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Natural variability in the disease course of SSc-ILD: implications for treatment

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The disease course of SSc-ILD is heterogeneous and variable. More data are needed to better understand the natural disease course of SSc-ILD, enabling risk stratification of patients to optimise the management and long-term outcomes. https://bit.ly/3qqITaZ

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ABSTRACT Interstitial lung disease (ILD) affects approximately 50% of patients with systemic sclerosis (SSc) and is the leading cause of death in SSc. Our objective was to gain insight into the progression of SSc-associated ILD (SSc-ILD). Using data from longitudinal clinical trials and observational studies, we assessed definitions and patterns of progression, risk factors for progression, and implications for treatment.

SSc-ILD progression was commonly defined as exceeding specific thresholds of lung function worsening and/or increasing radiographic involvement. One definition used in several studies is decline in forced vital capacity (FVC) of ⩾10%, or ⩾5–10% plus a decline in diffusing capacity of the lung for carbon monoxide ⩾15%. Based on these criteria, 20–30% of patients in observational cohorts develop progressive ILD, starting early in the disease course and progressing at a highly variable rate.

Risk factors such as age, FVC, extent of fibrosis and presence of anti-topoisomerase I antibodies can help predict progression of SSc-ILD, though composite risk scores may offer greater predictive power. Whilst the variability of the disease course in SSc-ILD makes risk stratification of patients challenging, the decision to initiate, change or stop treatment should be based on a combination of the current disease state and the speed of progression.

Introduction

Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis (SSc), affecting approximately 50% of all patients with SSc [1–3], though prevalence estimates vary depending on the diagnostic method used. Studies published in the last decade have shown that ILD is the leading cause of death in SSc, representing an estimated 17–35% of all SSc-related deaths [4–6]. Accurately assessing and defining disease progression in SSc-ILD could help identify patients at risk and help guide disease

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management. In this review, we assess the progression of ILD in SSc using data from clinical trials of investigational new drugs for SSc-ILD as well as observational cohort studies. The four areas of focus are: 1) definitions of progression; 2) patterns of progression; 3) single and composite risk factors for progression; and 4) implications for treatment. A video abstract summarising this review article is available at: www.globalmedcomms.com/respiratory/Vonk/SSc-ILD_Disease_Course_Review

Definitions of progression in SSc-ILD

Although there is no consistent definition of progression in the SSc-ILD literature, attempts have been made to define progression based on changes in pulmonary function (forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO})). One definition of clinically meaningful progression that has informed several observational studies and clinical trials is a ⩾10% relative decline in FVC, or ⩾5% to <10% relative decline in FVC together with ⩾15% relative decline in D_{LCO} [7–9]. This is consistent with definitions used in some studies of idiopathic pulmonary fibrosis (IPF) [10–12]. It is also comparable to a recent study of chronic fibrosing ILDs with a progressive phenotype, in which patients were required to have the following: a ⩾10% relative decline in FVC % predicted, or ⩾5% to <10% relative decline in FVC % pred and worsening respiratory symptoms/increased extent of fibrosis on high-resolution computed tomography (HRCT), or worsening of respiratory symptoms and increased extent of fibrosis [13]. A recent position paper also suggests that the chronic fibrosing ILD with progressive phenotype is defined by disease progression despite treatment and should take into consideration pulmonary function tests (PFTs), HRCT and patient symptoms [14]; however, an internationally accepted definition has not been agreed. Since decline in lung function in SSc-ILD is typically slower and less predictable than in IPF (survival 2–5 years), more sensitive cut-off criteria to define progression may be needed for SSc-ILD. Indeed, using 12 months of data from the Scleroderma Lung Study (SLS) I and II (n=300), one *post-hoc* analysis defined a change (±) in FVC of 3.0% as the minimum clinically important difference for progression, when interpreted in the light of changes in dyspnoea index score and self-reported patient outcomes at 12 months [15].

Clinically meaningful progression may be more reliably defined by combining several clinical measures. Several authors have proposed criteria for progression of SSc-ILD based on a combination of pulmonary function measures with radiographic extent of fibrosis on HRCT [6–9, 16–22]. Although extent of ILD on HRCT [16, 17] can indicate disease progression in SSc-ILD (especially when pulmonary function is unclear), conducting regular HRCT scans in clinical practice may not be feasible, and there is no consensus about how often patients should undergo a scan. In the future, advances in artificial intelligence may significantly modify the practice of radiology, increasing its accuracy in detecting structural changes [23].

In a series of evidence-based consensus statements on the diagnosis and management of SSc-ILD, developed by a panel of 27 Europe-based physicians with expertise in SSc-ILD, 100% of participants agreed that FVC % pred can indicate disease progression in SSc-ILD, and that lung function is an effective post-diagnostic, long-term, follow-up measurement for assessing disease progression in SSc-ILD [18]. However, specific thresholds in FVC were not given as part of these consensus statements. Diagnostic tools for identifying progression were defined as measurements of FVC and D_{LCO}, HRCT to assess changes in extent or pattern of fibrosis, and detection of worsening symptoms [18].

Patterns of disease progression in SSc-ILD

Pulmonary involvement typically occurs within the first few years of onset of SSc [24–26]. Indeed, in a minority of patients (~4%), ILD is the first manifestation of SSc [27, 28]. Unlike the progressive fibrosing disease course of IPF, which has been well characterised [29], the course of SSc-ILD is characterised by a high degree of heterogeneity. Lung function deterioration may occur both early and late in the disease course [26, 30], and patients could be classified as having rapid or slow disease progression, disease stability or improvement. This status can change during the disease course of SSc-ILD, and this heterogeneity reflects the need for ongoing patient monitoring [30].

Developing a better understanding of the natural variability in the disease course of SSc-ILD may allow for risk stratification of patients and a more tailored approach to treatment and clinical management. In this section, we explore the variability in the disease course of SSc-ILD by looking at data from: 1) clinical trials (table 1), which typically have restrictive inclusion and exclusion criteria; and 2) observational cohorts, such as single-centre or multicentre databases, which recruit a wider cross-section of patients receiving various therapeutic regimens.

Clinical trials in SSc and SSc-ILD

Clinical trials provide well-controlled longitudinal data in well-characterised SSc cohorts and enable comparison of disease progression between treatment and non-treatment arms. One approach to assessing

TABLE 1 Progression in clinical trials of systemic sclerosis-associated interstitial lung disease (SSc-ILD)

Study [ref.]	Duration	Sample size	Treatment centres n	Inclusion criteria	Measures of progression		
					FVC	HRCT	Deaths
SLS I [31]	12 months (double-blind)	Placebo: n=72 CYC: n=73	13	>18 years of age dcSSc or lcSSc Evidence of acute alveolitis on BAL examination or ground-glass opacity on HRCT Onset of first (non-Raynaud) SSc symptom within 7 years FVC % pred 45–85% Grade 2 exertional dyspnoea on Mahler Dyspnoea Index	Change in mean ±SE FVC % pred: Placebo: −2.6±0.9% CYC: −1.0±0.9%	Proportion of patients with worsening of fibrosis after 12 months [32]: Placebo: 26/49 (53%) CYC: 14/49 (29%)	During randomised treatment period: Placebo: 3/79 CYC: 2/79
SLS II [33]	24 months (double-blind)	CYC: n=63 MMF: n=63	14	18–75 years of age dcSSc or lcSSc FVC % pred 45–85% Any ground-glass opacity on HRCT (whether associated with reticulations or not) Onset of first (non-Raynaud) SSc symptom within 7 years Grade 2 exertional dyspnoea on Mahler Dyspnoea Index	Change in mean ±SE FVC % pred: CYC: +3.0±1.2% MMF: +3.3±1.1%	Change in whole lung scores: QLF score: CYC: +1.13% MMF: +2.15% QILD score: CYC: −1.84% MMF: −0.95%	During randomised treatment period: CYC: 11/73 MMF: 5/69
faSScinate [34]	48 weeks (double-blind) 96 weeks (open-label extension)	Placebo: n=44 TCZ: n=43 Placebo-TCZ: n=24 Continuous TCZ: n=27	35	>18 years of age Diagnosis of SSc as per 1980 ACR criteria Onset of first (non-Raynaud) SSc symptom within 5 years mRSS score 15–40 Active disease (defined by pre-specified mRSS/biomarker criteria)	Change in mean (95% CI) FVC % pred: Placebo −0.06% (−0.10–−0.03) at 48 weeks −0.03% (−0.07–0.01) at 96 weeks TCZ −0.02% (−0.04–0.00) at 48 weeks −0.01% (−0.03–0.02) at 96 weeks	Not recorded	No deaths reported

Continued

TABLE 1 Continued

Study [ref.]	Duration	Sample size	Treatment centres n	Inclusion criteria	Measures of progression		
					FVC	HRCT	Deaths
focuSSced [35]	48 weeks (double-blind) 96 weeks (open-label extension)	Placebo: n=106 TCZ: n=104	83	Diagnosis of SSc as per ACR/EULAR criteria, meeting criteria for active disease Total disease duration ⩽60 months mRSS score 10–35	Change in median (95% CI) FVC % pred: Placebo: −3.9% (−4.8–−1.6) TCZ: −0.6% (−2.4–−0.9)	Change in whole lung scores: QLF in double-blind period (mean (95% CI)): Placebo: 0.4 (0–0.7) TCZ: −0.4 (−0.9–0.1) QILD: Placebo: 0.1 (−1.4–1.6) TCZ: −1.7 (−3.0–−0.4)	In double-blind period: Placebo: 1/106 TCZ: 1/104
RTX *versus* CYC [36]	6 months (open-label)	RTX: n=30 CYC: n=30	1	18–60 years of age dcSSc, as per ACR classification criteria Scl-70 antibody positivity ILD confirmed by HRCT and PFTs (FVC % pred 45–85%) Onset of first (non-Raynaud) SSc symptom within 3 years Baseline dyspnoea level of NYHA class II and III	Change in mean FVC % pred: RTX: +6.2% CYC: −1.3%	Not recorded	RTX: 1/30 CYC: 1/30
SENSCIS [37]	52 weeks (double-blind)	Placebo: n=288 Nintedanib: n=287	195	>18 years of age SSc as per ACR/EULAR classification criteria Onset of first (non-Raynaud) SSc symptom within 7 years ILD confirmed by >10% fibrosis on HRCT within 12 months of screening FVC % pred >40% D_{LCO} % pred 30–89%	Annual rate±SE of decline in FVC % pred: Placebo: −2.6 ±0.4% Nintedanib: −1.4 ±0.4%	Data collected, to be reported	Placebo: 9/288 Nintedanib: 10/288
ASSET [38]	12 months (double-blind)	Placebo: n=44 Abatacept: n=44		⩾18 years old SSc as per ACR/EULAR criteria, and dcSSc defined as per early SSc criteria [39] Disease duration of ⩽36 months (time from the first non-Rayaud symptom)	Change in FVC % pred (LSM±SE): Placebo: −4.1 ±1.2% Abatacept: −1.3 ±1.2%	Not recorded	Placebo: 1/44 Abatacept: 2/44

Continued

TABLE 1 Continued

Study [ref.]	Duration	Sample size	Treatment centres n	Inclusion criteria	Measures of progression		
					FVC	HRCT	Deaths
ASSIST [40]	24 months (open-label)	CYC: n=9 HSCT: n=10	1	<60 years of age dcSSc (mRSS score >14 and cutaneous involvement proximal to the elbow or knee) Internal organ involvement: D_{LCO} % pred <80%; decline in FVC % pred >10% within past 12 months; lung fibrosis or ground-glass opacities on HRCT; ECG or GI involvement	Change in mean ±SD FVC % pred: At 12 months: CYC: −6% HSCT: +12% At 24 months: HSCT: +12%	Volume of diseased lung on HRCT: At 12 months: CYC: +108 mL HSCT: −272 mL At 24 months: HSCT: −341 mL	No deaths
ASTIS [41]	24 months[#] (open-label)	CYC: n=64 HSCT: n=67	29	18–65 years of age dcSSc as per ACR criteria Maximum disease duration of 4 years mRSS score >15 Involvement of heart, lungs or kidneys Prior treatment with CYC allowed up to a cumulative dose of 5 g intravenously, or up to 2 mg·kg^{-1} body weight orally for 3 months	Change in mean ±SD FVC % pred: HSCT: +6.3 ±18.3% CYC: −2.8±17.2%	Not recorded	HR for overall survival: 1 year=0.48 (95% CI 0.25–0.91; p=0.02) 2 years=0.29 (0.13–0.65; p=0.002) 4 years=0.29 (0.13–0.64; p=0.002)
SCOT [42]	54 months (open-label)	CYC: n=39 HSCT: n=36	26	18–69 years of age SSc as per ACR criteria Maximum disease duration of 5 years Active ILD (determined by BAL composition or chest CT) FVC or D_{LCO} <70% pred renal involvement	Not recorded	Change from baseline in QILD score (±SE) at 54 months [43]: CYC: 0±5% HSCT: −7±2% Change from baseline in QLF score (±SE) at 54 months [65]: CYC: +3±3% HSCT: −1±1%	Treatment-related mortality at 54 months: CYC: 0/39 HSCT: 1/36

FVC: forced vital capacity; HRCT: high-resolution computed tomography; SLS: Scleroderma Lung Study; RTX: rituximab; CYC: cyclophosphamide; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; BAL: bronchoalveolar lavage; MMF: mycophenolate mofetil; QLF: quantitative lung fibrosis; QILD: quantitative ILD; TCZ: tocilizumab; ACR: American College of Rheumatology; mRSS: modified Rodnan skin score; EULAR: European League Against Rheumatism; PFT: pulmonary function test; NYHA: New York Heart Association; D_{LCO}: diffusing capacity for carbon monoxide; LSM: least squares mean; HSCT: haematopoietic stem cell transplantation; GI: gastrointestinal; CT: computed tomography. [#]: after 10 years of follow-up, HSCT was associated with improved overall and event-free survival compared with CYC.

disease progression is to evaluate changes in end-points such as FVC % pred over time, which can indicate whether patients have declined, stabilised, or even improved in terms of their lung function over a given time period. The placebo arms of clinical trials can provide important information about the natural history of ILD and baseline predictors of progression, particularly in the absence of any background therapy. In this opening section, we assess changes in FVC % pred and other key end-points in clinical trials of investigational drugs for SSc and SSc-ILD.

Cyclophosphamide and mycophenolate mofetil

The treatment of SSc-ILD has, until recent years, focused on immunosuppressive therapies, in particular cyclophosphamide (CYC) and mycophenolate mofetil (MMF), based on the results of two pivotal clinical trials: SLS I and II [31, 33]. These studies recruited patients with evidence of active pulmonary inflammation, defined either by the presence of alveolitis on bronchoalveolar lavage and/or any ground-glass opacity on HRCT (SLS I), or by any ground-glass opacity on HRCT (SLS II) [31, 33] and the results are summarised in table 1. In the phase III SLS I, patients received either oral CYC or placebo for 12 months, and were then followed up for a further 12 months without therapy [31]. In total, 26% of patients in the placebo arm had improved FVC % pred at 12 months follow-up; 14% of patients had a decline in FVC % pred of 5–10%, and 12% had a decline in FVC % pred >10% during the 12-month follow-up [44, 45]. There was also variability in disease behaviour in the treatment arm, with 49% of patients showing improved FVC % pred after 12 months, 13% of patients showing a decline of 5–10%, and 7% showing a decline of >10% during the 12-month follow-up [31, 44]. In a separate, placebo-controlled study of intravenously administered CYC, mean±SD FVC % pred in the placebo arm was 81.0±18.8% at baseline and 78.0±21.6% at week 52 follow-up [46].

The phase II SLS II trial compared the efficacy and safety of 12 months of oral CYC (followed by 12 months of placebo) and 24 months of MMF [33]. Overall, 64.7% of patients in the CYC arm had improved FVC % pred at 24 months, 5% of patients had a decline of 5–10%, and 2% had a decline of >10% during the 24 months. In the MMF arm, 71.7% had improved FVC % pred at 24 months, 5% of patients had a decline of 5–10%, and 2% had a decline of >10% during the 24 months [45]. In an analysis of HRCT outcomes in SLS II, changes in quantitative lung fibrosis score and quantitative ILD score were defined as worse (>2%), stable (−2–2%) and better (>−2%). Using the quantitative ILD score, 32% *versus* 26% had worse fibrosis, 11% *versus* 18% had stable fibrosis, and 57% *versus* 56% had better fibrosis in the CYC and MMF arms, respectively, at the same time-point [17].

Tocilizumab

In studies of tocilizumab for the treatment of SSc, the primary focus was skin changes in patients with early diffuse cutaneous SSc (dcSSc) and not SSc-ILD, therefore change in FVC was an exploratory end-point. The phase II faSScinate [34] and phase III focuSSced [35] studies were enriched for patients with evidence of active systemic inflammation, *e.g.* elevation of the inflammatory mediator C-reactive protein (CRP). In the phase II faSScinate study, the mean (95% CI) change in FVC % pred in the placebo arm was −0.06% (−0.10–−0.03; n=32) during an initial 48-week double-blind period, and −0.03% (−0.07–0.01; n=25) after a subsequent 48-week extension period in which patients received open-label tocilizumab [34]. In the phase III focuSSced study, the decline in median (95% CI) FVC % pred over 48 weeks was 3.9% (−4.8–−1.6) in the placebo arm, and 0.6% (−2.4–−0.9) in the tocilizumab arm [35, 47]. These studies of tocilizumab, which focused on skin-related outcomes in dcSSc but assessed FVC as an exploratory end-point, highlight that FVC decline can occur despite normal lung function at baseline (>80% FVC % pred in both studies), with 3–4% loss of FVC % pred in the placebo arm after 1 year [34, 47, 48]. In addition, these studies provide some evidence that tocilizumab could play a role in preventing progression of ILD in patients with early dcSSc with inflammatory features.

Rituximab

In one study conducted in patients with SSc-ILD, the effects of rituximab in slowing lung function decline were compared with those of CYC (standard therapy) over 6 months. In the rituximab arm (n=30), mean ±SD FVC % pred was 61.3±11.3% at baseline and 67.5±13.6% at 6 months, equating to an increase of 6.2%. In the CYC arm (n=30), the equivalent values were 59.3±13.0% at baseline and 58.0±11.2% at 6 months [36], equating to a decrease of 1.3%. Other studies are ongoing, such as RECITAL, a UK-based, multicentre, prospective, randomised, double-blind, double-dummy trial comparing rituximab with CYC (administered over a 20-week period) in patients with severe, progressive SSc-ILD, idiopathic inflammatory myositis or mixed connective tissue disease. The primary end-point is absolute rate of change in FVC after 24 weeks, and patients will be followed up for 48 weeks from the first dose [49].

Nintedanib

The tyrosine kinase inhibitor nintedanib was approved by the US Food and Drug Administration in 2019, and subsequently by the European Medicines Agency in 2020, to slow the rate of decline in lung function in patients with SSc-ILD [50, 51]. In the large-scale phase III SENSCIS trial, in which 52 weeks of twice-daily nintedanib was compared with placebo, ILD was identified on the basis of >10% fibrosis on HRCT, with FVC % pred >40% and D_{LCO} predicted 30–89% (patients with both dcSSc and limited cutaneous SSc (lcSSc) were included). In the placebo arm, patients had a median (interquartile range) disease duration of 3.5 (0.4–7.2) years since the onset of first non-Raynaud's symptom. At baseline, 48.6% of patients were receiving MMF, and mean±SD FVC % pred was 72.7±16.6%. The mean±SE annual rate of decline in FVC % pred during 52 weeks of follow-up in the placebo arm was 2.6±0.4% [37]. Therefore, of studies with placebo arms that may include patients taking standard of care treatments, both SLS I and SENSCIS had a mean decline in FVC % pred of 2.6% at 12 months/52 weeks [31, 37].

In the placebo arms in the subgroup analyses of SENSCIS, numerically greater annual rates of decline in FVC have been reported in patients with the following characteristics at baseline: dcSSc (*versus* lcSSc) [52]; onset of first non-Raynaud's symptom <3 years [53]; elevated CRP; and higher modified Rodnan skin score [54, 55]. These data reflect a heterogeneous population with subgroups of patients having different lung function declines within a year, as expected in a disease with a variable course.

Pirfenidone

Pirfenidone has been investigated in a phase II study of patients with SSc and was found to have an acceptable tolerability profile, including in combination with MMF [56]. The efficacy and safety of MMF in combination with either pirfenidone or placebo are currently being investigated in SLS III, a double-blind, parallel-group, randomised, placebo-controlled trial in patients with SSc-ILD (use of CYC, MMF, azathioprine, or other oral (or short half-life) disease-modifying antirheumatic drugs for ⩽6 months is permitted within the year prior to screening). Completion is scheduled for March 2022 [57].

Abatacept

The safety and efficacy of abatacept were evaluated in a phase II study of patients with early dcSSc, focusing on skin improvement [38]. Abatacept was well tolerated but changes in modified Rodnan skin score were not significant. In the placebo arm, there was a 4.1% decline in FVC % pred at 12 months.

Autologous haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation has been investigated in phase II and III trials in patients with SSc. Key inclusion criteria were dcSSc (excluding Scleroderma: Cyclophosphamide or Transplantation), disease duration of <5 years and presence of internal organ involvement. Baseline patient FVC % pred ranged from 62% to 82% [40–42]. The phase II ASSIST and phase III ASTIS trials compared autologous haematopoietic stem cell transplantation with CYC in patients with early dcSSc. Table 1 contains information on different measurements of disease progression in these studies.

Observational cohorts

Information about the natural disease course of SSc-ILD is also available from observational cohorts. Observational studies can reveal a more diverse and representative range of disease patterns over time than clinical trials because they typically have greater study durations, providing a more long-term view of disease progression. They also include a more heterogeneous group of patients that more closely reflect real clinical practice because they are not limited by restrictive inclusion criteria. One of the largest databases of patients with SSc is the European Scleroderma Trials and Research (EUSTAR) group, which contains over 15 000 patients with SSc [58]. In an analysis of data from 826 patients with SSc, radiographic evidence of ILD and serial PFTs in the EUSTAR database from 2010 onwards, changes in FVC % pred were evaluated over 12±3 months. In total, 27% of patients showed progressive ILD over the 12-month period: 12% had significant progression (decline in FVC % pred >10%, or decline in FVC % pred 5–10% together with D_{LCO} % pred ⩾15%), and 15% had moderate progression (decline in FVC % pred 5–10%, but without a decline in D_{LCO} % pred ⩾15%) [30]. These data are consistent with those observed in SLS I, in which 12% of patients had a decline in FVC % pred >10% during the 12-month period. During the mean 5-year period of evaluation, ⩾3 FVC values were available for 535 (65%) patients in the EUSTAR database, allowing for long-term assessment of the overall disease course. Of the 200 patients who showed an overall decline in lung function during the 5-year period, 58% had a slow pattern of lung function decline, *i.e.* more periods of stability or improvement than decline. One (34%) in three patients had a slow pattern of lung function decline, but with more periods of decline than stability or improvement, and only 8% of patients had a rapid pattern of lung function decline, *i.e.* several consecutive episodes of FVC decline and no periods of stability or improvement [30]. These data indicate that patterns of progression

in SSc-ILD are highly variable, and that the majority of patients who experience progression have both progressive and stable periods of disease within an overall long-term trajectory of decline. The overall proportion of patients who had disease progression in this study (27%) is consistent with data from a UK cohort of patients with SSc-ILD, in which 21–32% of patients showed a progressive decline in lung function during a 12-month period (decline in FVC % pred >10% or decline in D_{LCO} % pred ⩾15%) [8].

National SSc databases have been established in countries such as Germany [59], the UK [8, 60], the USA [61], Australia [62], Canada [63], Norway [2], Singapore [64] and France [65]. However, the availability of long-term, follow-up data varies by country. In one US cohort of patients with SSc retrospectively assessed for up to 12 years, patterns of progression were highly variable (up to seven categories of progression were identified), consistent with a EUSTAR database study [30]. Most patients (85%) had slowly improving or stable trajectories (⩽1% increase in FVC per year), with 15% of patients declining at rates of 2–3% FVC per year. In this study, CYC therapy was associated with significant improvement in the group with low baseline FVC and fast decline in FVC pattern (p=0.027), and there was a trend towards FVC deterioration in the group with low baseline FVC and stable FVC pattern (p=0.06), indicating the presence of distinct patient groups [61]. In a Canadian, single-centre, observational study of 171 patients with SSc-ILD, subgroups with different phenotypes were described based on lung progression. To account for survival bias, patients were categorised into three prognostic groups based on their length of survival. Patients with short-term mortality (deceased <4 years) had a higher annual rate of decline in FVC % pred in the first 2 years than those with medium-term (deceased 4–8 years) or long-term (alive at 8 years) mortality (annual rate of decline −9.99% (95% CI −10.53–−9.46) *versus* −3.04% (−3.10–−2.98) *versus* −1.69% (−1.71–−1.67), respectively; n=171), highlighting the prognostic relevance of FVC decline in the early stages of the disease (up to 2 years post-diagnosis) [63]. In this study, no association was found between previous and current change in FVC in any given year, *i.e.* FVC change in a previous year was not a statistically significant predictor of FVC change in the subsequent year [63], again highlighting the high degree of heterogeneity and unpredictability in the disease course of SSc-ILD.

Risk factors for development and progression of SSc-ILD

SSc-ILD is a heterogeneous disease with varying rates of disease progression depending on the patient population. Several demographic factors are associated with the presence of ILD in SSc. For example, males with SSc more frequently develop ILD (RR 1.24 (95% CI 1.01–1.52)) and have an increased risk of ILD-associated mortality compared with females with SSc (HR 1.58 (95% CI 1.26–1.98)) [66]. In one large-scale analysis of SSc-related death in 11 193 patients from the EUSTAR database, respiratory causes (including ILD and pulmonary hypertension) were responsible for 17% of deaths over a median 2.3 years of follow-up, and men had a four-fold higher rate of death from respiratory diseases compared with the general population [5]. Ethnicity is also a predisposing factor for the development of ILD. In a multi-ethnic observational study of 1005 patients with SSc, ILD more frequently occurred in patients of Afro-Caribbean (53%; n=58) ethnicity compared with patients of European (31%; n=745), South Asian (46%; n=70), East Asian (41%; n=80), Hispanic (37%; n=30), Arab (33%; n=9), North American Indigenous (44%; n=7) or Persian (17%; n=6) ethnicities (p=0.007) [67]. In another multi-ethnic observational study of 572 patients with SSc, ILD was diagnosed earlier in patients of Chinese descent (median (range) 0.3 (−4.9–9.0) years)) compared with patients of European descent (median (range) 1.8 (−10.0–28.6) years; p=0.056), with similar median trough FVC in both groups (65% and 71% pred, respectively) [68]. In a EUSTAR study, Asian and black patients with SSc were more likely to have reduced FVC than white patients [69]. Other published risk factors for developing ILD include higher baseline skin score, dcSSc (*versus* lcSSc), dcSSc with an inflammatory skin phenotype, and particularly anti-topoisomerase I antibody positivity [37, 70–72]. In patients with SSc-ILD specifically, some studies have shown that PFT values, HRCT patterns and other factors in the early stages of the disease are correlated with long-term outcomes [2, 4, 5, 30, 71, 73–79]. In particular, low FVC seems to be strongly associated with faster disease progression as it was the most frequent risk factor in these studies (table 2).

Composite risk scores in SSc-ILD

Because single risk factors may not have sufficient power to identify patients with SSc-ILD at risk of progression, scores using a combination of clinical and laboratory parameters may be needed. For example, Goh *et al.* [60] developed a limited/extensive disease staging system for SSc-ILD using a combination of HRCT and PFT data. Disease was classified as limited (<20% fibrosis) or extensive (>20% fibrosis) using semi-quantitative HRCT. For patients with indeterminate disease by HRCT, a threshold of FVC 70% pred was then used to classify the remaining patients as having limited or extensive disease [60]. In a separate study by Goh *et al.* [8], the most accurate predictor of mortality was a relative annual decline in FVC ⩾10%, or a relative decline in FVC of 5–9% together with a relative decline in D_{LCO} ⩾15% [8]. In a SPAR (S_{PO_2} and ARthritis) model, oxygen desaturation and history of arthritis were independent

TABLE 2 Risk factors for mortality and disease progression in systemic sclerosis-associated interstitial lung disease (SSc-ILD)

First author [ref.]	Study design and patient numbers	Independent risk factor(s)	Measure of progression
Steen [73]	Analysis of 890 patients evaluated in a US centre between 1972 and 1989	Disease severity (FVC % pred)	10-year cumulative survival
Tyndall [4]	Analysis of data from 2940 patients in the EUSTAR database	FVC <80% pred and D_{LCO} <80% pred	Mortality
Zhang [74]	Analysis of 1043 patients from the Canadian Scleroderma Research Group (multicentre database)	Symptoms of oesophageal dysmotility	Low FVC (<70%)
Ahmed [75]	Observational cohort of 188 patients form the Toronto Scleroderma Programme	Baseline FVC pred <70% and D_{LCO} pred <77%, higher age at baseline (adjusted for FVC and D_{LCO})	Mortality
Nihtyanova [71]	Single-centre cohort of 398 consecutive patients with SSc followed for up to 15 years	Higher age at onset, dcSSc, lower FVC and D_{LCO}, presence of anti-topoisomerase I antibodies	Clinically significant pulmonary fibrosis (FVC or D_{LCO} <55% pred or documented decline in FVC or D_{LCO} <15%)
Ryerson [76]	Application of four risk-prediction models (derived from IPF) to 156 patients recruited from a specialised SSc-ILD clinic	Baseline FVC, 6-min walk distance	1-year mortality
Okamoto [77]	Retrospective analysis of 35 patients with SSc-ILD	Usual interstitial pattern on HRCT, higher score for ground-glass attenuation with traction bronchiectasis on HRCT	Mortality
Elhai [5]	Analysis of data from 11 193 patients in the EUSTAR database	ILD, D_{LCO} <60% pred, FVC <70% pred	Mortality
Volkmann [78]	Long-term, follow-up analysis of patients in SLS I and II (up to 12 years in SLS I (median 8 years), n=158; up to 8 years in SLS II (median 4 years), n=142)	Decline in FVC and D_{LCO} over 24 months, increased age, increased mRSS	Mortality
Becker [79]	Analysis of 706 patients with diffuse SSc and 12 months of follow-up from the EUSTAR database	Advanced age (>60 years), active digital ulcer; lung fibrosis (FVC <60% or FVC <70% with presence of fibrosis on HRCT), muscle weakness, elevated C-reactive protein	Disease progression[#]
Hoffmann-Vold [2]	Prospective Norwegian cohort study of 815 patients with SSc	>25% fibrosis on HRCT	Mortality
Hoffmann-Vold [30]	Analysis of 826 patients with FVC measures available at baseline and after 12 months from the EUSTAR database	Male sex, higher mRSS, presence of gastro-oesophageal reflux disease at baseline	FVC decline over a 5-year period

FVC: forced vital capacity; EUSTAR: European Scleroderma Trials and Research; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; dcSSc: diffuse cutaneous SSc; IPF: idiopathic pulmonary fibrosis; HRCT: high-resolution computed tomography; SLS: Scleroderma Lung Study; mRSS: modified Rodnan skin score. [#]: new renal crisis, decrease of lung or heart function, new echocardiography-suspected pulmonary hypertension or death.

predictors of progression (defined as a decline in FVC ⩾15%, or a relative decline in FVC of ⩾10% together with a relative decline in D_{LCO} ⩾15%) in patients with mild SSc-ILD (diagnosed by HRCT). However, combining both predictors (S_{PO_2} and ARthritis) increased the prediction rate from 25.5% to 91.7% [80]. In another study, a combination of smoking history, age and D_{LCO}% pred was used to predict risk of mortality [81] (interestingly, smoking alone has not been associated with a more rapid FVC decline in SSc) [82]. These studies suggest that composite measures and staging systems could be used in clinical practice to help discuss prognosis and guide clinical management. However, there is a risk that such staging systems may lead physicians to withhold treatment in patients with "less advanced" disease who may still be at risk of adverse outcomes [30].

Biomarkers

Reliable biomarkers could help to risk stratify patients. CC-chemokine ligand 18 (CCL18) and Krebs von den Lungen-6 (KL-6) have shown potential predictive value for the progression of SSc-ILD [83, 84]. High CCL18 serum levels were associated with a three-fold increased risk of a >10% decrease in FVC [83]. In a study of patients with SSc, KL-6 was highest in those with extensive ILD and lowest in those without

ILD [84]. In an analysis of patient data from SLS II, in which treatment effects were controlled for and the progression of ILD systematically monitored using multiple FVC measurements, patients with higher baseline KL-6 and CCL18 levels were more likely to progress despite therapy [85]. In a recent meta-analysis of 10 studies focused on circulating biomarkers in connective tissue disease-associated ILDs (eight of which included patients with SSc-ILD only), KL-6 was found to correlate most strongly with a diagnosis of SSc-ILD (OR 21.86 (95% CI 5.07–94.24), p<0.001), followed by surfactant protein D (OR 13.24 (3.84–45.71), p<0.001) and CCL18 (OR 3.31 (1.25–8.77), p=0.016). Furthermore, CCL18 (OR 2.62 (1.71–4.03), p<0.001) and KL-6 (OR 1.80 (1.02–3.17), p=0.04) were found to have prognostic value in terms of decline in FVC and/or mortality [86]. Another potential biomarker in SSc-ILD is exhaled nitric oxide, a widely used, noninvasive marker of airway inflammation in asthma. In one study, patients with SSc-ILD had significantly lower median conducting airway nitric oxide compared with control subjects (p=0.04) [87]. However, despite research efforts to date, large, longitudinal studies are needed to enable the translational use of biomarkers specific to SSc-ILD in routine clinical practice.

Implications for treatment

Disease progression in SSc-ILD is common but is generally slower than in IPF [88]. The variable nature of SSc-ILD and the lack of robust predictive markers make it challenging to determine which patients are likely to progress (more rapidly), and when is the optimal time to initiate therapy. Accurate risk stratification using evidence of lung function impairment, extent of fibrosis on HRCT and other parameters could help to inform treatment decisions. According to the criteria proposed by some experts or used in observational studies to date, initiation of treatment for SSc-ILD could be discussed under any of the following circumstances: 1) clear evidence of ILD on HRCT; 2) indeterminate evidence of ILD on HRCT combined with lung function impairment (*e.g.* >10% fibrosis on HRCT combined with FVC <70% pred) and/or poor prognostic factors, such as Scl-70 (though this is more controversial) and elevation of inflammatory parameters such as CRP; 3) a significant and sustained decline in lung function (*e.g.* FVC ⩾10% or FVC 5% to <10% with D_{LCO} ⩾15%, in the absence of pulmonary hypertension); or 4) clear evidence of radiographic progression of ILD, as determined by follow-up HRCT (if available) [60, 89–92].

Screening and regular monitoring with HRCT and/or PFTs is critical for early identification of ILD in patients with SSc and to be able to understand its disease course. Timely treatment with therapeutic agents is important for preserving or slowing the decline in lung function in SSc-ILD, especially considering the association between measurements of pulmonary function early in the disease course and long-term survival outcomes. Waiting to cross the currently pre-specified thresholds of lung function most common in the current literature (10% and 15% for FVC and D_{LCO}, respectively) or waiting for a demonstration of deterioration in lung function of FVC% pred <70% [60] before initiating treatment may result in a missed opportunity to slow disease progression and eventually preserve lung function and tissue. However, it remains unclear whether earlier treatment might be associated with the prevention of irreversible organ damage. Furthermore, the natural variability in the disease course of SSc-ILD has the potential to affect clinical interpretation, considering the recent finding that periods of apparent stability in lung function may represent a natural, short-term plateau within a wider arc of decline, and may not accurately predict mid- and long-term outcomes.

Despite a growing body of evidence, the available data sets that can be used to study the natural progression of SSc-ILD are still limited. Future large-scale studies of patients with SSc-ILD would add to our understanding of how the disease course of SSc-ILD differs between patients (in its overall pace, as well as short-term and long-term patterns of stability and decline).

The latest set of European League Against Rheumatism guidelines, published in 2017 and drafted prior to the publication of the SLS II and SENSCIS trials, provide no criteria for defining ILD progression [93]. An updated set of guidelines with proposed criteria for progression to guide clinical management, and to reflect the recent approvals of nintedanib for the treatment of SSc-ILD in the USA and Europe [50, 51], would be welcome. Until then, in the absence of formalised guidelines, consensus statements such as those published by a group of 27 Europe-based physicians with expertise in SSc-ILD may help to guide clinical decision-making. These consensus statements include close monitoring (every 3–6 months) of patients who are considered to have early, stable, or mild SSc-ILD, using HRCT, FVC, D_{LCO}, exercise-induced blood oxygen desaturation and/or deterioration of clinical symptoms [18]. The decision to initiate, change or stop treatment should be based on a combination of the current disease state and speed of progression; however, no pre-specified criteria for progression are given as part of these consensus statements [18].

Conclusions

The disease course of SSc-ILD is heterogeneous and variable, and different patterns have been observed in different studies, including clinical trials [31, 37, 47, 48]. Disease progression is frequent in patients with

SSc-ILD but usually occurs at a slower rate than in IPF [88]. The current evidence from observational cohorts suggests that 20–30% of patients will develop a progressive disease course [8, 30], starting within the first few years of disease onset and then progressing at a variable rate. Predicting which patients are most likely to progress, and at what rate, remains a challenge. Further research into composite measures of prediction, as well as biomarkers, should continue to be evaluated in future studies to inform risk stratification. A wider range of longitudinal data from observational cohorts worldwide would also help to clarify the association between baseline characteristics, disease progression and long-term mortality, with the aim of improving the prognostic accuracy of composite scores based on parameters early in the disease course.

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References

1 Steele R, Hudson M, Lo E, *et al.* Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. *Arthritis Care Res (Hoboken)* 2012; 64: 519–524.
2 Hoffmann-Vold AM, Fretheim H, Halse AK, *et al.* Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med* 2019; 200: 1258–1266.
3 Bergamasco A, Hartmann N, Wallace L, *et al.* Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clin Epidemiol* 2019; 11: 257–273.
4 Tyndall AJ, Bannert B, Vonk M, *et al.* Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69: 1809–1815.
5 Elhai M, Meune C, Boubaya M, *et al.* Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1897–1905.
6 Distler O, Assassi S, Cottin V, *et al.* Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020; 55: 1902026.
7 Khanna D, Mittoo S, Aggarwal R, *et al.* Connective tissue disease-associated interstitial lung diseases (CTD-ILD) – report from OMERACT CTD-ILD Working Group. *J Rheumatol* 2015; 42: 2168–2171.
8 Goh NS, Hoyles RK, Denton CP, *et al.* Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol* 2017; 69: 1670–1678.
9 Wu W, Jordan S, Graf N, *et al.* Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort. *Ann Rheum Dis* 2019; 78: 648–656.
10 McLellan T, George PM, Ford P, *et al.* Idiopathic pulmonary fibrosis: airway volume measurement identifies progressive disease on computed tomography scans. *ERJ Open Res* 2020; 6: 00290–2019.
11 Fernández Fabrellas E, Peris Sánchez R, Sabater Abad C, *et al.* Prognosis and follow-up of idiopathic pulmonary fibrosis. *Med Sci (Basel)* 2018; 6: 51.
12 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. *Am J Respir Crit Care Med* 2000; 161: 646–664.
13 Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
14 George PM, Spagnolo P, Kreuter M, *et al.* Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir Med* 2020; 8: 925–934.
15 Kafaja S, Clements PJ, Wilhalme H, *et al.* Reliability and minimal clinically important differences of forced vital capacity: results from the Scleroderma Lung Studies (SLS-I and SLS-II). *Am J Respir Crit Care Med* 2018; 197: 644–652.
16 Kim HJ, Brown MS, Elashoff R, *et al.* Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. *Eur Radiol* 2011; 21: 2455–2465.
17 Goldin JG, Kim GHJ, Tseng CH, *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: 1286–1295.
18 Hoffmann-Vold AM, Maher TM, Philpot EE, *et al.* The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; 2: e71–e83.

19 Morgan C, Knight C, Lunt M, *et al.* Predictors of end stage lung disease in a cohort of patients with scleroderma. *Ann Rheum Dis* 2003; 62: 146–150.
20 Distler O, Assassi S, Cottin V, *et al.* Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020; 55: 1902026.
21 Distler O, Volkmann ER, Hoffmann-Vold AM, *et al.* Current and future perspectives on management of systemic sclerosis-associated interstitial lung disease. *Expert Rev Clin Immunol* 2019; 15: 1–9.
22 Volkmann ER, Tashkin DP, Li N, *et al.* Development of a composite outcome measure for systemic sclerosis related interstitial lung disease. *Rheumatology (Sunnyvale)* 2015; 5: 154.
23 Jeny F, Brillet PY, Kim YW, *et al.* The place of high-resolution computed tomography imaging in the investigation of interstitial lung disease. *Expert Rev Respir Med* 2019; 13: 79–94.
24 Jaeger VK, Wirz EG, Allanore Y, *et al.* Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PLoS One* 2016; 11: e0163894.
25 Mcnearney TA, Reveille JD, Fischbach M, *et al.* Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. *Arthritis Rheum* 2007; 57: 318–326.
26 Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000; 43: 2437–2444.
27 Rubio-Rivas M, Corbella X, Pestana-Fernandez M, *et al.* First clinical symptom as a prognostic factor in systemic sclerosis: results of a retrospective nationwide cohort study. *Clin Rheumatol* 2018; 37: 999–1009.
28 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017; 390: 1685–1699.
29 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.
30 Hoffmann-Vold AM, Allanore Y, Alves M, *et al.* Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021; 80: 219–227.
31 Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide *versus* placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655–2666.
32 Goldin J, Elashoff R, Kim HJ, *et al.* Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study. *Chest* 2009; 136: 1333–1340.
33 Tashkin DP, Roth MD, Clements PJ, *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: 708–719.
34 Khanna D, Denton CP, Lin CJF, *et al.* Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Ann Rheum Dis* 2018; 77: 212–220.
35 Khanna D, Lin CJF, Furst DE, *et al.* Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; 8: 963–974.
36 Sircar G, Goswami RP, Sircar D, *et al.* Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomised, controlled trial. *Rheumatology (Oxford)* 2018; 57: 2106–2113.
37 Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis–associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.
38 Khanna D, Spino C, Johnson S, *et al.* Abatacept in early diffuse cutaneous systemic sclerosis – results of a phase 2 investigator-initiated, multicenter, double-blind randomised placebo-controlled trial. *Arthritis Rheumatol* 2020; 72: 125–136.
39 LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573–1576.
40 Burt RK, Shah SJ, Dill K, *et al.* Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011; 378: 498–506.
41 van Laar JM, Farge D, Sont JK, *et al.* Autologous hematopoietic stem cell transplantation *vs* intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomised clinical trial. *JAMA* 2014; 311: 2490–2498.
42 Sullivan KM, Goldmuntz EA, Keyes-Elstein L, *et al.* Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med* 2018; 378: 35–47.
43 Goldin J, Keyes-Elstein L, Crofford L, *et al.* Changes in quantitative scleroderma lung CT measures in patients treated with cyclophosphamide or transplantation. *Arthritis Rheumatol* 2018; 70: 901.
44 Tashkin DP, Elashoff R, Clements PJ, *et al.* Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med* 2007; 176: 1026–1034.
45 Tashkin D, Roth M, Furst D, *et al.* Scleroderma Lung Study II: comparison of therapy with mycophenolate mofetil *versus* oral cyclophosphamide in patients with symptomatic scleroderma interstitial lung disease. *Am J Respir Crit Care Med* 2016; 193: A6432.
46 Hoyles RK, Ellis RW, Wellsbury J, *et al.* A multicenter, prospective, randomised, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; 54: 3962–3970.
47 Khanna D, Lin CJF, Goldin J, *et al.* Preservation of lung function observed in a phase 3 randomised controlled trial of tocilizumab for the treatment of early SSc. *Ann Rheum Dis* 2019; 78: 202–203.
48 Khanna D, Denton CP, Jahreis A, *et al.* Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016; 387: 2630–2640.
49 Saunders P, Tsipouri V, Keir GJ, *et al.* Rituximab *versus* cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. *Trials* 2017; 18: 275.
50 U.S. Food and Drug Administration. FDA approves first treatment for patients with rare type of lung disease. www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-rare-type-lung-disease Date last updated: 6 September 2019; date last accessed: 31 October 2019.

51 Boehringer Ingelheim. Boehringer Ingelheim receives positive CHMP opinion for nintedanib for the treatment of systemic sclerosis-associated interstitial lung disease. www.boehringer-ingelheim.com/press-release/chmpopinionnintedanibssc-ild Date last updated: 28 February 2020; date last accessed: 6 March 2020.
52 Kuwana M, Highland K, Gahlemann M, *et al.* Effects of nintedanib in patients with diffuse and limited cutaneous systemic sclerosis and interstitial lung disease: subgroup analysis of the SENSCIS trial. *Arthritis Rheumatol* 2019; 71: 1644.
53 Distler O, Khanna D, Allanore Y, *et al.* Lung function decline in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) by time since first non-Raynaud symptom: subgroup analysis of the SENSCIS trial. *Am J Respir Crit Care Med* 2020; 201: A1524.
54 Allanore Y, Steen V, Kuwana M, *et al.* THU0330 Effects of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD) and differing extents of skin fibrosis: further analyses of the SENSCIS trial. *Ann Rheum Dis* 2020; 79: 395–396.
55 Riemekasten G, Carreira P, Saketkoo LA, *et al.* THU0363 Effects of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD) and normal *versus* elevated C-reactive protein (CRP) at baseline: analyses from the SENSCIS trial. *Ann Rheum Dis* 2020; 79: 413–414.
56 Khanna D, Albera C, Fischer A, *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: 1672–1679.
57 ClinicalTrials.gov. Scleroderma Lung Study III – combining pirfenidone with mycophenolate (SLSIII). https://clinicaltrials.gov/ct2/show/NCT03221257 Date last updated: 21 February 2020; date last accessed: 9 June 2020.
58 EUSTAR. http://eustar.org/ Date last accessed: 11 May 2020.
59 Kreuter M, Bonella F, Blank N, *et al.* Long term outcomes of immunomodulatory drugs in SSc-ILD – data from the German SSc-network. *Eur Respir J* 2019; 54: Suppl. 63, PA5185.
60 Goh NS, Desai SR, Veeraraghavan S, *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177: 1248–1254.
61 Man A, Davidyock T, Ferguson LT, *et al.* Changes in forced vital capacity over time in systemic sclerosis: application of group-based trajectory modelling. *Rheumatology (Oxford)* 2015; 54: 1464–1471.
62 Australian Rheumatology Association. Australian Scleroderma Interest Group (ASIG). https://rheumatology.org.au/patients/asig.asp Date last accessed: 8 June 2020.
63 Guler SA, Winstone TA, Murphy D, *et al.* Does systemic sclerosis–associated interstitial lung disease burn out? Specific phenotypes of disease progression. *Ann Am Thorac Soc* 2018; 15: 1427–1433.
64 Noviani M, Saffari SE, Tan JL, *et al.* Mortality and hospitalisation outcomes of interstitial lung disease and pulmonary hypertension in the Singapore systemic sclerosis cohort. *Semin Arthritis Rheum* 2020; 50: 473–479.
65 Pokeerbux MR, Giovannelli J, Dauchet L, *et al.* Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Res Ther* 2019; 21: 86.
66 Hussein H, Lee P, Chau C, *et al.* The effect of male sex on survival in systemic sclerosis. *J Rheumatol* 2014; 41: 2193–2200.
67 Al-Sheikh H, Ahmad Z, Johnson SR. Ethnic variations in systemic sclerosis disease manifestations, internal organ involvement, and mortality. *J Rheumatol* 2019; 46: 1103–1108.
68 Low AH, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with systemic sclerosis. *J Rheumatol* 2009; 36: 787–793.
69 Jaeger VK, Tikly M, Xu D, *et al.* Racial differences in systemic sclerosis disease presentation: a European Scleroderma Trials and Research group study. *Rheumatology (Oxford)* 2020; 59: 1684–1694.
70 Walker UA, Tyndall A, Czirjak L, *et al.* Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754–763.
71 Nihtyanova SI, Schreiber BE, Ong VH, *et al.* Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol* 2014; 66: 1625–1635.
72 Frantz C, Huscher D, Avouac J, *et al.* Outcomes of limited cutaneous systemic sclerosis patients: results on more than 12 000 patients from the EUSTAR database. *Autoimmun Rev* 2020; 19: 102452.
73 Steen VD, Conte C, Owens GR, *et al.* Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum* 1994; 37: 1283–1289.
74 Zhang X, Bonner A, Baron M, *et al.* Association of gastroesophageal factors and progression of interstitial lung disease in the Canadian Scleroderma Research Group (CSRG); a large, multi-center database. *Ann Rheum Dis* 2013; 71: 395–396.
75 Ahmed SS, Johnson SR, Meaney C, *et al.* Lung function and survival in systemic sclerosis interstitial lung disease. *J Rheumatol* 2014; 41: 2326–2328.
76 Ryerson CJ, O'Connor D, Dunne JV, *et al.* Predicting mortality in systemic sclerosis-associated interstitial lung disease using risk prediction models derived from idiopathic pulmonary fibrosis. *Chest* 2015; 148: 1268–1275.
77 Okamoto M, Fujimoto K, Sadohara J, *et al.* A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. *Respir Investig* 2016; 54: 445–453.
78 Volkmann ER, Tashkin DP, Sim M, *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: 122–130.
79 Becker M, Graf N, Sauter R, *et al.* Predictors of disease worsening defined by progression of organ damage in diffuse systemic sclerosis: a European Scleroderma Trials and Research (EUSTAR) analysis. *Ann Rheum Dis* 2019; 78: 1242–1248.
80 Wu W, Jordan S, Becker MO, *et al.* Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. *Ann Rheum Dis* 2018; 77: 1326–1332.
81 Morisset J, Vittinghoff E, Elicker BM, *et al.* Mortality risk prediction in scleroderma-related interstitial lung disease: the SADL model. *Chest* 2017; 152: 999–1007.
82 Jaeger VK, Valentini G, Hachulla E, *et al.* Brief report: smoking in systemic sclerosis: a longitudinal European scleroderma trials and research group study. *Arthritis Rheumatol* 2018; 70: 1829–1834.
83 Elhai M, Hoffmann-Vold AM, Avouac J, *et al.* Performance of candidate serum biomarkers for systemic sclerosis-interstitial lung disease. *Arthritis Rheumatol* 2019; 71: 972–982.
84 Stock C, Hoyles R, D'Accord C, *et al.* Serum KL-6 as a marker of disease progression in SSc-ILD. *Eur Respir J* 2018; 52: Suppl. 62, PA3664.

85 Volkmann E, Tashkin D, Kuwana M, *et al.* Progression of interstitial lung disease in systemic sclerosis: the importance of pneumoproteins Krebs von den Lungen 6 and CCL18. *Arthritis Rheumatol* 2019; 71: 2059–2067.
86 Elhai M, Avouac J, Allanore Y. Circulating lung biomarkers in idiopathic lung fibrosis and interstitial lung diseases associated with connective tissue diseases: where do we stand? *Semin Arthritis Rheum* 2020; 50: 480–491.
87 Kozij NK, Granton JT, Silkoff PE, *et al.* Exhaled nitric oxide in systemic sclerosis lung disease. *Can Respir J* 2017; 2017: 6736239.
88 Herzog EL, Mathur A, Tager AM, *et al.* Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? *Arthritis Rheumatol* 2014; 66: 1967–1978.
89 Silver KC, Silver RM. Management of systemic-sclerosis-associated interstitial lung disease. *Rheum Dis Clin North Am* 2015; 41: 439–457.
90 Au K, Khanna D, Clements PJ, *et al.* Current concepts in disease-modifying therapy for systemic sclerosis-associated interstitial lung disease: lessons from clinical trials. *Curr Rheumatol Rep* 2009; 11: 111–119.
91 Volkmann ER, Tashkin DP. Treatment of systemic sclerosis-related interstitial lung disease: a review of existing and emerging therapies. *Ann Am Thorac Soc* 2016; 13: 2045–2056.
92 Roofeh D, Jaafar S, Vummidi D, *et al.* Management of systemic sclerosis-associated interstitial lung disease. *Curr Opin Rheumatol* 2019; 31: 241–249.
93 Kowal-Bielecka O, Fransen J, Avouac J, *et al.* Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327–1339.