derived macrophages in systemic sclerosis [editorial]. Ann Rheum Dis 2019;78:e127.
27. Valenzi E, Bulik M, Tabib T, Morse C, Sembrat J, Bittar HT, et al. Single-cell analysis reveals fibroblast heterogeneity and myofibroblasts in systemic sclerosis-associated interstitial lung disease. Ann Rheum Dis 2019;78:1379–87.
28. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis [review]. Eur Respir J 2015;45:1434–45.
29. Denton CP, Ong VH, Xu S, Chen-Harris H, Modrusan Z, Lafyatis R, et al. Therapeutic interleukin-6 blockade reverses transforming growth factor-β pathway activation in dermal fibroblasts: insights from the faSScinate clinical trial in systemic sclerosis. Ann Rheum Dis 2018;77:1362–71.
30. Numajiri H, Kuzumi A, Fukasawa T, Ebata S, Yoshizaki-Ogawa A, Asano Y, et al. B cell depletion inhibits fibrosis via suppressing pro-fibrotic macrophage differentiation in a mouse model of systemic sclerosis. Arthritis Rheumatol 2021 doi: https://doi.org/10.1002/art.41798. E-pub ahead of print.
31. Mauer J, Chaurasia B, Goldau J, Vogt MC, Ruud J, Nguyen KD, et al. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol 2014;15:423–30.
32. Gao X, Jia G, Guttman A, DePianto DJ, Morshead KB, Sun KH, et al. Osteopontin links myeloid activation and disease progression in systemic sclerosis. Cell Rep Med 2020;1:100140.
33. Petrova DT, Brandhorst G, Koch C, Schultze FC, Eberle C, Walson PD, et al. Mycophenolic acid reverses TGF β-induced cell motility, collagen matrix contraction and cell morphology in vitro. Cell Biochem Funct 2015;33:503–8.
34. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action [review]. Immunopharmacology 2000;47:85–118.
35. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol 2020;2:e71–83.
36. Roofeh D, Jaafar S, Vummidi D, Khanna D. Management of systemic sclerosis-associated interstitial lung disease [review]. Curr Opin Rheumatol 2019;31:241–9.
37. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976–87.
38. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.
39. Remy-Jardin M, Giraud F, Remy J, Copin MC, Gosselin B, Duhamel A. Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: pathologic-CT correlation. Radiology 1993;189:693–8.
40. Takei R, Arita M, Kumagai S, Ito Y, Tokioka F, Koyama T, et al. Radiographic fibrosis score predicts survival in systemic sclerosis-associated interstitial lung disease. Respirology 2018;23:385–91.
41. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002;165:1581–6.
42. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44–68.
43. Kim HG, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol 2010;28:S26–35.
44. Goldin JG, Kim GH, Tseng CH, Volkmann E, Furst D, Clements P, et al. Longitudinal changes in quantitative interstitial lung disease on computed tomography after immunosuppression in the Scleroderma Lung Study II. Ann Am Thorac Soc 2018;15:1286–95.
45. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248–54.
46. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, et al. Predictors of mortality and progression in

scleroderma-associated interstitial lung disease: a systematic review. Chest 2014;146:422–36.

47. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TD, Maurer B, Jordan S, et al. Pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol 2015;67:3256–61.
48. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease [review]. Eur Respir J 2014;44:1428–46.
49. American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–17.
50. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little Brown & Co; 1994:253–6.
51. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988;93:580–6.
52. Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease [review]. Eur Respir J 2020;55:1902026.
53. Liu X, Mayes MD, Pedroza C, Draeger HT, Gonzalez EB, Harper BE, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res (Hoboken) 2013;65:1375–80.
54. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625–35.
55. Stock CJ, Hoyles RK, Daccord C, Kokosi M, Visca D, De Lauretis A, et al. Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. Respirology 2021;26:461–8.
56. Salazar GA, Kuwana M, Wu M, Estrada-Y-Martin RM, Ying J, Charles J, et al. KL-6 but not CCL-18 is a predictor of early progression in systemic sclerosis-related interstitial lung disease. J Rheumatol 2018;45:1153–8.
57. Jaeger VK, Valentini G, Hachulla E, Cozzi F, Distler O, Airó P, et al. Smoking in systemic sclerosis: a longitudinal European Scleroderma Trials and Research group study. Arthritis Rheumatol 2018;70:1829–34.
58. Roofeh D, Khanna D. Management of systemic sclerosis: the first five years [review]. Curr Opin Rheumatol 2020;32:228–37.
59. Young A, Moles VM, Jaafar S, Visovatti S, Huang S, Vummidi D, et al. Performance of the DETECT algorithm for pulmonary hypertension screening in a systemic sclerosis cohort. Arthritis Rheumatol 2021;73:1731–7.
60. Kim GH, Tashkin DP, Lo P, Brown MS, Volkmann ER, Gjertson DW, et al. Using transitional changes on high-resolution computed tomography to monitor the impact of cyclophosphamide or mycophenolate mofetil on systemic sclerosis–related interstitial lung disease. Arthritis Rheumatol 2020;72:316–25.
61. Namas R, Tashkin DP, Furst DE, Wilhalme H, Tseng CH, Roth MD, et al. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post hoc analyses from two randomized placebo-controlled trials. Arthritis Care Res (Hoboken) 2018;70:439–44.
62. Jaafar S, Lescoat A, Huang S, Gordon J, Hinchcliff M, Shah AA, et al. Clinical characteristics, visceral involvement, and mortality in at-risk or early diffuse systemic sclerosis: a longitudinal analysis of an observational prospective multicenter US cohort. Arthritis Res Ther 2021;23:170.
63. Highland KB, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med 2021;9:96–106.
64. Khanna D, Spino C, Johnson S, Chung L, Whitfield ML, Denton CP, et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. Arthritis Rheumatol 2020;72:125–36.
65. Chung L, Spino C, McLain R, Johnson SR, Denton CP, Molitor JA, et al. Safety and efficacy of abatacept in early diffuse cutaneous systemic sclerosis (ASSET): open-label extension of a phase 2, double-blind randomised trial. Lancet Rheumatol 2020;2:e743–53.
66. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology (Oxford) 2018;57:2106–13.
67. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. Lancet Rheumatol 2021;3:E489–97.
68. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med 2018;378:35–47.
69. Launay D, Marjanovic Z, de Bazelaire C, Florea L, Zohar S, Keshtmand H, et al. Autologous hematopoietic stem cell transplant in systemic sclerosis: quantitative high resolution computed tomography of the chest scoring. J Rheumatol 2009;36:1460–3.
70. Roofeh D, Lescoat A, Khanna D. Treatment for systemic sclerosis-associated interstitial lung disease. Curr Opin Rheumatol 2021;33:240–8.
71. Bernstein EJ, Peterson ER, Sell JL, D'Ovidio F, Arcasoy SM, Bathon JM, et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. Arthritis Rheumatol 2015;67:1314–22.
72. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1–15.
73. Jablonski R, Dematte J, Bhorade S. Lung transplantation in scleroderma: recent advances and lessons [review]. Curr Opin Rheumatol 2018;30:562–9.
74. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324–43.
75. Khanna D, Denton CP. Integrating new therapies for systemic sclerosis-associated lung fibrosis in clinical practice. Lancet Respir Med 2021;9:560–2.
76. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax 2017;72:610–9.
77. Nakayama K, Nakajima Y, Tanaka R, Hirata KI, Emoto N. Predictors of long-term outcomes in patients with connective tissue disease associated with pulmonary arterial hypertension. J Clin Rheumatol 2020. doi: https://doi.org/10.1097/RHU.0000000000001447. E-pub ahead of print.
78. Kanjrawi AA, Mathers L, Webster S, Corte TJ, Carey S. Nutritional status and quality of life in interstitial lung disease: a prospective cohort study. BMC Pulm Med 2021;21:51.
79. Jouneau S, Crestani B, Thibault R, Lederlin M, Vernhet L, Valenzuela C, et al. Analysis of body mass index, weight loss and progression of idiopathic pulmonary fibrosis. Respir Res 2020;21:312.
80. Suleman Y, Clark KE, Cole AR, Ong VH, Denton CP. Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung

function for anti-topoisomerase-positive patients. Rheumatology (Oxford) 2021;60:3945–6.

81. Khanna D, Furst DE, Clements PJ, Tashkin DP, Eckman MH. Oral cyclophosphamide for active scleroderma lung disease: a decision analysis. Med Decis Making 2008;28:926–37.
82. Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis 2019;78:122–30.
83. Lajoie AC, Lauzière G, Lega JC, Lacasse Y, Martin S, Simard S, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis [review]. Lancet Respir Med 2016;4:291–305.
84. Khanna D, Zhao C, Saggar R, Mathai SC, Chung L, Coghlan JG, et al. Long-term outcomes in patients with connective tissue disease–associated pulmonary arterial hypertension in the modern treatment era: meta-analyses of randomized, controlled trials and observational registries. Arthritis Rheumatol 2021;73:837–47.
85. Chandran S, Leung J, Hu C, Laszik ZG, Tang Q, Vincenti FG. Interleukin-6 blockade with tocilizumab increases Tregs and reduces T effector cytokines in renal graft inflammation: a randomized controlled trial. Am J Transplant 2020;21:2543–54.
86. Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, et al. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. J Rheumatol 2016;43:1672–9.
87. Volkmann ER, Tashkin DP, LeClair H, Roth MD, Kim G, Goldin J, et al. Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: results of Scleroderma Lung Study II. ACR Open Rheumatol 2020;2:362–70.