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Interstitial Lung Disease in Systemic Sclerosis: Lessons Learned from Idiopathic Pulmonary Fibrosis

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Abstract

Purpose of review Systemic sclerosis (SSc) has the highest cause–specific mortality of all the connective tissue diseases, and interstitial lung disease (ILD) is the number one cause of death among patients with SSc.
Recent findings Historically, therapeutic agents with widespread immunosuppressive effects have been used to treat SSc-ILD. However, data from recent landmark clinical trials in SSc-ILD have affirmed the prior observation that SSc-ILD is a uniquely heterogenous disease with marked variations in rates of response to immunosuppressive therapy. In the last few years, innovative research studies have advanced our understanding of the pathophysiology of SSc-ILD and stimulated interest in the development of novel candidate therapeutics with potential disease–modifying properties for SSc-ILD. Anti-fibrotics are a new class of drugs that may change our approach to the treatment of SSc-ILD similar to the paradigm shift that occurred for the treatment of idiopathic pulmonary fibrosis (IPF). The present review describes the most recent advances in our understanding of SSc-ILD in the context of lessons learned from the study of IPF.
Summary The article concludes with an outline of the most important unanswered questions in SSc-ILD research that could help inform future research efforts in this area.

Introduction

Interstitial lung disease (ILD), or pulmonary fibrosis, occurs in the majority of patients with systemic sclerosis (SSc). Despite being the leading cause of mortality in SSc [1], ILD as a clinical entity is poorly understood, both from a pathogenesis perspective and from a treatment standpoint. The disease course of ILD is heterogeneous and progression and treatment response rates vary considerably. Current treatments for SSc-ILD non-selectively target inflammatory pathways and do not consistently yield disease–modifying effects. Moreover, none of the existing treatments is curative, yet all possess undesirable adverse effects.

Advancing the field of SSc-ILD will require new ideas, research, and innovation, as well as thoughtful reflection on past treatment failures. Understanding ILD in the context of diseases other than SSc may provide a unique framework to direct future research efforts. In particular, understanding lessons learned from idiopathic pulmonary fibrosis (IPF) research could help inform the design of future preclinical and clinical studies in SSc-ILD. IPF is a progressive fibrotic lung disease with high morbidity and mortality rates [2].

The present review summarizes the epidemiology, pathogenesis, disease course, and treatment of both SSc-ILD and IPF. While highlighting notable similarities and differences between these two conditions, this review will focus on the emergence of anti-fibrotic agents as novel therapies with potential disease–modifying capabilities for both SSc-ILD and IPF. The review will conclude with an overview of the most important unanswered questions in SSc-ILD to help stimulate and energize future research efforts in this area.

Epidemiology

The prevalence of ILD in SSc varies across studies. This variation is likely due to the screening/diagnostic method employed to detect ILD (e.g., pulmonary function testing [PFT], high-resolution chest tomography [HRCT], pathology, chest x-ray). Using PFT testing to screen for ILD consistently underestimates the prevalence of ILD in SSc and pathological diagnosis is seldom performed if the patient has the characteristic extra-pulmonary signs of SSc (e.g., Raynaud's phenomenon, sclerodactyly, positive anti-nuclear antibody) [3, 4]. In a retrospective study of 90 patients with SSc followed for an average of 5 years, 62% developed signs of ILD on HRCT during the course of the study [5]. The prevalence of ILD based on HRCT is even higher among patients with abnormal PFTs as demonstrated by one study, in which over 90% of patients with abnormal PFTs were found to have HRCT-defined fibrosis [6].

Clinical characteristics may enhance the likelihood of developing ILD in SSc. Factors associated with an increased propensity for ILD in SSc include the presence of diffuse cutaneous disease and anti-topoisomerase I antibody [7, 8]. However, the absence of these factors should not preclude proper screening for ILD, as ILD can occur in a sizable percentage of patients with limited cutaneous disease and in patients who do not possess an anti-topoisomerase I antibody [7, 9].

The average age of onset for SSc is between 20 and 50 years of age [10]. A large study of over 1000 SSc patients from Spain found that the mean age of disease onset was 45 ± 15 years [11]. As with most autoimmune disease, there is a female predominance with a female to male ratio ranging from 3 to 14:1 [12]. This contrasts with IPF where the majority of patients are male [13, 14]. Among older patients, IPF is the most common idiopathic interstitial pneumonia [14, 15].

Both SSc (1 in 50–300 million) and IPF are rare diseases [16]. The prevalence of IPF varies by region with studies reporting prevalence rates ranging

from 0.7 to 63 per 10,000 [17]. In a frequently cited American study using the Medicare database, the incidence of IPF was reported to be 93.7 per 100,000 person-years [18]. Epidemiological studies have demonstrated that the prevalence of SSc varies according to ethnicity [19]. The highest prevalence rates have been reported in the Choctaw Native Americans; whereas the lowest prevalence rates have been observed in Japanese individuals [19]. ILD itself may occur more frequently in African-American SSc patients compared with White and Hispanic SSc patients based on observational studies [20, 21]. It is unclear whether the prevalence of IPF varies according to ethnicity. Studies suggest that the prevalence of IPF is highest in America, followed by Europe, and then Asia; however, methodological differences in study design may account for these observations [22].

Presenting features

As outlined in Table 1, the presenting signs and symptoms of ILD in SSc and IPF are strikingly similar. Fatigue, dyspnea, and cough are the three most common symptoms. Eliciting a history of dyspnea can be challenging in clinical practice as patients often modify their activities to avoid experiencing breathlessness. On examination, bibasilar crackles can be appreciated, although early in the course of the disease, these physical examination findings may not be apparent even to the most experienced practitioner.

The evolution of symptoms varies widely among patients with both SSc-ILD and IPF. For example, patients with limited cutaneous SSc may not develop signs and symptoms of ILD for several years after the onset of Raynaud's phenomenon. In contrast, patients with diffuse cutaneous SSc typically develop signs and symptoms of ILD within the first 1 to 2 years after the onset of Raynaud's phenomenon.

The symptomatology of IPF can also progress at different rates depending on when the diagnosis is made. For instance, a chest x-ray obtained as part of pre-operative evaluation in a patient without pulmonary symptoms may incidentally reveals signs of ILD. When these patients are referred for pulmonary evaluation, the progression rate may be substantially slower than a patient, for example, who is referred for pulmonary evaluation when symptoms have already commenced [23].

Along with a thorough history and examination, a careful review of chest imaging is essential in the evaluation of any patient with ILD. Reticulation, traction bronchiectasis, and volume loss are the hallmarks of ILD. On HRCT, the most common radiographic features of SSc-ILD are subpleural, ground-glass opacities with linear reticulation and architectural distortion. Honeycombing is a relatively rare finding in SSc-ILD. In contrast, in IPF, honeycombing occurs more commonly and the defining imaging features include peripheral, subpleural, and basilar predominant reticular opacities with architectural distortion and traction bronchiectasis.

If pathology is available, usual interstitial pneumonia (UIP) is the most common pattern observed in patients with IPF, while nonspecific interstitial pneumonia (NSIP) is generally observed in patients with SSc-ILD. Specific findings on HRCT (e.g., presence and extent of ground-glass opacity) can help discriminate ILD due to SSc from IPF in the absence of pathology [24].

Table 1. The presenting signs and symptoms of ILD in SSc and IPF

Presenting features	IPF	SSc-ILD
Common symptoms	Fatigue; dyspnea; cough	Fatigue; dyspnea; cough
		GERD; Raynaud's phenomenon; joint pain; skin tightening
Frequent physical examination findings	Bibasilar crackles; clubbing	Bibasilar crackles; sclerodactyly; cutaneous sclerosis; synovitis; digital ulcers; telangiectasias
Demographic features	Male predominance	Female predominance
	Average age > 65 years	Average age 30–60 years
HRCT imaging findings	Peripheral, subpleural, basilar predominance; reticular opacities; honeycombing; traction bronchiectasis; architectural distortion	Peripheral, subpleural, basilar, symmetrical distribution; ground-glass attenuation; lower lobe volume loss
Histopathological characteristics	Usual interstitial pneumonia pattern	Nonspecific interstitial pneumonia pattern
Pulmonary function changes	Decline in FVC, DLCO	Early on, a decline in DLCO may occur prior to a change in FVC

GERD gastrointestinal reflux disease, *FVC* forced vital capacity, *DLCO* diffusing capacity for carbon monoxide

Delineating the cause of the underlying ILD is based on all of the aforementioned factors (i.e., radiography, signs, symptoms, demographics, disease course, pathology). For this reason, multidisciplinary discussion (MDD) can improve the accuracy of the ILD diagnosis, particularly when the referring physician's initial diagnosis is uncertain [25–29]. A recent study found that MDD generated a diagnosis in 80% of cases referred by a provider who was unclear about the underlying diagnosis [30]. Moreover, the same study found that MDD led to a change in the diagnosis in 41% of cases [30].

Common pathogenic features of IPF and SSc-ILD

Immune, inflammatory, vascular, and fibrotic pathways have been implicated in the pathogenesis of ILD in both SSc and IPF. How these various pathways converge to perpetuate fibrosis in these two diseases is still unclear.

Parenchymal fibrosis leads to excessive deposition of extracellular matrix (ECM) comprised predominantly by fibrillar collagens. Compared with normal tissue, fibrotic tissue is mechanically stiff, avascular, and when present in the lungs, impairs pulmonary function due to restrictive physiology. Studies have identified key fibrotic mediators in SSc-ILD, including TGF-ß [31]. TGF-ß promotes ECM expansion and promotes fibroblast survival and senescence [32]. The integrin $\alpha_v\beta_6$ is an in vivo activator of latent TGF-β1 and 3 and plays a critical regulatory role in fibrinogenesis [33, 34]. Partial inhibition of TGF-β with antibodies to $\alpha_v\beta_6$ integrin blocked murine pulmonary fibrosis without exacerbating inflammation [35]. A phase 2 study recently evaluated the safety

and tolerability of a humanized monoclonal antibody against $\alpha_v\beta_6$ integrin in IPF, and the results are pending.

Multiple tyrosine kinase receptors (TKRs) are also involved in moderating TGF-β activity, and these include epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR) [36]. Higher expression of specific TKRs, such as PDGFR and FGFR, have been found on fibroblasts from patients with IPF compared with healthy controls [37]. Moreover, serum VEGF levels correlated with extent of radiographic fibrosis and predicted a decline in lung function in a small study of patients with IPF [38].

Although fibrosis is a unifying feature of SSc-ILD and IPF, how this pathological process unfolds remains unclear. In terms of IPF, an early hypothesis suggested that fibrosis was an abnormal reaction, or perhaps an over-reaction, to chronic injuries such as exposure to cigarette smoking or other fumes, infections, or other physical damage to the lung [39]. That paradigm had previously replaced an older idea that inflammation was the main driving force behind fibrogenesis [40].

In the prior inflammation model of IPF, fibrosis was thought to occur when inflammatory and immune effector cells accumulated in the alveoli. Bronchoalveolar lavage (BAL) samples from patients with IPF showed an increased numbers of neutrophils, as well as macrophages lymphocytes [41]. Similarly, patients with ILD associated with connective tissue disease also had increased numbers of neutrophils in BAL samples [42].

In the alveolar epithelial injury model of IPF, abnormal wound healing is thought to lead to the formation of the fibroblastic foci characteristic of the UIP pattern [39]. Inflammation was unlikely to be the driving force because histologically speaking, evidence of early inflammation was not present in tissue that had yet to fibrose [43]. Moreover, it became clear that anti-inflammatory treatment with steroids and other immunosuppressive agents, as discussed in the treatment section, was not effective.

Currently, there is less emphasis on exogenous injuries, and many consider loss of epithelial integrity a key player in the pathogenesis of IPF, without any prompting from exogenous sources [44]. Some view IPF as an unchecked proliferative process similar to cancer [45, 46]. For instance, myofibroblasts can become resistant to apoptosis when they are recruited to the injured lung, which would be a trait they share with cancer cells [47]. In another similarity to cancer biology, epigenetic changes of aging are thought to play a role in the pathogenesis of IPF [48]. Regardless of the conceptual framework regarding the dysregulated proliferation of fibroblasts, we know that the excess fibroblasts lay down an excess of collagen [49]. In fact, fibroblastic foci, the aforementioned characteristic histologic feature of the UIP pattern, are proliferating myofibroblasts that are actively synthesizing collagen [50].

In SSc-ILD, many consider inflammation to precede the development of fibrosis in the lungs; however, the evidence for this is limited. In Scleroderma Lung Study (SLS) I, 144 SSc-ILD patients underwent bronchoscopy, and the results revealed BAL cellularity in some patients, but not in all patients [51]. Furthermore, some patients had evidence of ground-glass on HRCT in the absence of positive BAL findings (defined in this study as $\geq 3\%$ neutrophils and/or $\geq 2\%$ eosinophils) [51]. There is still much to be learned about how fibrosis

starts and evolves in SSc-ILD, but the lessons learned from the study of IPF raise thought-provoking future research questions in this area.

Progression of SSc-ILD

As mentioned above, progression of ILD in SSc varies markedly. In terms of disease course, 4 main phenotypes of SSc-ILD exist: (1) patients with subclinical disease who do not experience progression of ILD; (2) patients with progressive ILD that improves in response to treatment; (3) patients with progressive ILD that stabilizes in response to treatment; (4) patients with progressive ILD that worsens despite treatment.

Our ability to predict ILD phenotypes in SSc at the time of diagnosis is limited. Certain factors have been associated with a worse prognosis in SSc-ILD based on observational studies, including the following: low baseline forced vital capacity (FVC) [52] and/or diffusing capacity for carbon monoxide (DLCO) [52, 53]; extent of ILD on HRCT [54]; male gender [10, 55, 56]; African-American race [57, 58]; diffuse cutaneous disease [52]. Additional biological markers may portend a worse prognosis in SSc-ILD, and these include the presence of the anti-topoisomerase 1 antibody, as well as higher circulating levels of interleukin-6, C-reactive protein, monocyte chemoattractant protein-1 (MCP-1), CCL-18, CXCL4, Krebs von den Lungen-6 (KL-6) and surfactant protein D [59].

Due to the variation in the ILD disease course, it is essential that the treating provider monitors patients with SSc-ILD closely for progression. There are no valid guidelines for monitoring progression or treatment response in SSc-ILD; however, many practitioners follow the same guidelines used to monitor progression in IPF as described below.

Because ILD is likely to progress the most within the first 5 years from the time of the SSc diagnosis, serial measurements of lung function (e.g., FVC, DLCO) should be performed regularly (every 3–4 months) during this time frame. A relatively large, single-center study demonstrated that within the first 5–6 years after diagnosis of SSc, the FVC dropped below 75% predicted in approximately 40% of the patients; whereas only 10–15% lost at least half of their FVC (i.e., to < 50% predicted) in the first 5–10 years [57].

Trends in the FVC and DLCO are likely better indicators of progression than single measurements. Several factors affect PFT parameter reliability including technical factors (ill-fitting mouthpiece, inexperienced technician), patient-related factors (poor effort), and diurnal variability. Thus, overall trends in these measurements, especially when performed at the same center, are more clinically meaningful than single measurements. In addition, recent studies have demonstrated that trends in the FVC and DLCO during the first 1 to 2 years from the time of treatment onset are important predictors of long-term mortality [60•, 61•].

HRCT is also a useful tool for monitoring progression of SSc-ILD, especially in cases where the trends in pulmonary function are unclear or there is a decline in symptoms in the absence of changes in pulmonary function. In addition, HRCT can help determine whether a decline in DLCO is related to progression of ILD versus the development of pulmonary hypertension (PH), another common cause of dyspnea and fatigue in SSc. Figure 1 depicts a proposed
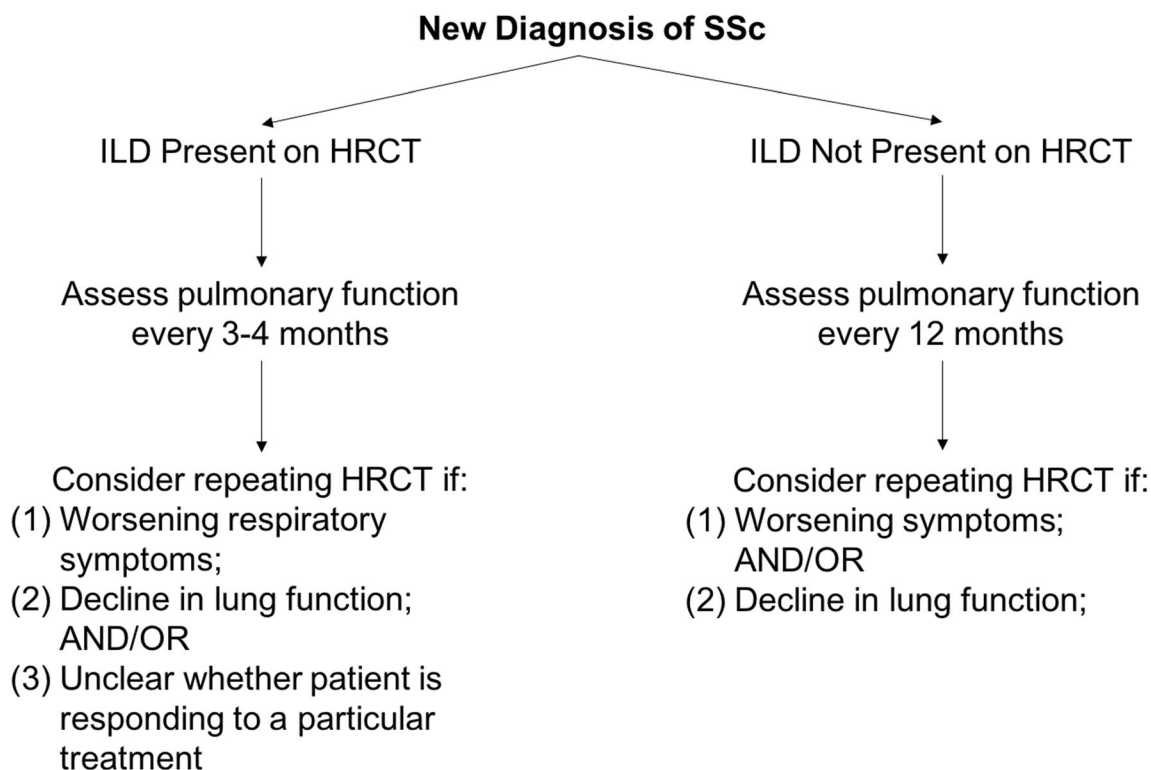
New Diagnosis of SSc

ILD Present on HRCT → Assess pulmonary function every 3-4 months → Consider repeating HRCT if:
(1) Worsening respiratory symptoms;
(2) Decline in lung function; AND/OR
(3) Unclear whether patient is responding to a particular treatment

ILD Not Present on HRCT → Assess pulmonary function every 12 months → Consider repeating HRCT if:
(1) Worsening symptoms; AND/OR
(2) Decline in lung function;

Fig. 1. Proposed algorithm for monitoring progression of ILD in a patient with a recent diagnosis of SSc: Focus on pulmonary function testing and HRCT chest imaging.

algorithm for monitoring progression of ILD in a patient with a recent diagnosis of SSc.

In patients with established SSc with a disease duration > 5 years and clinically stable ILD (i.e., no change in symptoms, stable PFT testing for 1 year), it is less clear how often the patient should be surveilled for progression of ILD. Many practitioners obtain annual PFTs in such patients to evaluate for ILD progression and screen for the development of PH. Given the non-invasive nature of PFT and relatively low cost, one could also consider performing these tests at 6-month intervals given that some patients may experience progression in the absence of worsening symptoms (Tables 2 and 3).

Progression of IPF

Compared with the disease course of SSc-ILD, progression of ILD is consistently more rapid in patients with IPF, with rare exceptions. A retrospective review published in 1999 reported a median survival of about 3 years [63]. A more recent review of the Medicare database from 2001 to 11 reported a median survival of 3.8 years [18]. It should be noted that it is the experience of many expert centers that some patients do outlive 5 years [23]. The best estimate of the natural rate of decline in lung function for patients with IPF with the current state of care is illustrated in the most recent phase 3 trials for the two currently used anti-fibrotic agents, pirfenidone and nintedanib. The rates of decline in

Table 2. Summary of ATS guidelines for monitoring disease progression in IPF[a]

Measure	Assessment timing
Dyspnea (objectively assessed using a valid questionnaire)	Every 3–6 months
FVC decline of 10% (sustained changes are most clinically meaningful)	Every 3–6 months
DLCO decline of 15% (sustained changes are most clinically meaningful)	Every 3–6 months
Extent of fibrosis on HRCT	Consider performing every 2 to 3 years
Acute exacerbation	Continuously monitor

[a]Adapted from American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thorax Society joint recommendations on management of IPF [62]
FVC forced vital capacity, *DLCO* diffusing capacity for carbon monoxide, *HRCT* high-resolution computed tomography

forced vital capacity (FVC) in the 3 studies were – 458 mL, – 240 mL, and – 207 mL [64, 65].

Similar to SSc-ILD, the FVC is often used to monitor the clinical course of ILD in IPF, along with the total lung capacity (TLC), forced expiratory volume in 1 s (FEV1), and DLCO. A recent study found that the FVC was the best predictor of survival in IPF [66]. In this study, when patients suffered a 10% decline in FVC, their 5-year survival was only 17–22% [66]. The 6-min walk test (6MWT) is also used to monitor ILD progression in IPF. During this test, technicians record the walk distance and oxygen saturation. Not surprisingly, oxygen desaturation during the 6MWT portends poorer prognosis in IPF [67]. This test is less often employed in SSc patients where co-morbidities such as arthritis can serve as confounding variables that limit the interpretability of the 6MWT. Moreover, obtaining reliable oxygen saturation readings from the fingertips is frequently problematic in patients with SSc (forehead pulse oximeters are recommended in this scenario).

A multivariable staging index, termed the GAP index, for gender (G), age (A), and 2 lung physiology measurements FVC and DLCO (P) was developed for IPF risk assessment [62]. The group that developed the index retrospectively reviewed many potential variables and found the 4 above variables as the most important in predicting mortality. In the GAP index, based on the results of the

Table 3. Current treatment options for SSc-ILD and IPF

	SSc-ILD	IPF
First-line therapy	Mycophenolate mofetil	Nintedanib
	Cyclophosphamide	Pirfenidone
Second-line therapy	Rituximab	
	Hematopoietic stem cell therapy	
Promising potential therapies	Nintedanib	
	Pirfenidone	
	Combination therapy	
Last resort therapy	Lung transplantation	Lung transplantation

above variable, a point total is assigned, and from the point total, a GAP stage between 1 and 3. For example, to get the highest score, male sex gets 1 point, age > 65 gets 2 points, FVC < 50% of predicted gets 2 points, and DLCO unable to perform gets 3 points, for a maximum total of 8 points. Those in stage III have a 61% 1-year survival and just a 23% 3-year survival [62]. The GAP index has not been tested in SSc-ILD.

An IPF management consensus guideline written on behalf of the major international pulmonary medicine societies recommended measuring the FVC and DLCO at 3–6-month intervals, with more frequent monitoring in those patients who may be suffering from a faster decline [68]. Alongside pulmonary function testing, the authors also recommended monitoring clinical history for worsening dyspnea and worsening oxygenation by pulse oximetry [69]. This guideline is often applied to the monitoring of patients with SSc-ILD.

Treatment SSc-ILD

The decision to commence ILD-targeted therapy in patients with SSc-ILD is often based on provider preferences. Because no currently approved targeted therapies for the treatment of SSc exist, some providers may be reluctant to start therapy unless there is a clear decline in lung function. The mortality prediction algorithm developed by Goh and colleagues is often employed to make treatment decisions [70]. In this algorithm, the presence of > 20% fibrosis on HRCT or an FVC < 70% predicted in the presence of less extent of fibrosis has predicted mortality in additional studies [71, 72]. However, some may consider starting therapy in patients with minimal fibrosis and normal lung function if specific poor prognostic indicators are present (e.g., rapidly worsening diffuse skin disease, presence of anti-topoisomerase I antibody).

Immunosuppression for SSc-ILD

Once the decision to commence therapy is made, the first-line agent is often mycophenolate mofetil (MMF). Although MMF did not receive a formal recommendation in the latest SSc EULAR treatment guidelines [72] (drafted prior to the publication of Scleroderma Lung Study (SLS) II), recent clinical studies support the use of this agent to treat SSc-ILD [59, 73•, 74, 75]. SLS II compared MMF for 24 months versus oral cyclophosphamide (CYC) for 12 months followed by 12 months of placebo [74]. The FVC improved to similar extent in both treatment arms, along with the extent of radiographic fibrosis; however, MMF was safer and better tolerated than CYC [74, 76]. Moreover, patients randomized to MMF experienced significantly less of a decline in the DLCO compared with the CYC [51].

While there have been no RCTs comparing MMF with placebo in SSc-ILD, a study comparing the MMF arm of SLS II with the placebo arm of SLS I (RCT comparing CYC with placebo in SSc-ILD) found that treatment with MMF was associated with significant improvements in FVC and DLCO in the MMF arm [59]. Because the entry criteria for SLS I and II were nearly identical, the patients in both cohorts were strikingly similar.

Intravenous CYC is still used to treat SSc-ILD; however, it usually initiated as induction therapy for 6–12 months due to safety concerns about its prolonged

use [77]. Azathioprine (AZA) and MMF are often used as maintenance therapies in this setting. One study found that AZA therapy given for 18 months following a 6-month induction course of intravenous CYC led to an improvement/ stabilization in the FVC in 70% of patients at 6 months and in 52% of patients at 2 years [78]. However, this study lacked a control arm so this improvement/ stabilization could also represent the natural history of the disease course in SSc-ILD. Another study compared intravenous CYC for 6 months followed by AZA versus placebo [79]. This study did not find any significant improvements in lung function in the active treatment arm compared with placebo at 1 year, although it may have been underpowered to detect a significant difference ($N =$ 45).

While the use of both CYC and MMF have been associated with short-term improvements in lung function in SSc-ILD, it is unclear whether the use of these agents leads to sustained benefits in lung function and/or survival advantages [51, 74]. For example, a recent study found that there was no difference in long-term survival in patients randomized to CYC versus placebo in patients who participated in SLS I and who were followed up to 12 years from the time of randomization [60•]. Nearly half (42%) of all of the patients died during the follow-up period, and the majority died of respiratory failure due to underlying SSc-ILD [60•]. The same report found no difference in long-term survival between patients randomized to MMF versus CYC in SLS II; however, the follow-up time for this study was shorter (median follow-up of 3.6 years from the time of randomization) [60•]. Early on, there was a trend for an MMF survival advantage; however, many patients in the CYC arm crossed over to MMF during/after the SLS II study period [60•].

Both SLS I and II have confirmed that some patients do experience improvement in SSc-ILD with immunosuppression; however, the extent to which this improvement is sustained or has any beneficial effect on long-term mortality is uncertain. Clearly, there is still a need to develop, newer targeted therapies for SSc-ILD as described further below.

Recent studies have demonstrated that alternate immunosuppressive agents may play a role in the management in of SSc-ILD, particularly in patients with treatment refractory disease. For example, treatment with rituximab, which targets CD20-positive B cells, has been associated with improvement/ stabilization in lung function in open-label trials [80]. An RCT comparing rituximab to CYC for connective tissue disease–related ILD is currently underway.

Tocilizumab is another immunosuppressant agent, which could conceivably emerge as a treatment option for patients with SSc-ILD. In a phase 2 RCT, designed to evaluate the effects of tocilizumab on cutaneous sclerosis, patients who received tocilizumab were less likely to experience a decline in lung function compared with placebo [81]. We are waiting publication of the phase 3 trial of this agent. Because the comparator arm in this study was placebo, it is unclear whether tocilizumab would perform better than existing therapies for SSc-ILD, such as MMF. Furthermore, since the primary endpoint for this study was not an ILD-related outcome, the study may not be adequately powered to detect effects of tocilizumab on lung function and fibrosis in SSc.

Anti-fibrotic therapy for SSc-ILD

Targeting anti-fibrotic pathways represents an alternative disease–modifying treatment strategy in SSc. Interestingly, although anti-fibrotics are currently used to treat IPF (discussed further below), immunosuppressive therapy was historically considered the mainstay of treatment for this condition [82]. The pivotal Prednisone, Azathioprine, and *N*-Acetylcysteine (NAC): A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis (PANTHER-IPF) trial helped propagate this paradigm shift in the treatment of IPF. The results of this study demonstrated that patients on the combination of prednisone, azathioprine, and NAC fared worse, with statistically significant increase mortality, than patients on placebo [83].

Because tyrosine kinases moderate TGF-ß responses in SSc, blocking these enzymes represents a potential approach for curtailing fibrosis. Early on, preclinical studies generated enthusiasm for the c-Abl-selective tyrosine kinase inhibitor, imatinib [84, 85]. However, clinical studies have failed to demonstrate efficacy signals to drive future studies on this agent [86, 87]. Newer and less selective tyrosine kinase inhibitors, such as nilotinib and dasatinib, are understudied, but their benefit remains uncertain [88, 89].

Nintedanib is multi-kinase inhibitor that blocks the receptors' several growth factors. Approved for the treatment of IPF, nintedanib blocks the receptors for FGF, VEGF, and PDGF [65]. In an SSc mouse model, nintedanib curtailed myofibroblast differentiation and pulmonary fibrosis [90]. In addition to mitigating fibrosis, this agent also acts on vascular pathways. Accumulating evidence suggests that vascular injury and dysfunction is a pathological hallmark of SSc and may contribute to fibrosis [69, 91]. Whether nintedanib improves lung function or cutaneous sclerosis remains unclear. A phase 3, placebo-controlled randomized controlled trial (RCT) evaluating the safety and efficacy of nintedanib in SSc-ILD has recently concluded (SENSCIS™), and the anticipated publication date of this study is in the Spring of 2019.

The efficacy of nintedanib in IPF was studied in two separately performed twin trials known as the INPULSIS studies. Nintedanib was shown to reduce the decline in FVC, although not improved, as compared to placebo in both trials. In the primary end point of decline of FVC at 52 weeks, there was a 125-mL reduction in the decline in the nintedanib arm as compared to placebo in one of the studies, and a 94-mL reduction in the decline in the second study [65].

Like nintedanib, pirfenidone is another anti-fibrotic agent approved for the treatment of IPF [64]. While our understanding of how pirfenidone ameliorate fibrosis in IPF is evolving, recent studies have demonstrated that it decreased Hedgehog pathway activity [92, 93]. Hedgehog is a development morphogen involved in fibroblast activation. Normally, in healthy adult tissues, minimal Hedgehog activity exists; however, SSc biopsies have demonstrated abnormal Hedgehog signaling [94]. A 16-week, open-label trial of pirfenidone in SSc-ILD ($N = 63$) demonstrated that 10 patients had an increase ($\geq 5\%$) in FVC%-predicted, while 5 patients had a decrease ($> 5\%$) (median change from baseline in FVC% predicted was 0.5%) [95]. Notably, 40% of patients were taking background mycophenolate in this study. A phase III study (SLS III) is currently underway, which compares mycophenolate against mycophenolate with pirfenidone for the treatment of SSc-ILD.

Pirfenidone was evaluated in IPF in the RCT, known as ASCEND. Seventeen percent of patients in the pirfenidone arm suffered such an absolute decline of 10% in the FVC (primary endpoint), compared to 32% of patients in the placebo arm [64]. Of note, this was the fourth phase three trial investigating the medication in IPF. In a prior Japanese study, pirfenidone was shown to slow the decline in FVC as compared to placebo [96]. In two separately run twin multinational trials, published together in 2011 and known as CAPACITY, one demonstrated a significant difference in the primary outcome of FVC change as compared to placebo at 72 weeks, while the other trial did not [97]. Although only one of two trials demonstrated a significant difference in the primary outcome, in both trials, there were fewer deaths in the pirfenidone arms than in the placebo arms [97].

Notably, neither the INPULSIS nor the ASCEND trials, each which lasted 52 weeks, demonstrated a mortality benefit. However, a pooled analysis of the three global prospective pirfenidone trials (CAPACITY-1, CAPACITY-2, and ASCEND) demonstrated a mortality benefit for pirfenidone (all-cause mortality hazard ratio 0.52, 95% CI 0.31–0.87). Moreover, pooled analysis of the INPULSIS trials and a phase two trial also demonstrated a mortality benefit for nintedanib (mortality hazard ratio 0.57, 95% CI 0.34–0.97) for deaths occurring between randomization and post-treatment follow-up [98, 99]. Whether nintedanib or pirfenidone affects mortality in SSc-ILD is unknown.

Cannabinoids (CB) are gaining traction as novel anti-fibrotic mediators. While CB1 receptors are expressed predominantly on neurons, CB2 receptors are expressed on circulating immune cells and tissue-resident stromal cells. Compounds that selectively target CB2 do not possess psychogenic effects and may decrease fibrosis [100, 101]. A small, phase 2 study of lenabasum for SSc showed promising clinical efficacy, particularly not only for improving the extent of cutaneous sclerosis, but also for minimizing loss of lung function [86]. A phase 3 RCT of this agent is ongoing.

Whereas immunosuppressive therapy for SSc-ILD is deemed most effective early in the course of the disease (based mostly on anecdotal experience), it is conceivable that anti-fibrotic therapy could have disease-modifying effects at later disease stages and could possibly lead to improvements in lung function in patients with severe restriction secondary to SSc-ILD. Furthermore, there may be less risk of infection associated the use of anti-fibrotic therapy compared with agents such as CYC and MMF. However, gastrointestinal toxicity remains an ongoing concern, particularly for nintedanib and pirfenidone, in patients with SSc who have underlying gastrointestinal tract dysfunction. Therefore, careful attention must be paid to the safety analyses of the aforementioned RCTs.

Hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (HSCT) has emerged as an exciting therapeutic option for patients with relatively early, rapidly progressive SSc-ILD. RCTs have demonstrated improvements in lung function in patients undergoing HSCT, as well as improvements in overall survival [102–104]. This approach may lead to more radical and sustained

effects on immune function as demonstrated by one study which found alterations in adaptive immunity 1 year after transplantation [105]. Given the risk of infection and mortality in the early post-transplant period, careful selection of patients for HSCT is prudent. HSCT may represent an ideal treatment strategy for SSc-ILD patients who experience a decline in lung function despite treatment with immunosuppression and who have minimal other co-morbidities that may heighten the risk of mortality in the early post-transplant period (e.g., cardiac involvement).

Lung transplantation

Both SSc-ILD and IPF can progress to end-stage lung disease. Lung transplantation (LT) is presently performed in carefully selected patients with SSc-ILD and IPF. Our experience and the experience of others is that post-LT survival rates are similar for patients with SSc-ILD versus patients with ILD due to other causes, such as IPF [106–110]. The median survival post-LT is about 5.8 years [111]. Because both age and elevated BMI increase the risk of mortality post-LT, these surgeries are offered primarily to non-obese patients under the age of 65 years [110]. While esophageal dysfunction in the past precluded patients with SSc-ILD from undergoing LT, more recent studies have demonstrated that the presence and severity of esophageal dysfunction is not associated with post-LT survival in SSc-ILD patients [108, 110].

A recent analysis of the Medicare database showed that in the 12 months following diagnosis, just 0.2% of IPF patients went on to receive LT [112]. Another study estimates that less than 1% of IPF patients receive LT in a given year [111]. Although a paucity of patients with IPF received lung transplantation, among all patients who receive LT, IPF is the most common. Nearly half of all patients listed for lung transplantation have IPF [111].

Future directions

Over the past 5 years, advances in SSc-ILD research have energized efforts to develop safer and more effective therapeutic options for managing this important dimension of SSc. A burgeoning pipeline of novel medicines now exists for SSc-ILD. Despite these efforts, ILD still remains the leading cause of death in SSc and numerous unanswered questions remain.

Combination therapy

Combination therapy is a cornerstone to the treatment of complex rheumatic diseases, including rheumatoid arthritis [113]. Studies assessing the efficacy and safety of combination therapy in SSc are lacking. SLS III will explore whether combining an anti-fibrotic (pirfenidone) with an immunosuppressive agent (mycophenolate) will lead to improved outcomes compared with mycophenolate alone. In addition, because the SENSCIS™ study allowed for background mycophenolate per the treating physician's discretion, a proportion of patients in this study will have received both nintedanib and mycophenolate. While combining therapies raises concerns about potential toxicity, these safety concerns may be tempered by improved and sustained efficacy outcomes. If there is

evidence that anti-fibrotic therapy improves lung function in SSc-ILD, future RCTs are needed to determine whether adding an immunosuppressive agent to an anti-fibrotic leads to a synergistic effect.

Duration of SSc-ILD therapy

There is a lack of consensus regarding the duration of ILD therapy in patients with SSc. Many treat patients with immunosuppression for 5 years because this is the period of time when the ILD is most likely to progress based on observational studies [57]. However, no one knows how long to continue therapy in SSc-ILD and what the potential risks are of maintaining a patient on long-term immunosuppression. Two years of MMF in patients who participated in SLS II was not associated with long-term safety concerns, such as malignancy [60•]. No studies have assessed long-term safety in patients randomized to longer durations of MMF therapy, although the majority of patients in SLS II who participated in the long-term follow-up study remained on MMF during the 5-year follow-up period.

If anti-fibrotics are effective in curtailing fibrosis in SSc-ILD, studies are needed to determine the optimal duration of therapy, as well as the optimal timing of therapy initiation. In general, immunosuppression is deemed most effective in SSc-ILD early in the disease course when inflammation predominates; however, it is conceivable that anti-fibrotics could potentially play a role in the long-term treatment of this disease beyond what we traditionally viewed as the optimal treatment window (e.g., within the first 5 years from the time of diagnosis of SSc-ILD).

Personalized medicine

There is no doubt that patients with SSc-ILD have varying responses to medications. Some patients in SLS I experienced an improvement in lung function with CYC, while others experienced a deterioration in lung function. Similarly, some patients in SLS II responded to MMF, while others did not. As the therapeutic armamentarium for SSc-ILD grows, so must our research efforts to understand why some patients respond preferentially to certain medications and not to others.

Biomarkers may play a key role in identifying patients who are more likely to experience improvement with specific agents. Measuring biomarkers early in the course of the disease may help identify patients with rapidly progressive SSc-ILD phenotypes who necessitate a more aggressive treatment approach. We have found that patients in SLS II who had higher KL-6 levels at baseline experienced a greater decline in lung function, despite treatment with CYC or MMF [114]. Biomarkers could also be employed to determine whether a patient is responding to therapy at earlier time points. For instance, changes in the levels of specific biomarkers early on after treatment initiation (with the first 3 months) could help predict a favorable therapeutic response prior to an appreciable change in lung function (often not appreciated for 6–12 months after treatment commences). Patients in SLS II who had the greatest decline in CXCL4 levels at 12 months had an improved course of lung function from 12 to 24 months [115]. Ideally, candidate biomarkers should be measured at early time points to help physicians make timely treat decisions.

Conclusion

The future of SSc-ILD therapeutics is bright. The knowledge gained from prior SSc-ILD and IPF clinical trials have tremendously helped to augment our understanding of these diseases and to inform the design of future studies in this area. Future clinical trials that enrich enrollment for specific SSc-ILD phenotypes and include biomarker discovery aims are likely to propel this field forward in meaningful directions that will ultimately lead to improved patient outcomes.

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Compliance with Ethical Standards

Conflict of Interest
Augustine Chung and James English declare that they have no conflict of interest.
Dr. Volkmann reports personal fees from Boehringer Ingelheim, during the conduct of the study.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1.   Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, 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(10):1809–15. https://doi.org/10.1136/ard.2009.114264.

2.   American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161(2 Pt 1):646–64. https://doi.org/10.1164/ajrccm.161.2.ats3-00.

3.   Showalter K, Hoffmann A, Rouleau G, Aaby D, Lee J, Richardson C, et al. Performance of forced vital capacity and lung diffusion cutpoints for associated radiographic interstitial lung disease in systemic sclerosis. J Rheumatol. 2018;45(11):1572–6. https://doi.org/10.3899/jrheum.171362.

4.   Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TDL, Maurer B, Jordan S, et al. Pulmonary function tests: high rate of false negatives in the early detection and screening of scleroderma interstitial lung disease. Swiss Med Wkly. 2015;145:9S-S.

5.   Launay D, Remy-Jardin M, Michon-Pasturel U, Mastora I, Hachulla E, Lambert M, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol. 2006;33(9):1789–801.

6.   De Santis M, Bosello S, La Torre G, Capuano A, Tolusso B, Pagliari G, et al. Functional, radiological and biological markers of alveolitis and infections of the lower respiratory tract in patients with systemic sclerosis. Respir Res. 2005;6:96. https://doi.org/10.1186/1465-9921-6-96.

7.   Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, 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(6):754–63. https://doi.org/10.1136/ard.2006.062901.

8. Briggs DC, Vaughan RW, Welsh KI, Myers A, duBois RM, Black CM. Immunogenetic prediction of pulmonary fibrosis in systemic sclerosis. Lancet. 1991;338(8768):661–2.

9. Gilchrist FC, Bunn C, Foley PJ, Lympany PA, Black CM, Welsh KI, et al. Class II HLA associations with autoantibodies in scleroderma: a highly significant role for HLA-DP. Genes Immun. 2001;2(2):76–81. https://doi.org/10.1038/sj.gene.6363734.

10. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin N Am. 2003;29(2):239–54.

11. Alba MA, Velasco C, Simeon CP, Fonollosa V, Trapiella L, Egurbide MV, et al. Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 patients. Medicine (Baltimore). 2014;93(2):73–81. https://doi.org/10.1097/MD.0000000000000018.

12. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360(19):1989–2003. https://doi.org/10.1056/NEJMra0806188.

13. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994;150(4):967–72. https://doi.org/10.1164/ajrccm.150.4.7921471.

14. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(7):810–6. https://doi.org/10.1164/rccm.200602-163OC.

15. Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2010;181(8):832–7. https://doi.org/10.1164/rccm.200906-0959OC.

16. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008;37(4):223–35. https://doi.org/10.1016/j.semarthrit.2007.05.003.

17. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. Clin Epidemiol. 2013;5:483–92. https://doi.org/10.2147/CLEP.S54815.

18. Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. Lancet Respir Med. 2014;2(7):566–72. https://doi.org/10.1016/S2213-2600(14)70101-8.

19. Reveille JD. Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics, and clinical manifestations. Curr Rheumatol Rep. 2003;5(2):160–7.

20. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum. 2007;57(2):318–26. https://doi.org/10.1002/art.22532.

21. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. Arthritis Rheum. 2012;64(9):2986–94. https://doi.org/10.1002/art.34482.

22. Caminati A, Madotto F, Cesana G, Conti S, Harari S. Epidemiological studies in idiopathic pulmonary fibrosis: pitfalls in methodologies and data interpretation. Eur Respir Rev. 2015;24(137):436–44. https://doi.org/10.1183/16000617.0040-2015.

23. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–23. https://doi.org/10.1056/NEJMra1705751.

24. Desai SR, Veeraraghavan S, Hansell DM, Nikolakopoulou A, Goh NS, Nicholson AG, et al. CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. Radiology. 2004;232(2):560–7. https://doi.org/10.1148/radiol.2322031223.

25. Jo HE, Glaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, et al. Clinical impact of the interstitial lung disease multidisciplinary service. Respirology. 2016;21(8):1438–44. https://doi.org/10.1111/resp.12850.

26. Flaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004;170(8):904–10. https://doi.org/10.1164/rccm.200402-147OC.

27. Thomeer M, Demedts M, Behr J, Buhl R, Costabel U, Flower CD, et al. Multidisciplinary interobserver agreement in the diagnosis of idiopathic pulmonary fibrosis. Eur Respir J. 2008;31(3):585–91. https://doi.org/10.1183/09031936.00063706.

28. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48. https://doi.org/10.1164/rccm.201308-1483ST.

29. Thomson CC, Duggal A, Bice T, Lederer DJ, Wilson KC, Raghu G. 2018 clinical practice guideline summary for practicing clinicians: diagnosis of idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2018. https://doi.org/10.1513/AnnalsATS.201809-604CME.

30. De Sadeleer LJ, Meert C, Yserbyt J, Slabbynck H, Verschakelen JA, Verbeken EK, et al. Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases: a retrospective observational study of 938 cases. Chest. 2018;153(6):1416–23. https://doi.org/10.1016/j.chest.2018.03.026.

31. Lafyatis R. Transforming growth factor beta–at the centre of systemic sclerosis. Nat Rev Rheumatol. 2014;10(12):706–19. https://doi.org/10.1038/nrrheum.2014.137.

32. Kim JB, Lee S, Kim HR, Park SY, Lee M, Yoon JH, et al. Transforming growth factor-beta decreases side population cells in hepatocellular carcinoma in vitro. Oncol Lett. 2018;15(6):8723–8. https://doi.org/10.3892/ol. 2018.8441.

33. Annes JP, Rifkin DB, Munger JS. The integrin alphaVbeta6 binds and activates latent TGFbeta3. FEBS Lett. 2002;511(1–3):65–8.

34. Henderson NC, Sheppard D. Integrin-mediated regulation of TGFbeta in fibrosis. Biochim Biophys Acta. 2013;1832(7):891–6. https://doi.org/10.1016/j. bbadis.2012.10.005.

35. Horan GS, Wood S, Ona V, Li DJ, Lukashev ME, Weinreb PH, et al. Partial inhibition of integrin alpha(v)beta6 prevents pulmonary fibrosis without exacerbating inflammation. Am J Respir Crit Care Med. 2008;177(1):56–65. https://doi.org/10.1164/rccm. 200706-805OC.

36. Beyer C, Distler JH. Tyrosine kinase signaling in fibrotic disorders: Translation of basic research to human disease. Biochim Biophys Acta. 2013;1832(7):897–904. https://doi.org/10.1016/j.bbadis.2012.06.008.

37. Hostettler KE, Zhong J, Papakonstantinou E, Karakiulakis G, Tamm M, Seidel P, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res. 2014;15:157. https://doi.org/10.1186/s12931-014-0157-3.

38. Ando M, Miyazaki E, Ito T, Hiroshige S, Nureki SI, Ueno T, et al. Significance of serum vascular endothelial growth factor level in patients with idiopathic pulmonary fibrosis. Lung. 2010;188(3):247–52. https:// doi.org/10.1007/s00408-009-9223-x.

39. Selman M, King TE, Pardo A, American Thoracic S, European Respiratory S, American College of Chest P. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med. 2001;134(2):136–51.

40. Keogh BA, Crystal RG. Alveolitis: the key to the interstitial lung disorders. Thorax. 1982;37(1):1–10.

41. Reynolds HY, Merrill WW. Analysis of bronchoalveolar lavage in normal humans and patients with diffuse interstitial lung diseases. Biserte G, Chretien J, Viisiu C, eds Proceedings of an international Inserm symposium on bronchoalveolar lavage in man. 1979;84:227–50.

42. Hunninghake GW, Gadek JE, Kawanami O, Ferrans VJ, Crystal RG. Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. Am J Pathol. 1979;97(1):149–206.

43. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157(4 Pt 1):1301–15. https://doi.org/10.1164/ajrccm.157.4.9707039.

44. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;3:17074. https://doi.org/10. 1038/nrdp.2017.74.

45. Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? BMC Med. 2015;13:220. https://doi.org/10.1186/s12916-015-0478-1.

46. Kulkarni T, de Andrade J, Zhou Y, Luckhardt T, Thannickal VJ. Alveolar epithelial disintegrity in pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2016;311(2):L185–91. https://doi.org/10.1152/ ajplung.00115.2016.

47. Klingberg F, Hinz B, White ES. The myofibroblast matrix: implications for tissue repair and fibrosis. J Pathol. 2013;229(2):298–309. https://doi.org/10.1002/path. 4104.

48. Yang IV, Pedersen BS, Rabinovich E, Hennessy CE, Davidson EJ, Murphy E, et al. Relationship of DNA methylation and gene expression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190(11):1263–72. https://doi.org/10.1164/ rccm.201408-1452OC.

49. Raghu G, Striker LJ, Hudson LD, Striker GE. Extracellular matrix in normal and fibrotic human lungs. Am Rev Respir Dis. 1985;131(2):281–9. https://doi.org/ 10.1164/arrd.1985.131.2.281.

50. Zhang K, Rekhter MD, Gordon D, Phan SH. Myofibroblasts and their role in lung collagen gene expression during pulmonary fibrosis. A combined immunohistochemical and in situ hybridization study. Am J Pathol. 1994;145(1):114–25.

51. 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(25):2655–66. https://doi.org/10.1056/ NEJMoa055120.

52. 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(6):1625–35. https://doi.org/10.1002/art.38390.

53. Assassi S, Mayes MD, Arnett FC, Gourh P, Agarwal SK, McNearney TA, et al. Systemic sclerosis and lupus: points in an interferon-mediated continuum. Arthritis Rheum. 2010;62(2):589–98. https://doi.org/10.1002/art.27224.

54. Khanna D, Saggar R, Mayes MD, Abtin F, Clements PJ, Maranian P, et al. A one-year, phase I/IIa, open-label pilot trial of imatinib mesylate in the treatment of systemic sclerosis-associated active interstitial lung disease. Arthritis Rheum. 2011;63(11):3540–6. https://doi.org/10.1002/art.30548.

55. Volkmann ER, Saggar R, Khanna D, Torres B, Flora A, Yoder L, et al. Improved transplant-free survival in patients with systemic sclerosis-associated pulmonary hypertension and interstitial lung disease. Arthritis Rheumatol. 2014;66(7):1900–8. https://doi.org/10. 1002/art.38623.

56. Domsic RT, Nihtyanova SI, Wisniewski SR, Fine MJ, Lucas M, Kwoh CK, et al. Derivation and external validation of a prediction rule for five-year mortality in patients with early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol. 2016;68(4):993–1003. https:// doi.org/10.1002/art.39490.

57. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum. 1994;37(9):1283–9.

58. Mendoza F, Derk CT. Systemic sclerosis mortality in the United States: 1999-2002 implications for patient care. J Clin Rheumatol. 2007;13(4):187–92. https://doi.org/10.1097/RHU.0b013e318124a89e.

59. Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, et al. Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of scleroderma lung studies I and II. Arthritis Rheumatol. 2017;69(7):1451–60. https://doi.org/10.1002/art.40114.

60.• 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(1):122–30. https://doi.org/10.1136/annrheumdis-2018-213708.
This was the first study to assess long-term morbidity and mortality outcomes in patients who participated in two of the largest clinical trials published to date in SSc-ILD.

61.• Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol. 2017;69(8):1670–8. https://doi.org/10.1002/art.40130.
This study found that short-term declines in pulmonary function are important predictors of long-term mortality in SSc-ILD based on an observational cohort study.

62. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156(10):684–91. https://doi.org/10.7326/0003-4819-156-10-201205150-00004.

63. Daniil ZD, Gilchrist FC, Nicholson AG, Hansell DM, Harris J, Colby TV, et al. A histologic pattern of non-specific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 1999;160(3):899–905. https://doi.org/10.1164/ajrccm.160.3.9903021.

64. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92. https://doi.org/10.1056/NEJMoa1402582.

65. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82. https://doi.org/10.1056/NEJMoa1402584.

66. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538–42. https://doi.org/10.1164/rccm.200211-1311OC.

67. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168(9):1084–90. https://doi.org/10.1164/rccm.200302-219OC.

68. 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(6):788–824. https://doi.org/10.1164/rccm.2009-040GL.

69. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med. 2016;194(3):265–75. https://doi.org/10.1164/rccm.201604-0801CI.

70. 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(11):1248–54. https://doi.org/10.1164/rccm.200706-877OC.

71. Hax V, Bredemeier M, Didonet Moro AL, Pavan TR, Vieira MV, Pitrez EH, et al. Clinical algorithms for the diagnosis and prognosis of interstitial lung disease in systemic sclerosis. Semin Arthritis Rheum. 2017;47(2):228–34. https://doi.org/10.1016/j.semarthrit.2017.03.019.

72. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford). 2013;52(1):155–60. https://doi.org/10.1093/rheumatology/kes289.

73.• Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39. https://doi.org/10.1136/annrheumdis-2016-209909.
This was the first RCT to evaluate the efficacy of mycophenolate for the treatment of SSc-ILD. The results demonstrated that mycophenolate was safer an better tolerated compared with cyclophosphamide.

74. 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(9):708–19. https://doi.org/10.1016/S2213-2600(16)30152-7.

75. Shenoy PD, Bavaliya M, Sashidharan S, Nalianda K, Sreenath S. Cyclophosphamide versus mycophenolate mofetil in scleroderma interstitial lung disease (SSc-ILD) as induction therapy: a single-centre, retrospective analysis. Arthritis Res Ther. 2016;18(1):123. https://doi.org/10.1186/s13075-016-1015-0.

76. Goldin JG, Kim GHJ, 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(11):1286–95. https://doi.org/10.1513/AnnalsATS.201802-079OC.

77. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737–47. https://doi.org/10.1002/art.38098.

78. Berezne A, Ranque B, Valeyre D, Brauner M, Allanore Y, Launay D, et al. Therapeutic strategy combining intravenous cyclophosphamide followed by oral azathioprine to treat worsening interstitial lung disease associated with systemic sclerosis: a retrospective multicenter open-label study. J Rheumatol. 2008;35(6):1064–72.

79. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, 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(12):3962–70. https://doi.org/10.1002/art.22204.

80. Sanges S, Guerrier T, Launay D, Lefevre G, Labalette M, Forestier A, et al. Role of B cells in the pathogenesis of systemic sclerosis. Rev Med Interne. 2017;38(2):113–24. https://doi.org/10.1016/j.revmed.2016.02.016.

81. 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(10038):2630–40. https://doi.org/10.1016/S0140-6736(16)00232-4.

82. Walter N, Collard HR, King TE Jr. Current perspectives on the treatment of idiopathic pulmonary fibrosis. Proc Am Thorac Soc. 2006;3(4):330–8. https://doi.org/10.1513/pats.200602-016TK.

83. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968–77. https://doi.org/10.1056/NEJMoa1113354.

84. Bhattacharyya S, Ishida W, Wu M, Wilkes M, Mori Y, Hinchcliff M, et al. A non-Smad mechanism of fibroblast activation by transforming growth factor-beta via c-Abl and Egr-1: selective modulation by imatinib mesylate. Oncogene. 2009;28(10):1285–97. https://doi.org/10.1038/onc.2008.479.

85. Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum. 2009;60(1):219–24. https://doi.org/10.1002/art.24186.

86. Spiera RF, Gordon JK, Mersten JN, Magro CM, Mehta M, Wildman HF, et al. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label

clinical trial. Ann Rheum Dis. 2011;70(6):1003–9. https://doi.org/10.1136/ard.2010.143974.

87. Pope J, McBain D, Petrlich L, Watson S, Vanderhoek L, de Leon F, et al. Imatinib in active diffuse cutaneous systemic sclerosis: results of a six-month, randomized, double-blind, placebo-controlled, proof-of-concept pilot study at a single center. Arthritis Rheum. 2011;63(11):3547–51. https://doi.org/10.1002/art.30549.

88. Gordon JK, Martyanov V, Magro C, Wildman HF, Wood TA, Huang WT, et al. Nilotinib (Tasigna) in the treatment of early diffuse systemic sclerosis: an open-label, pilot clinical trial. Arthritis Res Ther. 2015;17:213. https://doi.org/10.1186/s13075-015-0721-3.

89. Martyanov V, Kim GJ, Hayes W, Du S, Ganguly BJ, Sy O, et al. Novel lung imaging biomarkers and skin gene expression subsetting in dasatinib treatment of systemic sclerosis-associated interstitial lung disease. PLoS One. 2017;12(11):e0187580. https://doi.org/10.1371/journal.pone.0187580.

90. Huang J, Maier C, Zhang Y, Soare A, Dees C, Beyer C, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. Ann Rheum Dis. 2017;76(11):1941–8. https://doi.org/10.1136/annrheumdis-2016-210823.

91. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum. 2013;65(8):1953–62. https://doi.org/10.1002/art.37988.

92. Didiasova M, Singh R, Wilhelm J, Kwapiszewska G, Wujak L, Zakrzewicz D, et al. Pirfenidone exerts antifibrotic effects through inhibition of GLI transcription factors. FASEB J. 2017;31(5):1916–28. https://doi.org/10.1096/fj.201600892RR.

93. Xiao H, Zhang GF, Liao XP, Li XJ, Zhang J, Lin H, et al. Anti-fibrotic effects of pirfenidone by interference with the hedgehog signalling pathway in patients with systemic sclerosis-associated interstitial lung disease. Int J Rheum Dis. 2018;21(2):477–86. https://doi.org/10.1111/1756-185X.13247.

94. Distler JH, Feghali-Bostwick C, Soare A, Asano Y, Distler O, Abraham DJ. Review: Frontiers of Antifibrotic therapy in systemic sclerosis. Arthritis Rheumatol. 2017;69(2):257–67. https://doi.org/10.1002/art.39865.

95. Khanna D, Furst DE, Allanore Y, Bae S, Bodukam V, Clements PJ, et al. Twenty-two points to consider for clinical trials in systemic sclerosis, based on EULAR standards. Rheumatology (Oxford). 2015;54(1):144–51. https://doi.org/10.1093/rheumatology/keu288.

96. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9. https://doi.org/10.1183/09031936.00005209.

97. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9. https://doi.org/10.1016/S0140-6736(11)60405-4.

98. Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med. 2017;5(1):33–41. https://doi.org/10.1016/S2213-2600(16)30326-5.

99. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TO-MORROW and INPULSIS((R)) trials. Respir Med. 2016;113:74–9. https://doi.org/10.1016/j.rmed.2016.02.001.

100. Gonzalez EG, Selvi E, Balistreri E, Akhmetshina A, Palumbo K, Lorenzini S, et al. Synthetic cannabinoid ajulemic acid exerts potent antifibrotic effects in experimental models of systemic sclerosis. Ann Rheum Dis. 2012;71(9):1545–51. https://doi.org/10.1136/annrheumdis-2011-200314.

101. del Rio C, Navarrete C, Collado JA, Bellido ML, Gomez-Canas M, Pazos MR, et al. The cannabinoid quinol VCE-004.8 alleviates bleomycin-induced scleroderma and exerts potent antifibrotic effects through peroxisome proliferator-activated receptor-gamma and CB2 pathways. Sci Rep. 2016;6:21703. https://doi.org/10.1038/srep21703.

102. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014;311(24):2490–8. https://doi.org/10.1001/jama.2014.6368.

103. Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J, 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(9790):498–506. https://doi.org/10.1016/S0140-6736(11)60982-3.

104. 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(1):35–47.

105. Arruda LCM, Malmegrim KCR, Lima-Junior JR, Clave E, Dias JBE, Moraes DA, et al. Immune rebound associates with a favorable clinical response to autologous HSCT in systemic sclerosis patients. Blood Adv. 2018;2(2):126–41. https://doi.org/10.1182/bloodadvances.2017011072.

106. 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(5):1314–22. https://doi.org/10.1002/art.39021.

107. Khan IY, Singer LG, de Perrot M, Granton JT, Keshavjee S, Chau C, et al. Survival after lung transplantation in systemic sclerosis. A systematic review.

108. Respir Med. 2013;107(12):2081–7. https://doi.org/10.1016/j.rmed.2013.09.015.

108. Sottile PD, Iturbe D, Katsumoto TR, Connolly MK, Collard HR, Leard LA, et al. Outcomes in systemic sclerosis-related lung disease after lung transplantation. Transplantation. 2013;95(7):975–80. https://doi.org/10.1097/TP.0b013e3182845f23.

109. Crespo MM, Bermudez CA, Dew MA, Johnson BA, George MP, Bhama J, et al. Lung transplant in patients with scleroderma compared with pulmonary fibrosis. Short- and long-term outcomes. Ann Am Thorac Soc. 2016;13(6):784–92. https://doi.org/10.1513/AnnalsATS.201503-177OC.

110. Miele CH, Schwab K, Saggar R, Duffy E, Elashoff D, Tseng CH, et al. Lung transplant outcomes in systemic sclerosis with significant esophageal dysfunction. A comprehensive single-center experience. Ann Am Thorac Soc. 2016;13(6):793–802. https://doi.org/10.1513/AnnalsATS.201512-806OC.

111. Kistler KD, Nalysnyk L, Rotella P, Esser D. Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. BMC Pulm Med. 2014;14:139. https://doi.org/10.1186/1471-2466-14-139.

112. Mortimer K, Hartmann N, Chan C, Norman H, Wallace L, Enger C. Characterizing idiopathic pulmonary fibrosis patients using US Medicare-advantage health plan claims data. BMC Pulm Med. 2019;19(1):11. https://doi.org/10.1186/s12890-018-0759-5.

113. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307–18. https://doi.org/10.1056/NEJMoa1303006.

114. Volkmann E, Tashkin D, Kuwana M, Li N, Charles J, Hant FN et al., editors. Specific pneumoproteins predict progression of interstitial lung disease in systemic sclerosis patients undergoing treatment with immunosuppression. 2018 ACR/ARHP annual meeting; 2018.

115. Volkmann ER, Tashkin DP, Roth MD, Clements PJ, Khanna D, Furst DE, et al. Changes in plasma CXCL4 levels are associated with improvements in lung function in patients receiving immunosuppressive therapy for systemic sclerosis-related interstitial lung disease. Arthritis Res Ther. 2016;18(1):305. https://doi.org/10.1186/s13075-016-1203-y.

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