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INTERSTITIAL LUNG DISEASE (A. HAJARI CASE, SECTION EDITOR)

Connective Tissue Related Interstitial Lung Disease

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Abstract

Purpose of Review Interstitial lung disease (ILD) is a common complication of the connective tissue diseases (CTD) and results in significant morbidity and mortality. This review will focus on recent literature pertaining to the epidemiology, clinical presentation, diagnosis, and treatment of CTD-ILD.

Recent Findings Subclinical ILD can be found in the majority of patients with CTD. Clinically significant ILD is most commonly seen in scleroderma followed by polymyositis/dermatomyositis and rheumatoid arthritis, although it can occur in all of the CTDs. Nonspecific interstitial pneumonia is the most common radiographic and histologic pattern, although usual interstitial pneumonia occurs more frequently in rheumatoid arthritis. Pathogenesis is likely related to a combination of autoimmunity/inflammation, disordered fibrogenesis, and vascular injury. Treatment strategies are evolving to target all three of these pathways.

Summary Although further research into treatment strategies is needed, the clinician should be aware of the risk factors and clinical presentation of ILD in the various CTDs in order to identify patients who should be screened and/or have modifications in treatment strategies in order to mitigate the morbidity and mortality associated with CTD-ILD.

Keywords Interstitial lung disease · IPAF · Scleroderma · Dermatomyositis · Polymyositis · Rheumatoid arthritis · Sjögren's syndrome · Systemic lupus erythematosus

Abbreviations

6MWT	Six-minute walk test
AIP	Acute interstitial pneumonia
ALP	Acute lupus pneumonitis
ANA	Antinuclear antibody
AZA	Azathioprine
BAL	Bronchoalveolar lavage
CCP	Cyclic citrullinated peptide
CRP	C-Reactive protein
CTD	Connective tissue disease
CYC	Cyclophosphamide
DLCO	Diffusion limitation of carbon monoxide
DM	Dermatomyositis
ESR	Erythrocyte sedimentation rate
FVC	Forced vital capacity
HRCT	High resolution computed tomography of the chest
HSCT	Hematopoietic stem cell transplantation
IIM	Idiopathic inflammatory myopathies
ILD	Interstitial lung disease
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
JVD	Jugular venous distension
LIP	Lymphocytic interstitial pneumonia
MCTD	Mixed connective tissue disease
MMF	Mycophenolate mofetil
NSIP	Nonspecific interstitial pneumonia
OP	Organizing pneumonia
PAH	Pulmonary arterial hypertension
PFT	Pulmonary function test
PH	Pulmonary hypertension
PM	Polymyositis
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
TLC	Total lung capacity
TPMT	Thiopurine methyltransferase levels
TR	Tricuspid regurgitation murmur
ab	Antibody
UCTD	Undifferentiated connective tissue disease
UIP	Usual interstitial pneumonia

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Introduction

Connective tissue diseases (CTD) and rheumatoid arthritis (RA) are frequently associated with pulmonary complications including interstitial lung disease (ILD), pulmonary hypertension (PH), bronchiectasis, bronchiolitis, pleurisy, and pleural effusions [1, 2] leading to significant morbidity and mortality [3, 4]. Overall, ILD is the most common pulmonary complication affecting nearly 15% of all CTD patients, and approximately 15% of all subjects with ILD have an underlying CTD [5] (Table 1). Scleroderma (SSc), mixed connective tissue disease (MCTD), RA, dermatomyositis (DM)/polymyositis (PM), Sjögren's syndrome (SS), and systemic lupus erythematosus (SLE) are six well-differentiated rheumatologic diseases, which involve the lung and are associated with ILD. Undifferentiated connective tissue disease (UCTD) is a term used when a patient has autoimmune features that otherwise do not meet criteria for a well differentiated CTD [6], and interstitial pneumonia with autoimmune features (IPAF) is new terminology that describes patients with "lung dominant" UCTD [7••].

CTD-ILDs commonly present with insidious and progressive dyspnea on exertion and nonproductive cough, although symptoms may be overlooked due to focus on extrapulmonary manifestations such as arthritis or muscle weakness, which may result in patients being more sedentary. Acute presentations with respiratory failure can occur, as well as subclinical ILD identified co-incidentally on imaging. ILD may occur before extrapulmonary manifestations in up to 1/3 of patients with CTD making differentiation from an idiopathic interstitial pneumonia difficult; for example, subjects with idiopathic and CTD-associated nonspecific interstitial pneumonia (NSIP) have no differences in pulmonary symptoms, physiology, or imaging [8]. The severity of ILD does not correlate with extrapulmonary manifestations, and patients may have a "*forme fruste*" presentation, as seen in systemic sclerosis siné scleroderma, for example. Therefore, all patients with a new diagnosis of ILD should be carefully evaluated for rheumatologic disease [5, 9]. Special attention should be paid to findings/history of arthritis, myalgias or proximal muscle weakness, rashes, alopecia, photosensitivity, skin thickening or puffy fingers, gastroesophageal reflux, dysphagia, SICCA symptoms, oral/nasal ulcers, Raynaud phenomenon, and digital ulcers/pits. Serum antibody profiles play a pivotal role in further characterization of the underlying rheumatic diseases and often indicate risk for the development of ILD. Pulmonary function testing typically reveals exertional hypoxemia and a restrictive ventilatory defect with a decreased diffusion capacity. High resolution computed tomography of the chest (HRCT) is indicated in all patients with ILD and may be suggestive of the underlying histopathology, which most frequently is nonspecific interstitial pneumonia (NSIP) (Fig. 1a, b). Some experts believe that NSIP is pathognomonic of an autoimmune disease process as over 88% of patients, in one

Table 1 Risk factors for severe connective tissue disease associated ILD

Scleroderma
• Early disease (< 5 years)
• African American race
• Male gender
• Ground glass or fibrosis on high resolution chest computed tomography
• Anti-topoisomerase (anti-Scl-70) antibody
• Primary cardiac disease
Mixed connective tissue disease
• Esophageal dysfunction
• Advanced age
• Ground glass or fibrosis on high resolution chest computed tomography early in disease course
• Low baseline forced vital capacity
• Decreased functional status
Polymyositis/dermatomyositis
• African American race
• Antisynthetase antibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS, anti-tyrosyl-tRNA synthetase)
• Anti-SSA antibody
• Anti-PM/Scl antibody
• Anti-CADM-140/anti-MDA-5 antibody
Rheumatoid arthritis
• Male sex
• History of tobacco use
• Age > 60 years
• Usual interstitial pneumonia on imaging or pathology
• Active articular disease
• Low baseline forced vital capacity
• > 10% decline in forced vital capacity
• Low baseline diffusion capacity
• High titer rheumatoid factor
• High titer anti-cyclic citrullinated peptide
Sjögren's syndrome
• High titer antinuclear antibody
• High titer rheumatoid factor
• High titer anti-SSA antibody
• High titer anti-SSB antibody
• Hypergammaglobulinemia
• Advanced age
• Raynaud phenomenon
• Peripheral arthritis
• Esophageal dysfunction
Systemic lupus erythematosus
• Acute lupus pneumonitis
• Long disease duration (> 10 years)
• Raynaud phenomenon
• Anti-U1 RNP antibody
• Sclerodactyly
• Abnormal nailfold capillaroscopy

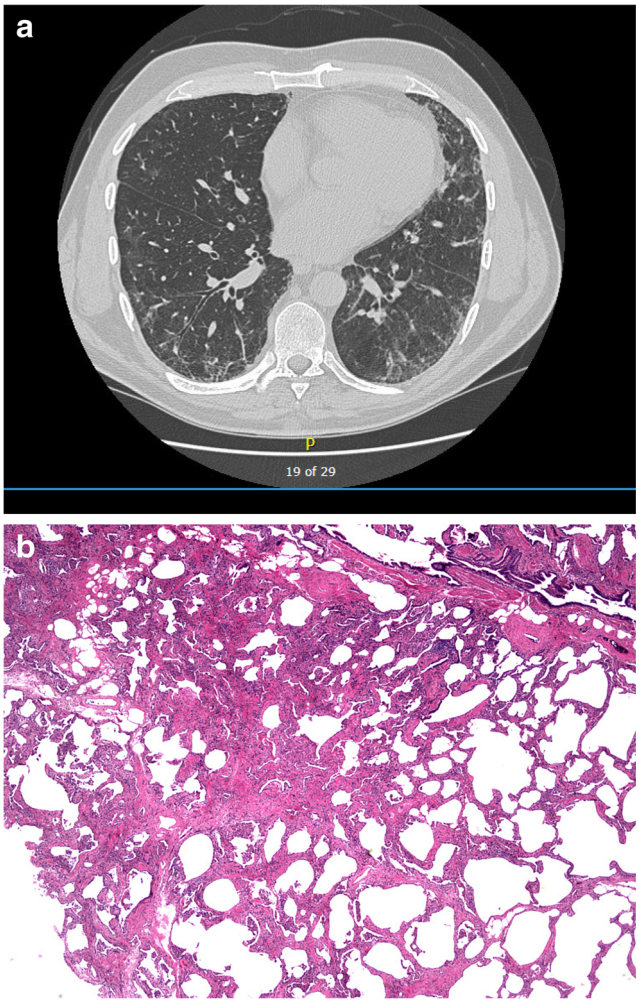

Fig. 1 **a** High resolution chest tomography of patient with fibrotic nonspecific interstitial pneumonia. Note peripheral, lower lobe predominant reticulation, traction bronchiectasis, and ground glass opacity. Subpleural sparing is also present. **b** Surgical lung biopsy from patient with NSIP, cellular type: alveolar walls with scattered lymphocytes and evidence of fibrosis (Hematoxylin and eosin, ×100)

study [10], initially classified as "idiopathic" NSIP were reclassified as having undifferentiated connective tissue disease on further examination. Although the gold standard for diagnosis of ILD is a surgical lung biopsy, this is generally not necessary in patients with CTD-ILD.

In this review, we delve deeper into specific CTD-ILDs and describe the current evidence for their diagnosis and treatment.

Interstitial Pneumonia with Autoimmune Features

Current guidelines recommend evaluation of all patients with ILD for the possibility of an underlying rheumatologic disorder [11], which will yield a subset of patients with symptoms and autoantibodies suggestive of an autoimmune condition, who do not fulfill criteria for a well-defined CTD [12]. Terminology such as undifferentiated connective tissue disease associated ILD (UCTD-ILD), lung-dominant CTD, or autoimmune featured ILD were proposed [12–14]. Subsequently, the European Respiratory Society and American Thoracic Society issued a research statement defining "interstitial pneumonia with autoimmune features" (IPAF) [7••] (Table 2). The classification criteria for IPAF are organized around the presence of a combination of features from three domains: a clinical domain consisting of specific extra-thoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic or pulmonary physiologic features. Individuals with IPAF have features suggestive of, but not definitive for a CTD. This research statement is designed to identify a cohort for further investigation. Currently there are no randomized controlled trials or case-control studies reporting the efficacy or safety of immunosuppressive agents in IPAF, although there are limited case series suggesting a benefit from MMF [15] and rituximab [16].

Multidisciplinary Approach

Currently, a multidisciplinary team including pulmonologists, radiologists, and pathologists is the gold standard for the diagnosis of ILD [17••, 18]. With the new criteria for IPAF, rheumatologic assessment has increasing importance. In a prospective study [19] of newly diagnosed ILD patients, the addition of routine rheumatology assessments reclassified 21% of patients with IPF as CTD and the number of ILD patients with "autoimmune features" was increased by 77%. This is relevant as immunosuppressive therapies may be indicated in patients with CTD whereas they are generally ineffective or can be harmful in IPF, and it is unclear whether antifibrotics have a role in CTD-ILD. Patients with CTD-ILD generally have a more favorable prognosis than patients with IPF and require surveillance for extrapulmonary disease manifestations that may be associated with their underlying CTD.

Scleroderma

The hallmark of scleroderma (systemic sclerosis, SSc) is excess collagen (sclero-) causing skin thickening (-derma). ILD is a key clinical criterion in the diagnosis of SSc, which occurs in approximately 25% of patients [20, 21] and leads to significant morbidity and mortality with a median survival of 5–7 years.

Systemic sclerosis is classified into two major categories: limited cutaneous-SSc mainly involves the skin of the fingers and face, defined as skin distal to the elbows and knees and above the clavicles. Diffuse cutaneous-SSc has a more extensive cutaneous involvement affecting the skin proximal to the elbows and knees and below the clavicles. Approximately half of the patients (45–70%) with diffuse cutaneous-SSc patients have evidence of ILD

Table 2 Classification criteria for "interstitial pneumonia with autoimmune features" (IPAF) [7••]

Presence of ILD (by HRCT or surgical lung biopsy)
and,
Exclusion of alternative etiologies
and,
Does not meet criteria of a defined CTD
and,
At least one feature from at least two of these domains:
A. Clinical domain
• Distal digital fissuring (i.e., "mechanic hands")
• Distal digital tip ulceration
• Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60 min
• Palmar telangiectasia
• Raynaud's phenomenon
• Unexplained digital edema
• Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)
B. Serologic domain
• ANA ≥ 1:320 titer, diffuse, speckled, homogeneous patterns or
  a. ANA nucleolar pattern (any titer) or
  b. ANA centromere pattern (any titer)
• Rheumatoid factor ≥ 2× upper limit of normal
• Anti-CCP
• Anti-dsDNA
• Anti-Ro (SS-A)
• Anti-La (SS-B)
• Anti-ribonucleoprotein
• Anti-Smith
• Anti-topoisomerase (Scl-70)
• Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
• Anti-PM-Scl
• Anti-MDA-5
C. Morphologic domain
• Suggestive radiology patterns by HRCT
  a. NSIP
  b. OP
  c. NSIP with OP overlap
  d. LIP
• Histopathology patterns or features by surgical lung biopsy:
  a. NSIP
  b. OP
  c. NSIP with OP overlap
  d. LIP
  e. Interstitial lymphoid aggregates with germinal centers
  f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
• Multi-compartment involvement (in addition to interstitial pneumonia):
  a. Unexplained pleural effusion or thickening
  b. Unexplained pericardial effusion or thickening
  c. Unexplained intrinsic airways disease[a] (by PFT, imaging, or pathology)
  d. Unexplained pulmonary vasculopathy

HRCT high-resolution computed tomography, *ANA* antinuclear antibody, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *PFT* pulmonary function testing

[a] Includes airflow obstruction, bronchiolitis, or bronchiectasis

on HRCT, whereas ILD occurs in only one quarter of patients (26%) with limited cutaneous-SSc [22, 23]. Importantly, interstitial lung disease may be a presenting manifestation in systemic sclerosis and/or have a *forme fruste* presentation without skin involvement (systemic sclerosis *siné* scleroderma).

Although rare, SSc is the most commonly encountered CTD associated with ILD, and thus is the most well studied. ILD typically occurs within the first 5 years of diagnosis of SSc [24]. Risk factors for rapid decline in forced vital capacity (FVC) in SSc include early disease, African American race, male sex, presence of ground glass opacities or fibrosis on HRCT, presence of anti-topoisomerase I antibody (anti-Scl-70), and primary cardiac disease [25, 26]. Patients with these risk factors should have a baseline HRCT and pulmonary function tests (PFTs) every 3–6 months.

HRCT typically shows a pattern consistent with NSIP, which is also the most common histopathology seen in SSc [27]. Frequently, there is a dilated and/or patulous esophagus, which is a clue that the patient may have SSc or an underlying rheumatologic disorder. Bronchoalveolar lavage (BAL) may show increased neutrophils and/or eosinophils suggestive of alveolitis, but data from the Scleroderma Lung Study I (SLS I) found that BAL does not add incremental value to HRCT findings as a predictor of progression or treatment response [28]. Nevertheless, BAL may be useful in excluding infection. Surgical lung biopsy is generally not needed and may confer an increased risk due to the possibility of co-existence pulmonary hypertension [29•].

SSc-ILD can be staged into "limited" and "extensive" categories based on degree of involvement on HRCT and pulmonary function. Patients with < 20% involvement by HRCT have "limited" disease, and those with > 20% involvement by HRCT have "extensive" disease. For those patients that are "indeterminant" or have 10–30% involvement by HRCT, an FVC < 70% would result in categorization of "extensive" disease. Patients with "extensive" disease should be considered for therapy secondary to poorer survival [30]. Other indications for therapy include significant dyspnea attributable to ILD, recent (within 3–12 months) decline in FVC% predicted by more than 10%, or an FVC < 70% predicted [30, 31].

Steroids should be used sparingly in patients with Ssc-ILD due to increased risk for development of scleroderma renal crisis [32]. Small studies have demonstrated efficacy of corticosteroids

in patients with active alveolitis when used as combination or adjuvant therapy with other immunosuppression, confounding results [33, 34]. Use of low-dose corticosteroids should be limited to patients with extensive ground glass opacities in the lungs (active alveolitis or flare of underlying ILD), but only in combination with another immunosuppressant.

The European League Against Rheumatism (EULAR) scleroderma treatment guidelines recommend that "cyclophosphamide should be *considered* for treatment of patients with SSc and progressive ILD" [35••]. This recommendation is largely based on data from the first Scleroderma Lung Study (SLS 1), which investigated oral cyclophosphamide (CYC) in a randomized multi-center, placebo-controlled trial that enrolled 158 patients with SSc-ILD defined by either alveolitis on BAL or HRCT [36]. There was a statistically significant improvement in mean FVC, for subjects treated with oral cyclophosphamide at 52 weeks, compared with placebo (2.53% adjusted FVC% predicted, $p < 0.03$), although the effects on lung function at 2 years (1 year off of cyclophosphamide) were not sustained [37]. Intravenous cyclophosphamide was investigated in a study of 45 patients with Ssc-ILD [38]. All patients received low-dose prednisolone prior to intravenous cyclophosphamide followed by oral azathioprine or placebo. While the study failed to demonstrate a statistically significant change in lung function or imaging, there appeared to be a trend towards better FVC in the intravenous cyclophosphamide plus azathioprine group. Although the choice between intravenous and oral formulation and cyclophosphamide remains unclear, the majority of experts prefer intravenous cyclophosphamide over oral due to a better adverse event and toxicity profile. A meta-analysis of three trials and six prospective observational studies looked at the effect of intravenous and oral CYC on SS-ILD and showed that it did not lead to clinically significant improvement in lung function (FVC and DLCO) [39].

In an attempt to mitigate the toxicity associated with CYC, mycophenolate mofetil (MMF) was compared to oral cyclophosphamide in SLS 2 [40••]. One hundred forty-two patients were randomly assigned to either MMF ($n = 69$) or CYC ($n = 73$). The MMF arm received a target dose of 1500 mg twice daily for 24 months, whereas the oral CYC arm received a target dose 2.0 mg/kg per day for 12 months followed by placebo for 12 months. The primary endpoint was a change in FVC as a percentage of the predicted normal value (FVC%). The adjusted % predicted FVC improved from baseline to 24 months by 2.19 in the MMF group (95% CI 0.53–3.84) and 2.88 in the CYC group (1.19–4.58), which was not statistically different. However, the MMF group had lesser incidence of side effects and lesser rates of discontinuation. Most scleroderma experts take this as evidence that MMF is a suitable alternative to CYC and now use CYC as a second line, after MMF, for initial treatment of SSc-ILD.

SLS 1 and 2 report stabilization or improvement in pulmonary function for CYC and MMF only for a period of 12 to 24 months. There is no data that informs decisions regarding maintenance immunosuppression beyond this time frame, although most experts continue MMF indefinitely, whereas CYC use is generally limited to 6–12 months usually due to its severe side effect profile.

Azathioprine (AZA) is typically not used in Ssc-ILD unless patients cannot tolerate CCY or MMF due to conflicting results reported in the literature [38, 41, 42]. Prior to initiation of azathioprine, it is important to check for thiopurine S-methyltransferase levels (TPMT). Deficiency of this enzyme predisposes patients to bone marrow suppression.

Rituximab has been used as a rescue therapy in SSc-ILD refractory to standard therapy, based on promising results from small observational and small non-randomized clinical trials [43–45]. An open label, multi-center clinical trial compared Rituximab with standard therapy (CYC, MMF, and AZA) in 51 patients with SSc-ILD, and showed a mean improvement in FVC of 6.3% of expected, compared to no significant improvement in the standard therapy arm over a period of 2 years [46] [31]. Although early data looks exciting, we await results from a large randomized controlled trial of rituximab (RECOVER), which will provide further evidence on the utility of rituximab for SSc-ILD (Clinicaltrials.gov Identifier: NCT01862926).

Autologous hematopoietic stem cell transplantation (HSCT) in SSc has gathered more interest and data in the last decade. The ASTIS trial (Autologous Stem cell Transplantation International Scleroderma) randomized 79 patients received to HSCT and 77 to intravenous cyclophosphamide [47]. The primary endpoint was event-free survival and the HSCT group was superior to the CYC group (at 2 years: hazard ratio (HR) 0.35 (95% CI, 0.16–0.74), at 4 years: HR 0.34, 95% CI 0.16–0.74). Approximately 87% of patients enrolled in the ASTIS trial had pulmonary involvement with evidence of restrictive lung disease and a moderate diffusion impairment. The HSCT cohort had a mean improvement in FVC of 6.3% predicted compared with the CYC group, which experienced a decline of − 2.8%. The total lung capacity (TLC) also improved in the HSCT group (5.1% predicted vs. − 1.3% predicted). However, the group randomized to receive HSCT experienced more deaths (13.9%) than the CYC group (9%) largely related to treatment-related adverse events. A similar improvement in event-free survival was reported in the SCOT trial (Scleroderma Cyclophosphamide or Transplantation) (79 vs 50%, $p = 0.02$) [48•]. In this trial, 36 patients who underwent myeloablative CD34+ selected HSCT were compared with 39 patients treated with CYC. All patients in the SCOT trial had evidence of modest SSc-ILD (FVC ~ 70% predicted). Similarly, the treatment-related mortality was higher in the HSCT group (3% at 54 months vs 0% in the CYC group). Based on these studies, the EULAR treatment guidelines recommend that "HSCT should be considered for treatment of rapidly progressive SSc at risk of organ failure." The recommendations further state that "in

view of the high risk of treatment-related side-effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance" [35••].

Elevated levels of IL-6 may be a predictor of mortality and disease progression in SSc-ILD. Consequently, tocilizumab, an interleukin-6 (IL-6) antagonist, was investigated in SSc [49•]. There was stabilization in FVC and improvement in skin score (compared to placebo) for up to 96 weeks in a phase II trial. A phase 3 trial has recently been completed and we await those results (Clinical trials.gov identifier NCT024532560).

Recently, anti-fibrotic agents (pirfenidone and nintedanib) have been approved for the treatment of idiopathic pulmonary fibrosis (IPF) [50, 51]. Nintedanib is a tyrosine kinase inhibitor that targets several pathways including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor [51]. Pirfenidone, an inhibitor of transforming growth factor beta (TGF-β), has pleiotropic effects that regulate important profibrotic cascades, fibroblast proliferation, and collagen synthesis [50]. Both agents decelerate progression of the fibrotic process in IPF and mitigate the rate of FVC decline. Nintedanib has been demonstrated in preclinical models of systemic sclerosis to inhibit macrophage activation and ameliorate fibrosis in the skin and lung [52] and a phase III, multi-national, randomized, placebo-controlled trial (SENSCIS) that enrolled 580 subjects is nearing completion. Subjects were able to be on background MMF, but this was not a requirement for entry into the study [53] (ClinicalTrials.gov identifier NCT02597933). Pirfenidone has been studied in a small cohort of SSc-ILD patients and demonstrated safety and tolerability, despite increased gastrointestinal adverse events (nausea, vomiting) [54]. Pirfenidone is further being studied in combination with MMF in Scleroderma Lung Study III (ClinicalTrials.gov Identifier: NCT03221257).

In addition to inflammation and abnormalities in fibrotic pathways, vascular injury may also be an important factor in the pathogenesis of SSc-ILD. This is suggested by elevated levels of thrombin in BAL fluid from SSc-ILD patients. Thrombin has been shown in vitro studies to transform the fibroblast into a myofibroblast. Preclinical data support inhibition of thrombin with dabigatran *exelitate* in SSc-ILD [55], and a phase II study exploring the safety and tolerability of dabigatran in patients with SSc-ILD is also nearing completion (ClinicalTrials.gov Identifier NCT02426229).

Mixed Connective Tissue Disease

MCTD was first described in 1972 and is defined by the combined presence of U1-ribonucleoprotein autoantibodies and clinical features including Raynaud phenomenon, "puffy" hands, sclerodactyly, arthralgias/arthritis, pleuritis, pericarditis, myositis, esophageal dysmotility, renal disease, pulmonary hypertension, and interstitial lung disease [56]. Controversy persists on whether this disease is actually a distinct disorder as many patients with anti-U1-RNP antibodies often satisfy the criteria for SLE, SSc, PM/DM, and/or RA during the course of their disease [57, 58].

PH and ILD are an integral part of the classification criteria for MCTD [59–62] and are associated with significant morbidity and mortality. Abnormal pulmonary function testing, predominantly a restrictive ventilatory defect, has been reported in as many as 90% of patients [63–69], and evidence of ILD by HRCT has been reported in 48–66% of patients [70, 71]. Although many patients with subclinical ILD may be asymptomatic, the presence of dyspnea, cough, and bibasilar crackles suggests active ILD that needs to be treated [71].

Abnormalities on HRCT in patients with MCTD-ILD include the presence of ground glass attenuation, interlobular septal and nonseptal linear opacities, and subpleural sparing with a peripheral and lower lobe predominance consistent with NSIP [70, 72, 76]. This is consistent with the reported histology of ILD in MCTD, which includes nonspecific interstitial pneumonia and usual interstitial pneumonia [72–75].

Although a causal relationship between esophageal and pulmonary involvement remains unproven, there is a strong association between esophageal dysfunction and ILD in patients with MCTD [76]. Other risk factors for severe fibrosis include advanced age, presence of ILD early in the disease course, and worse baseline lung function/functional status.

Retrospective reports and small case series suggest improvement with corticosteroids, alone or with the addition of cyclophosphamide or mycophenolate mofetil. In a case series of 96 patients with MCTD-ILD [71], 46.9% of patients responded well to 2 mg/kg/day corticosteroids, whereas 53.1% of patients required combination of corticosteroids and cyclophosphamide. Unfortunately, more than 20% of patients will go on to become hypoxemic [63], and 30% will develop significant fibrosis despite therapy [71]. The presence of ILD increases the risk of death with a reported 7.9% overall mortality for patients with ILD compared with 3.3% for those with a normal HRCT over a mean follow-up period of 4.2 years. Patients with severe fibrosis had a 20.8% mortality and the death rate for patients with baseline HRCT abnormalities was 12.3% [77].

Rheumatoid Arthritis

Rheumatoid arthritis is a systemic, chronic inflammatory disease involving the diarthrodial joints that results in progressive, symmetric, and erosive destruction of the cartilage and bone [78••]. Interstitial lung disease is a significant contributor to excess mortality in patients with RA with nearly a 3-fold increased risk of premature death compared to patients without this complication, and 10% of the deaths in RA are

attributable to ILD [79]. Reported 1- and 5-year mortality rates are 13.9 and 39% in RA-ILD [80].

The clinical presentation of RA-ILD is similar to any other ILD with insidious onset of dyspnea and a nonproductive cough [81], although symptoms may be missed in the early stages due to reduced physical activity masking dyspnea. RA-ILD usually presents in patients with a known diagnosis of RA, however in 20% cases, ILD can predate articular manifestations or may occur simultaneously [82–84]. Studies show that up to 80% of RA patients have radiographic and/or autopsy evidence of ILD, although clinical ILD develops in only 5–10% of RA patients [85, 86]. The most common radiographic findings on CT are reticular changes including honeycombing, ground glass opacities, traction bronchiectasis, and consolidation [87, 88]. A study which evaluated radiographic progression in a small cohort of RA patients indicated that even in patients with asymptomatic disease, radiographic progression by expert radiologist evaluation occurs in nearly 60% of patients over an 18-month period [89]. Among RA patients biopsied for a diagnosis of ILD, usual interstitial pneumonia (UIP) (Fig. 2a, b) is the most common histopathologic pattern [90], the same pattern seen in patients with idiopathic pulmonary fibrosis. This is in contrast to most other forms of CTD, in which NSIP predominates [90]. This may account, in part, for the poorer prognosis associated with RA-ILD in comparison with other CTD-ILDs. The second most common radiologic pattern in RA-ILD is NSIP with bilateral patchy ground glass opacities, sparing the subpleural area, areas of consolidation, evolving fibrosis, and prominent bronco-vascular markings, although its correlation with pathologic NSIP is relatively poor. Less common pathologies include lymphocytic interstitial pneumonia and organizing pneumonia (OP) [78••, 91–93]. OP is often related to complications of RA therapy [91–93].

Risk factors for increased mortality in RA-ILD include male sex, tobacco use, age greater than 60, UIP pattern on HRCT, active articular disease, a low baseline FVC% predicted or greater than 10% decline in FVC% predicted from baseline to any time during follow-up, low diffusion capacity, and higher serum titers of rheumatoid factor and anti-cyclic citrullinated peptide antibody [78••, 94, 95].

Currently available treatment for RA has achieved a great improvement in the control of articular disease as measured by disease activity and quality of life instruments [96]. Unfortunately, these benefits have not extended to RA-associated lung disease. There are currently no randomized clinical trials for RA-ILD that inform treatment decisions. Treatment decisions are further complicated by the unknown natural history of asymptomatic/subclinical RA-ILD, the lack of proven biomarkers predictive of disease progression, and the potential for some immunomodulators to result in pulmonary toxicity.

Treatment recommendations mostly comes from case series and small observational studies or are extrapolated from other CTDs. Asymptomatic patients with UIP pattern do not need initiation of therapy. Moderate to high dose corticosteroids remain first-line therapy for those that do need to be treated. Factors which predict steroid responsiveness include symptomatic patients with ground glass opacities, NSIP pattern, and younger age [97, 98]. Patients who are responsive to steroids can be transitioned to steroid sparing agents such as AZA, MMF, CYC, methotrexate, cyclosporine, or tocilizumab with significant but modest reported improvements in FVC and DLCO [15, 98–101]. Anti-tumor necrosis factor (anti-TNF) therapy has been associated with reports of rapid severe progression of RA-ILD; however, there are also reports suggesting a beneficial response to anti-TNF agents in patients with RA-ILD. In a study that looked at 367 patients with pre-existing RA-ILD, investigators found that mortality following treatment with anti-TNF therapy was not increased when compared with traditional DMARDS although the proportion of deaths attributable to RA-ILD was higher in the anti-TNF

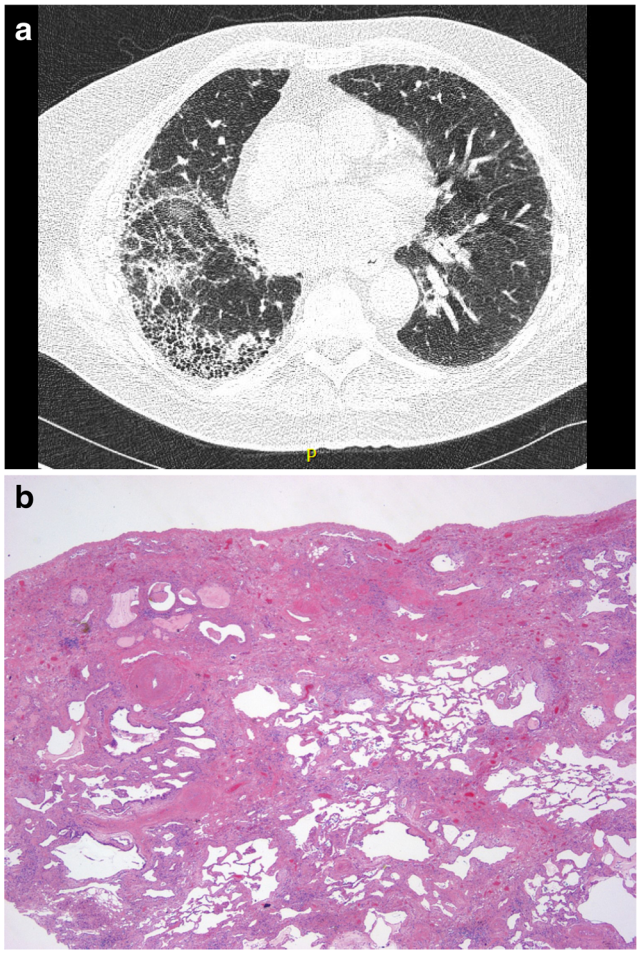

Fig. 2 **a** High resolution chest topography of patient with rheumatoid arthritis and usual interstitial pneumonia. Note peripheral, lower lobe predominant reticulation and honeycombing with an absence of ground glass opacity. **b** Surgical lung biopsy from subject with usual interstitial pneumonia. Note spatial heterogeneity with areas of fibrotic lung and more normal lung. Temporal heterogeneity is demonstrated by areas of mature fibrosis and areas of younger fibrosis including fibroblastic foci

cohort [102••]. Similarly, conflicting reports have been reported for rituximab and RA-ILD. However, in a recent observational study [103•] of 700 patients with rheumatoid arthritis that included 56 (8%) patients with RA-ILD treated with rituximab, most patients (68%) remained stable or had a slight improvement in pulmonary function and/or imaging after treatment over a prolonged follow-up period. Patients who deteriorated or died had the most severe ILD pre-rituximab treatment suggesting that rituximab was not contributory. Furthermore, the incidence of RA-ILD following rituximab treatment was only 0.4% suggesting that rituximab may inhibit the development and/or progression of RA-ILD.

Given the fact that UIP is the most common histopathology seen in RA-ILD, there may be a potential benefit for the antifibrotic therapies approved for IPF. The TRAIL-1 study is an ongoing randomized, double-blind, placebo-controlled, phase 2 study of the safety, tolerability, and efficacy of pirfenidone in patients with RA-ILD (ClinicalTrials.gov Identifier NCT02808871). Similarly, the PF-ILD trial is a double-blind, randomized, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease that includes patients with RA-ILD (ClinicalTrials.gov Identifier NCT02999178).

Myositis

The idiopathic inflammatory myopathies (IIM) are characterized by varying degrees of muscle inflammation. The main forms of adult IIM include PM, DM, inclusion body myositis (IBM), and amyopathic dermatomyositis [104–106]. ILD is common in PM/DM, occurring in 21–78% of patients [104] and leads to higher morbidity and mortality and is an independent risk factor for death [105]. ILD can occur gradually over weeks to months, or progress more rapidly with respiratory failure developing over days to weeks and even present as acute respiratory distress syndrome [106]; ILD precedes the diagnosis of DM/PM in approximately 13 to 37.5% of patients [104, 107–109].

Myositis specific antibodies targeting various tRNA synthetases are most strongly linked with the presence of ILD. Anti-Jo-1, the most common antisynthetase antibody, as well as anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, and anti-tyrosyl-tRNA synthetase collectively define the antisynthetase syndrome that is characterized by the combination of myositis, arthritis, fever, Raynaud phenomenon, mechanic's hands, and ILD [106]. Among patients with antisynthetase antibodies, the prevalence of ILD is estimated to be 67–100% depending upon the antibody detected [110, 111]. Anti-CADM-140/anti-MDA-5 antibody, anti-PM/Scl, and anti-Ro are other myositis specific antibodies that are associated with a high risk for ILD [112, 113].

The most common histopathology seen in myositis-associated ILD is NSIP, accounting for 60–80% of cases confirmed by biopsy [106]. Other pathologies include organizing pneumonia, usual interstitial pneumonia, and a small percentage of patients with diffuse alveolar damage/acute interstitial pneumonia, and chest imaging typically corresponds to the underlying histopathologic abnormalities [106].

Corticosteroids are the first-line therapy for ILD associated with inflammatory myopathies with the response to steroids dependent upon histologic subtype with organizing pneumonia more responsive to glucocorticoids whereas DAD/AIP is often relentlessly progressive [114]. Multiple immunosuppressive agents have been used for myositis-associated ILD, but no large randomized controlled trials exist to inform treatment decisions. MMF has been described most commonly in the literature. Other agents described in small case series or reports include azathioprine, methotrexate CYC, cyclosporine, tacrolimus, rituximab, adalimumab, and intravenous immunoglobulin [106, 113].

Sjögren's Syndrome

SS is a chronic inflammatory disease characterized by lymphocytic infiltration of the exocrine glands, classically the salivary and lacrimal glands leading to SICCA syndrome. Primary Sjögren's syndrome occurs alone, whereas secondary Sjögren's syndrome occurs in association with another connective tissue disease.

ILD is well described in SS and is associated with increased morbidity and mortality [153]. Recent studies report that 3–23% of patients with SS will develop ILD [116–118], and it may precede, follow, or occur concomitantly in relationship to the extrapulmonary manifestations of SS [119]. Risk factors for SS-ILD include the presence of a high titer antinuclear antibody (ANA), rheumatoid factor, anti-SSA and anti-SSB antibodies, hypergammaglobulinemia, older age, the presence of Raynaud phenomenon, peripheral arthritis, or esophageal involvement. Patients with these risk factors should be screened for ILD in order to identify patients that may benefit from earlier treatment [119, 120••].

Concomitant airway involvement is common in SS and patients often struggle with cough and 25% of patients have a mixed restriction and obstruction on pulmonary function testing [121]. Similarly, HRCT scans often show evidence of airway involvement including bronchial wall thickening (8–68%), bronchiectasis (5–46%), and air trapping (32%) [122].

NSIP (both cellular and fibrotic forms) is the most common radiographic and histopathologic patterns, followed by organizing pneumonia. Usual interstitial pneumonia is uncommon [78••, 80–82, 89, 93, 95, 96, 116, 120••, 121–130].

It is estimated that 1% of patients with SS will develop lymphocytic interstitial pneumonia (LIP), and approximately

25% of LIP cases are associated with SS [131•]. LIP is characterized by interlobular septal and bronchovascular bundle thickening, centrilobular and subpleural nodules, cysts, and ground glass opacities. Cysts are thin-walled (Fig. 3), vary in size, and have a "dissolving lung appearance" [131•, 132]. Histology reveals T and B lymphocyte-rich infiltrates along with plasma cells in the interstitial septa and in the alveolar space [120••, 123, 124, 126]. Cysts can also be seen in amyloidosis and lymphoma, so lung biopsy and assessment of clonality may be needed [115].

Case reports and case series suggest that corticosteroids are the mainstay of therapy followed by immunosuppressive agents such as hydroxychloroquine, azathioprine, cyclosporine, mycophenolate, cyclophosphamide, rituximab, tumor necrosis factor antagonists, chlorambucil, tocilizumab, tacrolimus, and abatacept [131•, 133–135]. Outcomes are variable and unpredictable and are contingent on histopathology. The 5-year survival rate of NSIP in SS is estimated to be 39–83% depending upon the case series [115, 116, 127]. The prognosis of UIP is poor. LIP and organizing pneumonia are usually corticosteroid responsive and have a good prognosis, although progressive fibrosis can occur [120••, 131•]. Acute exacerbations of underlying ILD have been reported in up to 16% of SS patients, although infection needs to be excluded first.

Systemic Lupus Erythematosus

SLE is a chronic inflammatory disease characterized by the production of ANAs and the formation and deposition of immune complexes, which results in end-organ damage [136].

Acute lupus pneumonitis (ALP) occurs in 1–4% of patients with SLE [137–139]. ALP may be a presenting manifestation of SLE and typically occurs during an SLE flare with multisystem involvement including nephritis, serositis, and arthritis [137, 140, 141]. Patients typically present with fever, pleuritic chest pain, dyspnea, nonproductive cough, are found to be hypoxemic, and have crackles on examination [137, 142]. Imaging reveals diffuse alveolar infiltrates suggestive of pneumonia, and associated pleural effusions may be present in up to 50%; the diagnosis should be suspected when there is lack of improvement with empiric antibiotics. Bronchoalveolar lavage may be indicated to exclude alveolar hemorrhage and infection and lung biopsy is indicated in those that fail to respond to immunosuppressive therapy; pathology reveals acute interstitial pneumonia (AIP) with inflammation with hyaline membrane formation without evidence of vasculitis or hemorrhage [140, 143].

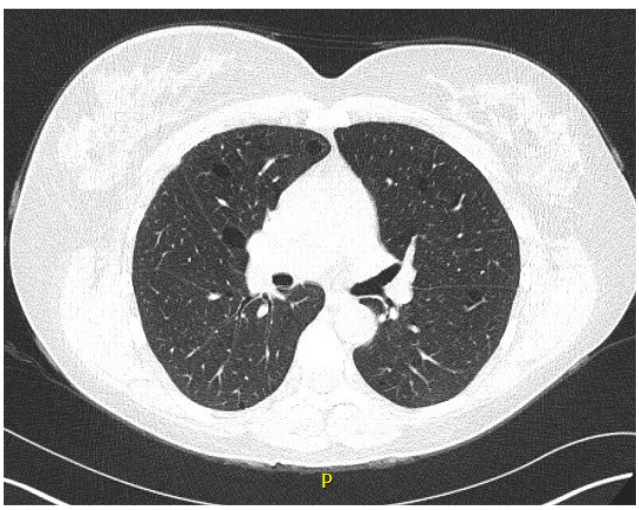

Fig. 3 High resolution chest computed tomography of patient with primary Sjögren syndrome and lymphocytic interstitial pneumonia. Imaging reveals lower lobe predominant perivascular subpleural cysts

Chronic ILD (SLE-ILD) is uncommon affecting approximately 1–15% of patients with SLE [144•, 145••] and may be a consequence of ALP in those who survive [145••]. Other risk factors for SLE-ILD include longstanding disease (> 10 years), Raynaud phenomenon, anti-U1 RNP (U1 ribonucleoprotein) antibodies, sclerodactyly, and abnormal nailfold capillaroscopy [143]. NSIP (both cellular and fibrotic) is the most common radiographic and histopathologic finding in SLE-ILD [141, 144•], but UIP, organizing pneumonia, LIP, follicular bronchiolitis, and nodular lymphoid hyperplasia have also been reported [146]. Laboratory abnormalities seen in SLE-ILD include hypocomplementemia, elevated high sensitivity C-reactive protein, and cryoglobulinemia. Anti-Ro/SSA antibodies have been reported in both ALP and SLE-ILD [141].

Treatment recommendations for both ALP and SLE-ILD are based on case reports and small case series [143, 144•, 145••]. Prednisone (0.5–2 mg/kg per day) has been most commonly reported with pulse dose glucocorticoids (methylprednisolone 1 g/day for three consecutive days) for patients with respiratory failure, refractory ALP, or SLE-ILD acute exacerbations [140]. Steroid sparing immunosuppressive agents should be started concomitantly, and case reports/case series report the use of cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab [139, 143, 144•, 145••, 146–149]. Intravenous Immunoglobulin (IVIG) and/or plasmapheresis may be used in refractory cases of ALP [141, 145••]. The mortality rate in ALP is as high as 50%. However, the prognosis of SLE-associated ILD is usually better than idiopathic ILDs and other CTD-associated ILDs. These patients tend to have a slow course and stabilize/improve over time.

Other Considerations

All patients with CTD-ILD should receive influenza and pneumonia vaccines. The need for supplemental oxygen should be assessed with ambulatory and/or nocturnal oximetry. Most patients should be treated aggressively for gastroesophageal reflux (GERD) as GERD can aggravate cough and microaspiration likely contributes to recurrent lung injury in these patients.

Patients should be routinely evaluated for other common comorbidities including coronary artery disease and obstructive sleep apnea. Pulmonary hypertension is a frequent comorbidity in patients with SSc and MCTD and may be suggested by an elevated forced vital capacity to diffusion ratio (FVC/DLCO) greater than 1.6, signs/symptoms of right heart failure, or worsening dyspnea without significant changes in pulmonary function testing or imaging. Patients should also be monitored carefully for toxicities, including pulmonary, which may be associated with immunosuppressive therapy.

Acute Exacerbations

Acute exacerbations may occur in patients with established CTD-ILD, and certain CTD-ILDs are known to present with acute exacerbations including DM/PM (antisynthetase syndrome), RA-ILD, and ALP. The patient typically presents with acute or acute on chronic onset of severe shortness of breath along with worsening hypoxemia. Imaging reveals worsening infiltrates, diffuse ground glass opacities, and/or organizing pneumonia [150•]. Patients often need to be admitted and managed in inpatient or intensive care settings. The most important management consideration in an acute exacerbation of CTD-ILD is to rule out infections. Clinical features of fever and purulent sputum should prompt bronchoscopy with BAL. A leukocytosis with neutrophilia suggests infection, and antibiotic therapy should be considered. BAL also is useful in evaluating for *Pneumocystis jerovecii* pneumonia (PJP) which can mimic an acute exacerbation [151]. Viral infections including influenza may also present with worsening infiltrates and should be kept in the differential in the appropriate season. High dose IV methylprednisolone (1000 mg in pulse dose or divided doses over 24 h for 3–5 days) is considered the standard therapy for severe acute exacerbations. This is typically followed by a tapering dose of steroids and initiation of CYC (IV or oral). Alternatives immunosuppressive therapies depend on specific CTD-ILD and may include rituximab, IVIG, and plasmapheresis. Other management considerations in the acute setting include assessment of volume status and appropriate diuresis. Overall, acute exacerbations of CTD-ILD have a poor prognosis with a high short-term mortality rate of 50–100% [152].

Lung Transplantation

CTD-ILD patients with severe disease refractory to maximal medical therapy should be considered for lung transplantation. While IPF is the most common ILD indication for lung transplant, nearly 1.3% of total transplantations performed are done for CTD-ILD [81]. However, evaluation for lung transplant candidacy mandates careful consideration of the specific comorbidities unique to this population including osteoporosis, gastroesophageal reflux, and pulmonary hypertension.

Esophageal dysmotility and gastroesophageal reflux have been associated with allograft dysfunction [153, 154] and may worsen post lung transplantation due to nerve injury of the vagus, recurrent laryngeal, and superior laryngeal nerves [155, 156]. Anti-reflux surgery may curb decline or even improve lung function peri-transplantation [157]. Fortunately, esophageal dysfunction alone rarely excludes a patient from being a candidate from lung transplantation and has not been demonstrated to adversely affect short- and long-term outcomes [158, 159]. Evidence from several single center studies and a systematic review report comparable outcomes for patients with CTD-ILD with similar 1-, 3-, and 5-year survivals when compared to transplant recipients for other fibrotic lung diseases [158, 160–163]. Female gender and presence of concomitant pulmonary arterial hypertension may portend higher risk for lower survival [161].

Conclusions

Connective tissue diseases are systemic disorders that are characterized by heterogeneous clinical manifestations and when complicated by interstitial lung disease are associated with significantly increased morbidity and mortality. NSIP and UIP are the most common radiographic and histopathologic findings. These diseases likely are a consequence of autoimmunity and inflammation, disordered fibrogenesis, epithelial cell damage, and vascular/endothelial injury resulting in dysregulated angiogenesis. Therapies that are able to target these multiple pathways are likely to be the most effective.

CTDs are a common cause of interstitial lung disease, and all patients with ILDs should be evaluated for an underlying CTD. Many challenges remain including false positive serologies and "undifferentiated" presentation as seen in IPAF. CTD-ILDs may be indistinguishable from idiopathic interstitial pneumonias, and ILD may precede other manifestations of ILD by years. Other challenges include the dearth of well-designed clinical trials that can inform treatment decisions. Further complicating treatment decisions is the fact that the natural history of subclinical CTD-ILD is not well understood, pulmonary symptoms may be "overshadowed" by extrapulmonary manifestations, and the severity of extrapulmonary manifestations does not correlate with the severity of ILD. Lastly, many of the medications used to treat CTD-ILD are associated with pulmonary toxicities. The next 5 years should provide a wealth of information that will help answer these questions.

Compliance with Ethical Standards

Conflict of Interest Abhishek Gadre declares no conflict of interest. Highland receives grants/contracts, does consulting, and/or is on the Speaker's Bureau of Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Pharmaceuticals, Gilead Sciences, Reata

Pharmaceuticals, and United Therapeutics. Dr. Highland is the global coordinating investigator for the SENSCIS trial (nintedanib versus placebo for scleroderma associated lung disease). She is also a consultant for Boehringer Ingelheim and is on their Speaker's Bureau. She is also a consultant for Boehringer Ingelheim and is on their Speaker's Bureau.

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.

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- • Of importance
- •• Of major importance

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