

Management of interstitial lung disease associated with connective tissue disease

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ABSTRACT

The lung is a common site of complications of systemic connective tissue disease (CTD), and lung involvement can present in several ways. Interstitial lung disease (ILD) and pulmonary hypertension are the most common lung manifestations in CTD. Although it is generally thought that interstitial lung disease develops later on in CTD it is often the initial presentation (“lung dominant” CTD). ILD can be present in most types of CTD, including rheumatoid arthritis, scleroderma, systemic lupus erythematosus, polymyositis or dermatomyositis, Sjögren’s syndrome, and mixed connective tissue disease. Despite similarities in clinical and pathologic presentation, the prognosis and treatment of CTD associated ILD (CTD-ILD) can differ greatly from that of other forms of ILD, such as idiopathic pulmonary fibrosis. Pulmonary hypertension (PH) can present as a primary vasculopathy in pulmonary arterial hypertension or in association with ILD (PH-ILD). Therefore, detailed history, physical examination, targeted serologic testing, and, occasionally, lung biopsy are needed to diagnose CTD-ILD, whereas both non-invasive and invasive assessments of pulmonary hemodynamics are needed to diagnose pulmonary hypertension. Immunosuppression is the mainstay of treatment for ILD, although data from randomized controlled trials (RCTs) to support specific treatments are lacking. Furthermore, treatment strategies vary according to the clinical situation—for example, the treatment of a patient newly diagnosed as having CTD-ILD differs from that of someone with an acute exacerbation of the disease. Immunosuppression is indicated only in select cases of pulmonary arterial hypertension related to CTD; more commonly, selective pulmonary vasodilators are used. For both diseases, comorbidities such as sleep disordered breathing, symptoms of dyspnea, and cough should be evaluated and treated. Lung transplantation should be considered in patients with advanced disease but is not always feasible because of other manifestations of CTD and comorbidities. Clinical trials of novel therapies including immunosuppressive therapies are needed to inform best treatment strategies.

Introduction

Interstitial lung disease (ILD) is one of the most common and clinically important manifestations of connective tissue disease (CTD). Although ILD often occurs in patients with known CTD, it can also be the first and only manifestation of previously unrecognized CTD. Therefore, patients presenting with ILD require thoughtful evaluation for the presence of CTD, particularly as the treatment of CTD-ILD is often markedly different from that of other idiopathic interstitial pneumonias such as idiopathic pulmonary fibrosis (IPF). The spectrum of ILD associated with CTD is broad, so careful evaluation for autoantibodies or other features of autoimmune disease is crucial. Furthermore, ILD can occur as a complication of treatment for CTD.

In addition, other forms of lung involvement can occur in CTD and should be considered in the evaluation of a patient with either known or suspected CTD (table 1). In this review, we will describe approaches to the diagnosis of CTD-ILD and potential diagnostic limitations. We will review the current state of disease directed treatment as well as supportive care, which should be integrated into the overall care of these patients.

There are two major presentations of ILD in the context of CTD. The first is the development of ILD in a patient with known CTD. The second presentation, which is possibly more challenging, is as the first or only manifestation of CTD. These presentations will be considered separately.

Table 1 | Features of lung involvement in connective tissue diseases

Lung involvement	Type of connective tissue disease					
	SSc	RA	SS	MCTD	PM/DM	SLE
ILD						
Occurrence	Likely	Common	Possible	Common	Likely	Unusual
Type of ILD	NSIP (80-90%) UIP (10-20%)	UIP (50-60%) NSIP, OP, DIP	NSIP (28-60%) LIP (20%)	NSIP	NSIP, OP, UIP, DAD	
PH						
Occurrence	Likely	Unusual	Unusual	Likely	Unusual	Unusual
Type	PAH, PH-ILD			PAH, PH-ILD		
Airways disease						
Occurrence	Unusual	Common	Common	Possible	Unusual	Possible
Type		FB, BO, BE	FB, BO, BE	BO		BO
Other PVD						
Occurrence	Unusual	Unusual	Possible	Likely	Possible	Likely
Type			PE	PE	PE	PE, CTEPH
Pleural						
Occurrence	Unusual	Common	Possible	Possible	Unusual	Likely
Type		Pleuritis	Pleuritis	Pleural effusion		Pleural effusion Pleural thickening
DAH						
Occurrence	Unusual	Unusual	Unusual	Unusual	Unusual	Common
Abbreviations: BE=bronchiectasis; BO=bronchiolitis obliterans; CTEPH=chronic thromboembolic pulmonary hypertension; DAD=diffuse alveolar damage; DAH=diffuse alveolar hemorrhage; DIP=desquamative interstitial pneumonia; FB=follicular bronchiolitis; ILD=interstitial lung disease; LIP=lymphocytic interstitial pneumonia; MCTD=mixed connective tissue disease; NSIP=non-specific interstitial pneumonia; OP=organizing pneumonia; PAH=pulmonary arterial hypertension; PE=pulmonary embolism; PH-ILD=pulmonary hypertension related to ILD; PM/DM=polymyositis/dermatomyositis; PVD=pulmonary vascular disease; RA=rheumatoid arthritis; SLE=systemic lupus erythematosus; SSc=scleroderma; SS=Sjögren's syndrome; UIP=usual interstitial pneumonia.						

Sources and selection criteria

We searched PubMed, Medline, and the Cochrane Library from January 1966 to January 2015 using combinations of words or terms that included lung or pulmonary, interstitial lung disease, pulmonary hypertension, connective tissue disease, rheumatologic disease (including rheumatoid arthritis, scleroderma, systemic lupus erythematosus (SLE), polymyositis/dermatomyositis, myositis, Sjögren’s syndrome, mixed connective tissue disease), treatment, therapy, and management. Articles from the reference list of articles and text chapters were reviewed and relevant publications identified. Non-English abstracts and articles were excluded. We considered evidence on the basis of the appropriateness and quality of the study design, with double masked RCTs regarded as the most suitable design and prospective cohort studies and retrospective case series as less suitable.

ILD in known autoimmune disease

ILD is common in patients with known autoimmune disease and prevalence varies by CTD type and the method of ascertainment.

Rheumatoid arthritis

Rheumatoid arthritis (RA) affects about 0.5-1% of the US population,¹⁻³ and ILD is the most common pulmonary manifestation in these patients, occurring in 10-20% of patients.⁴ Estimates of the prevalence of ILD vary according to the ascertainment technique: pulmonary function testing, chest computed tomography, or lung biopsy.

High resolution chest computed tomography is more sensitive than spirometry for identifying ILD. It is abnormal in 19% of an unselected population of patients with rheumatoid arthritis and 60-80% of patients with rheu-

matoid arthritis and respiratory symptoms.⁵⁻⁶ The most common radiographic findings on computed tomography include reticular honeycombing, ground glass opacities, traction bronchiectasis, and consolidation.⁵⁻⁷

Pathologic evaluation of a lung biopsy specimen is the most sensitive technique. In a case series of people with rheumatoid arthritis who were not selected for respiratory symptoms, ILD was present in 80% of surgical lung biopsies.⁸ Among patients with rheumatoid arthritis who are diagnosed as having ILD at biopsy, usual interstitial pneumonia (UIP) is the most common disease process, although others have been described.⁹ Respiratory disease, particularly ILD, is a substantial contributor to excess mortality in patients with rheumatoid arthritis. A longitudinal cohort study showed that RA-ILD is responsible for about a 10% increase in mortality.¹⁰ Similarly, a recent national study of mortality in rheumatoid arthritis showed that nearly 10% of deaths are attributable to ILD, which is consistent with an earlier single center study.¹¹⁻¹²

Scleroderma

Although scleroderma or systemic sclerosis is less common than rheumatoid arthritis, lung involvement is more common in scleroderma. Typically, scleroderma is defined clinically by the extent of skin involvement: sine (no obvious lesions), limited (skin below the elbows and knees affected, but not the trunk; face and neck may be affected), and diffuse (skin on the trunk, shoulder, pelvis, and face affected). Associations between disease type and site of internal organ involvement have been used in the past.

Lung involvement in scleroderma takes the form of both ILD (>70% of patients at autopsy) and pulmonary arterial hypertension (PAH) (8-12% of patients); ILD may be more common in diffuse scleroderma and PAH more common in limited scleroderma.¹³⁻¹⁴ Scleroderma associ-

ated lung disease is currently the major cause of death in patients with scleroderma. One study assessed the cause of death in patients with scleroderma between 1972 and 2002. It found a fundamental shift away from mortality due to scleroderma renal crisis and towards death due to ILD and PAH.¹⁵

The recent development of PAH specific treatment has led to a measurable improvement in mortality in patients with scleroderma and PAH, from one year and two year survival rates of 68% and 47% to 81% and 71%, respectively, over the past 20 years. However, these estimates may be confounded by lead time bias because expert consensus now recommends routine screening for PAH in patients with scleroderma, so patients may be diagnosed earlier in the disease course.^{16–17} Among patients with scleroderma, pulmonary hypertension can occur in isolation (PAH) or in association with ILD (PH-ILD). Pulmonary hypertension that occurs in the context of ILD, confers a fivefold increased risk of death compared with PAH alone (hazard ratio 5.15, 95% confidence interval 1.73 to 15.3).¹⁸

Predictors of disease progression in scleroderma-ILD

In general, patients with diffuse scleroderma (based on the extent of skin involvement) have a higher risk of developing ILD than those with limited scleroderma.^{19–20} However, this may be associated with antibody profile rather than the pattern of skin involvement.²¹ The most common autoantibodies in diffuse scleroderma are anti-topoisomerase I antibodies; more than 85% of patients with these antibodies develop ILD. Furthermore, titers of this antibody correlate with disease severity and activity of ILD.^{22–23}

Additional risk factors for the development of ILD include esophageal dysmotility and gastroesophageal reflux disease.²⁰ Although many studies of biomarkers for the risk of developing ILD are under way, currently no individual biomarker or group of biomarkers has been sufficiently validated for clinical application. The identification of predictors of mortality in scleroderma-ILD is also an important area of study. A 2014 systematic review of 27 studies noted several common factors that were identified in multiple studies but also a significant degree of divergence between studies as well as failure to adjust for confounders.²⁴ Overall, the meta-analysis identified patient specific (increased age, male sex, lower forced vital capacity, and lower diffusing capacity of the lungs for carbon monoxide (DLCO)), ILD specific (radiographic extent of disease and presence of honeycombing), and scleroderma specific (shorter duration of scleroderma) variables.

Systemic lupus erythematosus

Although the lung is involved in 33–50% of patients with SLE, ILD is less common than in other forms of CTD and affects only 1–15% of patients.²⁵ Patients with SLE have increased rates of infection of the lung and lung cancer. In addition, all compartments of the lung—pleural space, parenchyma, airways, and vasculature—can be affected by the disease itself.^{26–27}

Risk factors for development of ILD

Longstanding disease (>10 years) is a risk factor for the development of ILD.²⁸ In addition, Raynaud's phenomenon, anti-U1 RNP (U1 ribonucleoprotein) antibodies, sclerodactyly, and abnormal nailfold capillary loops are associated with radiographic evidence of ILD. This suggests that the presence of the overlap syndrome or mixed CTD with features of scleroderma is linked with the occurrence of ILD in SLE.²⁹ Older age is also a risk factor for the development of ILD in SLE, similar to reports in rheumatoid arthritis.³⁰ Within the spectrum of SLE lung disease, lupus pneumonitis is an acute and often fatal form of lung injury, with about a 50% in-hospital mortality rate.³¹ Non-fatal lupus pneumonitis is hypothesized to be a precursor of chronic ILD in some patients. Diffuse alveolar hemorrhage in SLE is also associated with poor outcome.

Shrinking lung syndrome

In addition to ILD, a second restrictive lung process in SLE has been termed “shrinking lung syndrome.” This disorder does not affect pulmonary parenchyma. The reported frequency varies, but it is seen in 0.5% of patients.^{32–33} It is probably caused by diaphragmatic dysfunction.³⁴ Risk factors include longer disease duration, presence of anti-RNP, and a history of pleuritis.³³

Polymyositis and dermatomyositis

The idiopathic inflammatory myopathies include polymyositis (PM), dermatomyositis (DM), and clinically amyopathic dermatomyositis (CADM). Each of these is associated with varying degrees of involvement of the muscle, skin, joints, and lung. Pulmonary involvement in the form of ILD can range from subclinical to rapidly progressive and fatal.^{26–35} The reported prevalence of ILD in myositis ranges from 20% to 78% and is associated with increased morbidity and mortality.^{36–39}

Prognostic factors

A retrospective study evaluated prognostic factors of survival in 114 consecutive patients diagnosed as having DM-ILD, PM-ILD, or CADM-ILD between 1990 and 2012 at a single Japanese tertiary care center.⁴⁰ Mortality rates for PM-ILD, DM-ILD, and CADM-ILD were 16.7%, 24.4%, and 37.2%, respectively, with an overall mortality rate for the entire cohort of 27.2%. These results are similar to those of smaller studies, which found mortality rates of 7.5–44%.^{37–39} Acute or subacute ILD and a diagnosis of CADM (versus PM) were associated with more than a fourfold increased risk of death.⁴⁰ This is consistent with previous studies showing that the acute and subacute forms of ILD are more often refractory to treatment and therefore associated with a poor prognosis.^{38–42}

Sjögren's syndrome

It is difficult to estimate the prevalence of pulmonary involvement in patients with Sjögren's syndrome because the classification criteria have changed over time. The estimated prevalence of clinically significant lung involvement ranges from 9% to 24%.^{43–45} By contrast, in one large study of patients with Sjögren's syndrome, 75% of asymptomatic patients showed abnormalities on pulmonary function tests, bronchoalveolar lavage, and com-

Table 2 | Autoimmune serologic tests and their interpretation

Test	Interpretation
ANA	Non-specific, but at high titer associated with subsequent diagnosis of autoimmune disease
Rheumatoid factor	Occurs in rheumatoid arthritis but also non-specific in context of other autoimmune diseases
Scl-70	Associated with scleroderma
RNP	Associated with mixed connective tissue disease
Jo-1	Myositis specific antibody
Extended myositis panel:	Includes other myositis specific and myositis associated antibodies
Antisynthetase	Includes PL-7, PL-12, EJ, OJ antibodies—all associated with presence of ILD
MDA-5	Associated with erosive Gottron's papules and aggressive ILD
PMscl	Overlapping features of polymyositis and scleroderma
Ro-52	Associated with more aggressive ILD
CPK	Raised in myositis but can be normal in CADM
Aldolase	May be raised at low level in CADM
SSA/SSB	Sjögren's syndrome associated antibodies
CCP	Associated with rheumatoid arthritis
ANCA	Less commonly associated with pure ILD, but ILD can occur

ANA=anti-nuclear antibody; ANCA=anti-neutrophil cytoplasmic antibodies; CADM=clinically amyopathic dermatomyositis; CCP=anti-cyclic citrullinated peptide; CPK=creatinine phosphokinase; ILD=interstitial lung disease; Jo-1=anti-Jo-1 antibody; MDA-5=anti-MDA5 antibody; PMscl=anti-PMscl antibody; RNP=anti-ribonucleoprotein antibody; Ro-52=anti-Ro-52 antibody; Scl-70=anti-Scl-70 antibody; SSA/B=Sjögren's associated antibody A/B.

puted tomography.⁴⁶ Similar to rheumatoid arthritis and SLE, pulmonary manifestations in Sjögren's syndrome generally develop late in the course of disease and are rarely the presenting feature.⁴⁷

The entire respiratory system can be affected in Sjögren's syndrome. Small airways disease, such as follicular bronchiolitis, is a common histologic finding in patients with pulmonary involvement. Patients who have related lung disease have reduced quality of life and physical functioning compared with other patients with Sjögren's syndrome.⁴³ Furthermore, pulmonary involvement in Sjögren's syndrome is associated with a fourfold increased risk of mortality after 10 years of disease.

ILD subtypes

Early studies identified the major form of ILD in primary Sjögren's syndrome as lymphocytic interstitial pneumonitis. However, in a more recent case series only 17% of patients with primary Sjögren's syndrome and ILD had a histologic diagnosis of lymphocytic interstitial pneumonitis.⁴⁸ This change in prevalence may be due to revisions of diagnostic criteria for lymphocytic interstitial pneumonitis leading to more patients being categorized as having non-specific interstitial pneumonia. Currently, non-specific interstitial pneumonia is the most common subtype of ILD in patients with Sjögren's syndrome, with a prevalence of 28-61%.^{48 49} The presence of antibodies to Sjögren's syndrome related antigen A alone, in the absence of other criteria for Sjögren's syndrome, is associated with a non-specific interstitial pneumonia pattern on imaging and more severe impairment of lung function, suggesting a possible role of the antibody in the pathogenesis of lung disease.⁵⁰

Mixed connective tissue disease (MCTD)

MCTD was first defined in 1972 and it remains a controversial designation.⁵¹ In general, it is defined by the presence of antibodies to U1 RNP. However, three classification systems have established distinct criteria for

the diagnosis. Two of these include lung involvement as diagnostic features. Indeed, lung involvement is common in patients with MCTD, varying from 47% to 78%.⁵² A recent Hungarian study of 201 patients with MCTD with a mean follow-up of 12.5 (standard deviation 7.2) years found that nearly 53% had ILD, 36% had pleuritis or pericarditis, and 24% had pulmonary hypertension.⁵³ A study of 126 patients from Norway with MCTD found that 52% had abnormalities on high resolution computed tomography, including evidence of severe fibrosis in 19%. Severe fibrosis was associated with older age, but not with length of diagnosis or smoking.⁵⁴ A more recent study by the same group with a slightly larger national cohort of 147 patients showed an association between the presence of anti-Ro52 and the severity of lung fibrosis. These antibodies were associated with an odds ratio of 4.4 (1.8 to 10.3; P<0.002) for the presence of lung fibrosis.⁵⁵ A cluster analysis based on the clinical features of the 201 patients in the Hungarian cohort found increased mortality in patients with pulmonary hypertension compared with those with ILD.⁵³ Thus, lung involvement in MCTD is both common and associated with increased mortality.

Evaluation of CTD in patients with a new diagnosis of ILD

It is increasingly recognized that ILD may be the first or only manifestation of an underlying CTD. In this situation, patients may present with two overlapping patterns—an acute form or a more subacute form.

Acute onset ILD in patients without known CTD

The acute presentation with rapidly progressive ILD typically occurs in younger patients and is often heralded by a few weeks to months of increasing dyspnea in previously healthy people. Patients in this group often present to hospital and are rapidly moved to the intensive care unit because of hypoxemic respiratory failure in the setting of progressive ground glass opacities on high resolution computed tomography.

In such patients, the crucial initial steps are early consideration of ILD; evaluation of infection, including bronchoalveolar lavage if the patient is stable; and early serological evaluation. Table 2 provides a list of the initial tests and considerations in interpretation. Because many of these recommendations are based on small patient series or single center experience, diagnostic specificity and sensitivity are often not available. The results of such tests are often not available or complete in time to be useful when treating patients who present acutely, so treatment will often need to be started before a definite diagnosis of CTD is available. Several additional tests can be considered as additional circumstantial data to support such a diagnosis.

Patients with raised muscle enzymes (creatinine phosphokinase or aldolase) can be evaluated for evidence of myositis using magnetic resonance imaging of the thigh, electromyography, or muscle biopsy (or a combination thereof). Each of these methods may add relevant information in patients who present as clinically "amyopathic" or without overt evidence of muscle weakness.

Because of the high prevalence of dysmotility in some forms of CTD, such as scleroderma, evidence of

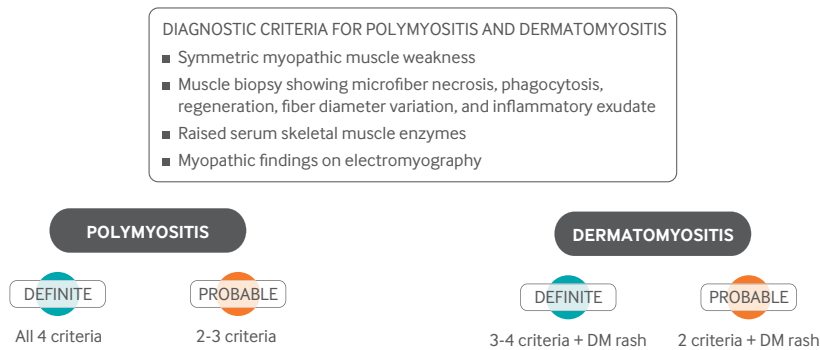


Fig 1 | Bohan and Peter criteria for myositis^{59 60}

esophageal dysmotility, such as a dilated or patulous esophagus on chest computed tomography, may also support a presumed diagnosis of CTD.

Echocardiographic evidence of pulmonary hypertension is useful when considering the possibility of unrecognized thromboembolic disease, which often accompanies acute presentations of ILD, and for identifying patients in whom pulmonary hypertension is the primary manifestation of CTD.⁵⁶ Importantly, a recent study found a more than twofold increased risk of venous thromboembolism in patients with scleroderma compared with normal controls, highlighting the need for thorough evaluation for venous thromboembolism in this population.⁵⁷ Although PAH is most commonly associated with a diagnosis of scleroderma, it can also occur in patients with dermatomyositis or polymyositis and other CTDs. Furthermore, patients with CTD are also at risk of pulmonary hypertension related to chronic thromboembolic disease, especially those with SLE.

Subacute presentation in patients without known CTD

A key step in the evaluation of all patients with idiopathic interstitial pneumonia is the identification of known causes of ILD. This step is so crucial that it is the first step in the current American Thoracic Society/European Respiratory Society (ATS/ERS) algorithm for the diagnosis of IPF.⁵⁸ Unfortunately, in practice the evaluation for new onset ILD often follows the more invasive approach of lung biopsy. Because surgical lung biopsy is recommended only if diagnostic uncertainty exists,⁵⁸ few if any patients should undergo biopsy before a thoughtful evaluation for CTD has been completed. Although serologic evaluation is crucial in the diagnosis of CTD, it is no substitute for taking a careful personal medical and family history and performing a review of systems and a clinical examination. Patients have often experienced symptoms that they have not associated with pulmonary symptoms, such as Raynaud’s phenomenon, skin rash or hair loss, muscle pain or weakness, gastroesophageal reflux, and joint pain or swelling. It is therefore often useful to encourage patients to describe any new or recent symptoms. Given the multiple organ systems that can be affected in CTD, in patients with atypical features it is often useful to consult with rheumatologists, dermatologists, and other specialists.

Limits of testing based on available serological tests

There are two common concerns when evaluating CTD in patients with ILD as the main or only symptom. The first concern is that the patient has a recognized autoantibody but does not meet the defining criteria for the associated CTD. This concern has increasingly been raised as serologic testing has become available for “myositis specific” antibodies, including antisynthetase antibodies. Figure 1 shows the defining criteria for myositis.^{59 60} At the time of the definition, the muscle and skin manifestations were the major features of the disease that were recognized. Since the discovery of the Jo-1 antibody and other antisynthetase antibodies, it has become apparent that many patients who carry these highly specific antibodies have little or no muscle or skin involvement at the time of presentation. Indeed, the term “clinically amyopathic dermatomyositis” was coined to describe acute pulmonary presentation in the absence of muscle involvement.⁴¹ The lesson to be learnt is that our understanding of CTD is limited by available technology. An ongoing conversation with rheumatology organizations is needed to redefine CTD including the inclusion of the lung as a primary organ of involvement.

The second concern is that although the patient has suggestive clinical features, a non-specific antibody such as a positive ANA is present but a more disease specific antibody is not. This often occurs in the context of suggestive findings such as Raynaud’s phenomenon. As a result a new category of CTD has been proposed, which is sometimes described as autoimmune flavored ILD.⁵⁰ A recent ATS/ERS consensus statement provides some guidelines on the classification of interstitial pneumonia with autoimmune features (IPAF) specifically for research purposes.⁶¹ Although the addition of this new designation may facilitate ongoing research, it does not help with diagnostic uncertainty in some patients.

Another problem is that the diagnosis of CTD is currently limited by the availability of clinical testing and the recognition of autoantibodies. A prime example of this is the recently described MDA-5 antibody. This antibody was initially described as recognizing a 140 kDa protein in patients with CADM.⁶² The identification of this protein as MDA-5 as well as the development of clinical testing allowed an important group of patients with previously undefined ILD to be placed into the category of CTD associated ILD. Furthermore, with the availability of testing at clinical and research levels the spectrum of MDA-5 associated ILD has been broadened from that of acute ILD to a more benign picture.⁶³ Recent clinical testing by a reference laboratory suggested that patients with currently undefined CTD carry autoantibodies that are yet to be identified. Until these autoantibodies are fully described, it might be useful to re-evaluate the diagnostic criteria of existing CTDs.

Forms of ILD: radiologic and pathologic review

High resolution computed tomography is used to evaluate patients with possible CTD-ILD. This technique has considerable diagnostic and prognostic benefits, although accurate interpretation is crucial (fig 2) Several groups have developed algorithms for identifying features of

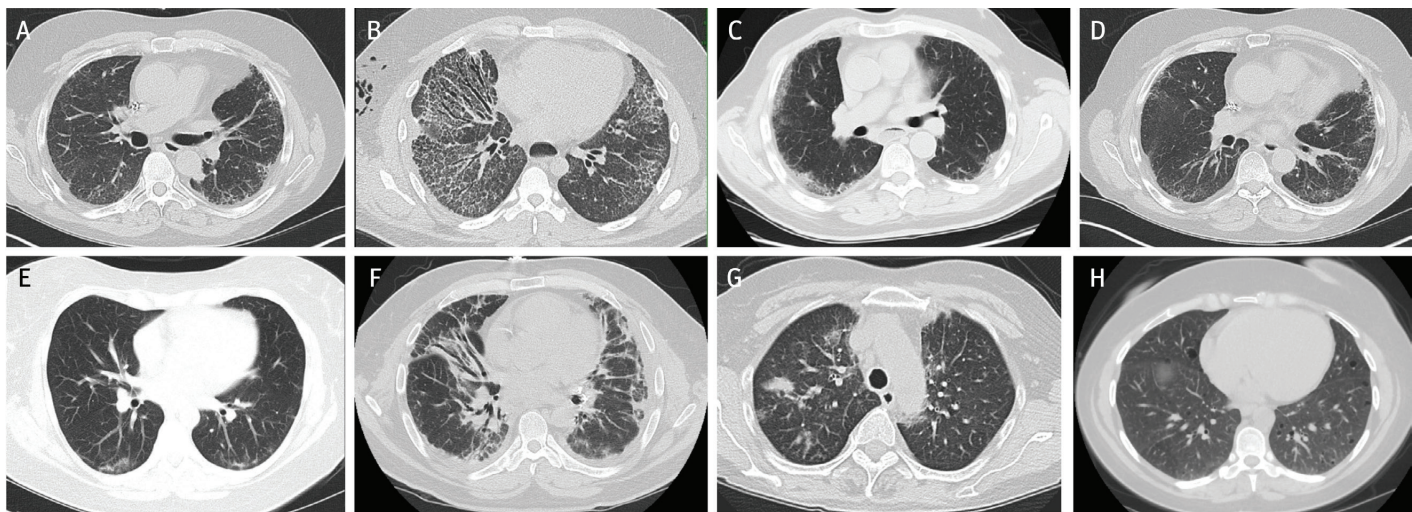


Fig 2| Radiographic appearance of connective tissue disease (CTD) associated interstitial lung disease can vary both within a given CTD and between different CTDs. (A) Scleroderma with stable reticular changes. (B) Scleroderma with rapidly progressive interstitial lung disease and pulmonary hypertension; esophageal dilatation is seen. (C) Scleroderma with reticular changes and esophageal dysmotility with food in the esophagus. (D) Scleroderma with minimal reticular changes. (E) Jo-1 associated antisynthetase syndrome presenting with organizing pneumonia. (F) PL-7 associated antisynthetase syndrome with acute respiratory failure. (G) Lupus pneumonitis. (H) Cystic changes in Sjögren's syndrome, probably secondary to lymphocytic interstitial pneumonitis

usual interstitial pneumonia on these scans. The ATS/ERS criteria for the diagnosis of IPF provide a useful guide for recognizing this radiographic pattern.⁵⁸⁻⁶⁴ Patients with CTD and usual interstitial pneumonia seem to have a worse prognosis than those with other histopathologic forms of CTD-ILD. It is therefore useful to distinguish between usual interstitial pneumonia, non-specific interstitial pneumonia, and organizing pneumonia when considering individual patients' likelihood of response to treatment. However, no radiographic pattern seems to be completely resistant to treatment, so treatment should be started regardless of radiographic pattern.

Although several radiographic staging systems have been developed for IPF, few have been validated in patients with CTD-ILD.⁵⁸ However, a simple staging system for patients with scleroderma associated ILD has been proposed.⁶⁵ This system averages the extent of radiographic lung involvement (extent of reticulation, proportion of ground glass opacities, and coarseness of reticulations) on high resolution chest tomography at five separate levels in the thorax and combines this with forced vital capacity to determine whether the patient has "limited" or "extensive" parenchymal involvement. In the study cohort, 215 patients with extensive lung disease had a more than threefold increased risk of death compared with those with limited lung disease (hazard ratio 3.46, 2.19 to 5.46; $P < 0.0005$), suggesting clinical relevance. Whether this system predicts responsiveness to treatment for ILD or is valid in other CTD-ILD cohorts remains to be determined.

The role of surgical lung biopsy in patients with recognized or suspected CTD-ILD is still unclear. The main arguments for invasive biopsy are the potential role of biopsy pattern in predicting prognosis (usual interstitial pneumonia versus other patterns) and the potential to detect alternative diagnoses such as cancer. Balanced against these potential benefits are the risks of direct complications of surgery (persistent or non-resolving pneumothoraces),

cardiopulmonary complications of surgery (myocardial infarction or thromboembolic events), and exacerbations of ILD associated with surgery. When considering surgical biopsy, the potential for benefit (including the impact on therapy) must be weighed against the potential for harm. The patient's preference must be central to decision making. As an alternative to surgical lung biopsy, bronchoscopy with lavage to assess for infection and cell count may be appropriate in some patients.

ILD as a complication of treatment for autoimmune disease

An additional consideration in patients with ILD and known CTD is the role of drugs used to treat CTD. Many disease modifying anti-rheumatic drugs and biological agents commonly used in CTD have been associated with ILD. The box contains a list of commonly used drugs. A comprehensive and updated list of drugs used to treat CTD that are associated with pulmonary toxicity including ILD can be found at pneumotox.com.

Owing to a lack of evidence based guidelines the following observations and advice are based on clinical experience. When considering patients in whom ILD may be caused by the CTD or its treatment, timing of the onset of therapy may or may not be helpful. In a subset of patients, symptoms begin soon after a new drug is started. In such patients, stopping the drug, along with careful follow-up (with or without a short burst of steroids) may be sufficient. In other patients symptoms of ILD can

Common drugs used for connective tissue disease associated with interstitial lung disease
Methotrexate
Tumor necrosis factor inhibitors
Gold
Penicillamine
Leflunomide
Sulfonamide

develop insidiously, months after a drug is started. This is common in patients with rheumatoid arthritis, in whom both the CTD and the treatment can be associated with ILD. Thus, drugs are often stopped for a while to assess the impact on the ILD. During this time, steroids can be used to bridge the CTD and treat the ILD. Once patients have improved, specific drugs can be reintroduced with careful pulmonary follow-up, including pulmonary function testing, so long as the patient is advised about the potential for recurrent symptoms and is empowered to report any change in symptoms.

Treatment of CTD-ILD

General strategies

Given the wide variation in manifestations of ILD in autoimmune disease, no one management strategy is appropriate for every possible clinical scenario. Patients with mild stable disease may not need treatment. However, general principles can be applied to many situations including acute and chronic disease as discussed below. Although there are no specific guidelines for the management of CTD-ILD, general strategies recommended for the management of IPF are often applied in CTD-ILD. These include use of supplemental oxygen in patients with resting hypoxemia and treatment of asymptomatic gastroesophageal reflux disease.⁶⁴

Acute presentations of ILD

Typically, acute presentations of ILD in patients with autoimmune disease manifest in two ways: de novo acute interstitial pneumonia or acute exacerbations of underlying ILD. In both scenarios, exclusion of other causes of respiratory decompensation should be sought. Although not specifically studied in CTD-ILD, precipitants of acute decompensation of IPF include infection, pulmonary embolism, coronary artery disease, new onset of arrhythmia, pulmonary edema, pneumothorax, and surgery—particularly lung biopsy.^{66 67}

Patients with pulmonary hypertension related to ILD may be at higher risk of acute exacerbations, and this may be influenced by non-adherence with dietary and fluid restrictions.⁶⁸ Exposure to ambient air pollution, particularly ozone and nitrogen dioxide, may also cause acute exacerbations of ILD.⁶⁹ Patients with CTD-ILD may be at higher risk of other processes such as diffuse alveolar hemorrhage (more common in SLE), aspiration (scleroderma), and drug induced toxicity (methotrexate and biologic agents such as infliximab, abatacept, and rituximab). These drugs should be systematically excluded.

While no specific guidelines exist for the management of acute interstitial pneumonia or acute exacerbations of ILD in CTD, common practice patterns extrapolated from observational data in IPF are often followed. These interventions include:

- Broad spectrum antimicrobials covering typical and atypical bacterial pathogens
- Coverage for *Pneumocystis jirovecii* and fungi based on additional testing or risk factors such as pre-existing immunosuppression
- Removal of the offending agents in cases of suspected drug toxicity

- High doses of pulse methylprednisolone (1 g intravenous daily for three days).^{64 70}

An analysis of three RCTs in 2013 suggested that treatment of gastroesophageal reflux disease decreases the risk of acute exacerbations of ILD, so augmentation of antireflux therapy should be considered.⁷¹ In cases of diffuse alveolar hemorrhage refractory to conservative measures and correction of underlying coagulopathy, plasmapheresis has been used with varying success.⁷² However, despite these interventions, mortality for both acute interstitial pneumonia and acute exacerbations of ILD in patients with CTD remains high at 33-100%.⁷³⁻⁷⁵ In the case of ILD associated with autoimmune myositis, intravenous immunoglobulins and pulse steroids may be beneficial.^{76 77} Intravenous or oral cyclophosphamide may also be considered in acute presentations of CTD-ILD.

Chronic presentations of ILD

Despite the clinical impact of pulmonary complications in CTD, there are few RCTs of drugs in this population. Only two adequately powered, RCTs have been conducted in CTD-ILD; both examine the utility of cyclophosphamide in the treatment of scleroderma associated ILD and are discussed below.^{78 79} Thus, because of the limitations of the available data, treatment of chronic CTD-ILD is based on case series and extrapolation from the literature in scleroderma associated ILD and other ILDs such as IPF. Given the marked differences in manifestations of ILD within various CTDs and between CTD-ILD and IPF, this practice is not ideal. Individual immunosuppressive agents used in the management of CTD-ILD are discussed below.

Drugs

Corticosteroids

Corticosteroids remain the mainstay of clinical management of CTD-ILD but few data exist to guide their use. A recent retrospective study of 71 patients with scleroderma-ILD from a single center found improved forced vital capacity (FVC; on average 158 mL) in patients who received continuous corticosteroids over one year compared with a decline (61 mL) in those who did not receive corticosteroids, suggesting beneficial effects on lung function. However, few other data support their use in these patients.⁸⁰ Furthermore, given concerns about the risk of precipitating scleroderma renal crisis, dosing of prednisone should generally not exceed 20 mg daily in these patients.^{81 82} For other forms of CTD-ILD, the dose, route, duration, and tapering of corticosteroids are often determined by the individual clinician and the clinical scenario. Organizing pneumonia is a common pattern of ILD found on lung biopsy in patients with idiopathic inflammatory myopathy (IIM). Case series of patients with cryptogenic organizing pneumonia in which high dose corticosteroids (prednisolone 1 mg/kg/day) were used suggest that patients with this form of ILD may be more sensitive to treatment with corticosteroids.^{83 84} However, other forms of IIM-ILD may be less responsive to corticosteroids.⁸⁵ Similarly, variable responses to corticosteroids have been reported in the chronic management of other forms of CTD-ILD.

Azathioprine

Azathioprine is a purine analog that inhibits T cell and B cell proliferation. It is commonly used in combination with corticosteroids for the management of various forms of CTD-ILD. However, there are few data to support its use, particularly as monotherapy in CTD-ILD. One RCT in scleroderma-ILD examined the efficacy of azathioprine as maintenance therapy for six months after intravenous cyclophosphamide. It found no significant difference in FVC in the treatment arm compared with the placebo arm at 12 months (4.19%; $P=0.08$).⁷⁹ Observational studies in scleroderma-ILD have shown similar results, with maintenance of improvements in lung function at 12 months with azathioprine after intravenous cyclophosphamide.^{86–87} A retrospective analysis of a Taiwanese cohort of patients with IIM-ILD showed improved survival with azathioprine.³⁸ However, no data are available on the utility of azathioprine in other forms of CTD-ILD.

Azathioprine is commonly used as part of combination therapy for CTD-ILD. One study compared triple combination therapy with azathioprine, prednisone, and N-acetylcysteine with N-acetylcysteine alone and placebo in patients with mild to moderate IPF. It found a higher risk of hospital admission and death in patients in the combination arm, prompting early termination of the study.⁸⁸ However, because such studies have not been undertaken in CTD-ILD, there is no evidence that the use of combined azathioprine and prednisone in patients with CTD-ILD and a usual interstitial pneumonia pattern on lung biopsy may be harmful.

Cyclophosphamide

Cyclophosphamide—an alkylating agent that has multiple effects on T cells that lead to impaired immunologic memory—is the only immunosuppressive agent studied in CTD-ILD in RCTs. The two studies were both conducted in patients with scleroderma associated ILD. The first trial, known as the Scleroderma Lung Study, compared oral cyclophosphamide (2 mg/kg/day) with placebo for one year and found a small but significant improvement in FVC (2.53%; $P=0.03$). Overall there were no significant differences in serious adverse events, but patients in the treatment arm experienced more episodes of leukopenia and hematuria.⁷⁸ The second trial examined initial combination therapy with low dose corticosteroids and cyclophosphamide (600 mg/m² body surface area intravenously at monthly intervals for six months) followed by maintenance with azathioprine (2.5 mg/kg/day) compared with placebo.⁷⁹ It found a non-significant trend towards improvement in FVC ($P=0.08$) in the treatment arm. Although the change in FVC in these studies is small and of questionable importance, several observational studies have also shown improvement in FVC with cyclophosphamide.^{89–92} Furthermore, as noted by experts in the field, referral bias based on prevalent clinical open label use of cyclophosphamide in patients with more severe disease may have skewed enrollment into both RCTs towards patients with less severe disease in whom a larger effect size would not be expected.⁹³ Nonetheless, subsequent longitudinal data from the Scleroderma Lung Study suggest that the duration of the observed

effect wanes over time.⁹⁴ Furthermore, the optimal duration, mode (pulsed intravenous versus daily oral), and sequence (cyclophosphamide followed by azathioprine or mycophenolate mofetil) of treatment remain unclear.

As mentioned, no RCTs of cyclophosphamide in other CTD-ILDs have been performed. Case series of patients with PM-ILD, DM-ILD, and MCTD-ILD have been reported and suggest similar improvement in FVC with similar side effect profiles.

Methotrexate

Methotrexate inhibits folic acid and purine metabolism along with T cell activation. It is commonly used in the treatment of joint disease in CTDs such as rheumatoid arthritis and in the prevention of relapse of vasculitis.⁹⁵ However, its role in the management of CTD-ILD is less clear and is tainted by its capacity to cause pulmonary toxicity.⁹⁶ However, in an ongoing prospective study of patients with CTD on methotrexate, the prevalence of methotrexate pulmonary toxicity (defined according to Carson's criteria) was only 2/223 patients at six months and 2/188 patients at one year. This corresponds to an incidence of one case for every 192 person years, lower than in previous retrospective studies.^{97–98} Most patients in this study had rheumatoid arthritis, in whom the risk of pulmonary toxicity may be higher; however, most participants did not have evidence of underlying ILD at enrollment. This may limit the generalizability of these findings to patients with other CTDs or pre-existing ILD. In practice, methotrexate is occasionally used in scleroderma-ILD after failure or intolerance of azathioprine or mycophenolate mofetil. It is also used in PM/DM-ILD, where it may be effective in the treatment of myositis.^{99–100} Few studies have described the use of methotrexate in patients with other forms of CTD-ILD.

Mycophenolate mofetil

Mycophenolate mofetil reduces T cell and B cell proliferation by inhibition of inosine monophosphate dehydrogenase, a crucial factor in purine synthesis. This drug has been studied in various CTD-ILD populations with generally favorable results. In 2013 a case series of 125 patients with ILD associated with various CTDs, including scleroderma ($n=44$), polymyositis or dermatomyositis ($n=32$), and rheumatoid arthritis ($n=19$), reported sustained improvement in FVC and reduced steroid requirement with those taking mycophenolate mofetil.¹⁰¹ Similar findings have been reported in smaller case series of patients with scleroderma associated ILD, as noted in a literature review.¹⁰² Furthermore, a retrospective review of 12 patients with scleroderma-ILD and an inadequate clinical response to cyclophosphamide, who were subsequently started on mycophenolate mofetil, reported improvements in FVC in 25% and stabilization of computed tomography findings in over 50%.¹⁰³ However, a case-control study in 2013 of 20 patients with scleroderma-ILD who received cyclophosphamide or mycophenolate mofetil suggested no difference in lung function parameters but perhaps worsening radiographic findings in the mycophenolate mofetil group after two years of follow-up.¹⁰⁴

Importantly, the recently completed Scleroderma Lung Study II should provide further insight into the role of mycophenolate mofetil in patients with scleroderma associated ILD (NCT00883129). In this study, patients were randomized to two years of mycophenolate mofetil or one year of oral cyclophosphamide followed by one year of placebo, with a primary outcome of change in predicted FVC. Secondary outcome measures include pulmonary function (total lung capacity, DLCO), computed tomography findings (fibrosis score), symptoms, health related quality of life, and skin involvement. At this time, results from this study have been presented only in abstract form.

The role of mycophenolate mofetil in other forms of CTD-ILD has not been well characterized. A retrospective case series of PM/DM-ILD suggested stabilization of lung function in nine patients who received mycophenolate mofetil, with a reduction in steroid requirement and symptoms that was sustained for one year.¹⁰⁵ Improvement in FVC was also noted in DM/PM-ILD and RA-ILD in the retrospective cohort study reported above.¹⁰¹ Although the drug is generally well tolerated, recent case series in patients with renal transplants suggest that it may lead to hypogammaglobulinemia and thus predispose patients to recurrent infections. These patients may in turn be at risk of developing bronchiectasis.¹⁰⁶ However, this effect may not be unique to mycophenolate mofetil. In a cohort study of 45 patients with SLE without ILD who were treated with mycophenolate mofetil or cyclophosphamide, rates of hypogammaglobulinemia were similar for both treatments, although IgA levels were significantly lower in those treated with mycophenolate mofetil.¹⁰⁷ No data on subsequent development of ILD were provided.

Calcineurin inhibitors

Typically used to prevent rejection in solid organ transplantation by inhibiting T cell activation and signal transduction, recent case studies and case series have reported the use of the calcineurin inhibitors tacrolimus and ciclosporin in patients with DM/PM-ILD and IIM-ILD. A recent retrospective study of 49 Japanese patients with PM/DM-ILD comparing outcomes in patients who received conventional therapy (prednisone with intravenous cyclophosphamide or ciclosporin) versus those who received conventional therapy and tacrolimus found significant improvements in event-free survival in those patients who received tacrolimus.¹⁰⁸ However, as noted in an accompanying editorial, the results may not be generalizable to other populations given the high prevalence of anti-MDA-5-positive disease (40% of IIM-ILD in Japan in one study), a particularly aggressive form of CTD-ILD.^{109–110} Furthermore, because more patients in the tacrolimus group received cyclophosphamide, it is unclear whether the improved outcomes were related to cyclophosphamide or tacrolimus.

In another retrospective cohort of patients with IIM-ILD who were treated with ciclosporin or tacrolimus, lung function improved or stabilized in most patients (13/15).¹¹¹ There are no head to head comparisons of calcineurin inhibitors in any form of CTD-ILD or reports of the use of these inhibitors in other forms of CTD-ILD.

Furthermore, dosing of tacrolimus or ciclosporin for this indication is not standardized, although current practice suggests 2–5 mg/kg/day for ciclosporin and 1–3 mg/day for tacrolimus, with monitoring of trough levels to avoid toxicity.

Biologic agents

Rituximab, a monoclonal antibody against the B cell surface antigen CD20, leads to rapid and sustained depletion of B cells from the peripheral circulation for six to nine months. Initially developed as a treatment for certain leukemias and lymphomas, its mechanism of action and potential impact on the pathogenesis of immune disease has extended its use for off label indications such as CTD-ILD. A small study in which patients with scleroderma-ILD who received four cycles of rituximab were followed for two years found a significant improvement in FVC compared with baseline.¹¹² Despite a predominantly negative outcome in a large randomized trial of rituximab in IIM focused on myositis outcomes specifically, case series have suggested a role for rituximab in various forms of CTD-ILD, including PM/DM-ILD, RA-ILD, and MCTD-ILD.^{113–115} A randomized clinical study of rituximab versus cyclophosphamide in progressive CTD-ILD (including scleroderma-ILD, IIM-ILD, and MCTD-ILD), with change in FVC as the primary outcome, is ongoing and is expected to complete in 2017 (RECITAL study, NCT01862926).

Imatinib, a tyrosine kinase inhibitor of a specific tyrosine kinase, BCR-Abl, which is involved in protein phosphorylation, was also developed as a chemotherapeutic agent but has since been used to treat CTD-ILD, notably scleroderma-ILD. However, unlike rituximab, the results have been mixed and problems with tolerability may limit its utility in CTD-ILD. One study reported that use of imatinib in 24 patients with scleroderma-ILD for one year led to improvements in FVC by more than 6% on average. However, another study in 20 patients with scleroderma-ILD found that imatinib was poorly tolerated and only 60% of the patients completed the study.^{116–117} The dose was higher in the second study (600 v 400 mg daily) and this may have contributed to the intolerance and side effects, which included gastrointestinal distress, rash, and renal dysfunction. Thus, the role of imatinib in the treatment of CTD-ILD is unclear and requires further study.

Other biologic agents, such as tocilizumab, eculizumab, and alemtuzumab may have a role in the treatment of CTD-ILD in the future, but experience with these drugs is currently limited. Of note, biologic agents that target tumor necrosis factor—infliximab and etanercept—may be associated with an increased risk of developing ILD, particularly in patients with rheumatoid arthritis.^{118–119} These agents should be used with caution in RA-ILD and perhaps in other forms of CTD-ILD.

Treatment of comorbid conditions of CTD-ILD

Pulmonary hypertension

Pulmonary hypertension is a chronic disease of the pulmonary vasculature characterized by pulmonary vascular injury and remodeling, that leads to increased pulmo-

nary vascular resistance, right ventricular failure, and, ultimately, death.¹⁴ It is associated with many diseases, including CTD, and can result from processes that primarily affect organ systems other than the pulmonary vasculature, such as the heart, lung parenchyma, liver, and kidneys. Direct pulmonary vascular involvement can occur from pulmonary embolism and from pulmonary vascular remodeling in response to endothelial damage, without overt venous thromboembolism, known as PAH.

Pulmonary hypertension is defined by mean pulmonary artery pressure ≥ 25 mm Hg and therefore can be diagnosed only by right heart catheterization. It is currently classified into one of five groups on the basis of associated diseases and risk factors.¹²⁰ Because CTD can affect multiple organ systems, PH-CTD can be associated with any of the five groups of pulmonary hypertension. Most commonly, pulmonary hypertension in CTD is group I (PAH), group II (related to heart disease), or group III (related to lung disease); patients with scleroderma may be more likely than those with other forms of CTD to develop pulmonary hypertension of any of these groups.¹⁴

Pulmonary hypertension commonly complicates ILD in CTD, particularly in patients with scleroderma. Although the true prevalence of this disease in scleroderma-ILD is unknown because of the lack of cohort studies using routine right heart catheterization, it has a great impact on survival. In a cohort of patients with scleroderma-ILD, those with pulmonary hypertension (defined by echocardiographic measurement of right ventricular systolic pressure >45 mm Hg) had a five times greater risk of death than those without pulmonary hypertension in multivariable analyses.¹²¹ Overall, median survival for patients with scleroderma-ILD-PH is two to three years.^{18 122} However, despite improved outcomes for patients with PAH related to CTD in general, targeted treatment of pulmonary hypertension in patients with CTD-ILD-PH has been less effective. Although no RCTs of specific pulmonary vasodilators in CTD-ILD-PH have been reported, observational studies of scleroderma-ILD-PH have found these patients do not exhibit consistent improvement in symptoms, functional capacity, or survival in response to off label use of newer drugs for PAH. In a cohort of 70 patients with scleroderma-ILD-PH who were treated with PAH specific drugs, no changes were seen in symptoms, six minute walk distance, or hemodynamics compared with baseline values and median survival was less than two years.¹²³ However, a recent single center cohort study of 99 patients with scleroderma-ILD-PH showed improvement in outcomes after use of continuously infused treprostinil, a prostacyclin analog, with a two year survival of nearly 60%, suggesting that escalation of PAH specific therapy may improve outcomes.¹²⁴ Some of these observed differences in response to treatment may be related to differences in patient characteristics between cohorts, such as extent of parenchymal lung involvement.

Importantly, the classification system used to define “extensive” and “limited” ILD in scleroderma that showed prognostic value in scleroderma-ILD has yet to be studied as a predictor of response to PAH specific therapies.⁶⁵ This classification system could potentially provide a framework to identify patients who are likely to

benefit from treatment of pulmonary hypertension. Thus, further targeted studies of PAH specific therapies in CTD-ILD-PH, in particular scleroderma-ILD-PH, are warranted.

Sleep disorders

Sleep disordered breathing may also complicate CTD-ILD. Insomnia and sleep disruption due to cough related arousals, nocturnal desaturations, and increased respiratory drive are common, and drugs such as steroids can negatively affect sleep architecture, efficiency, and quality.¹²⁵ Sleep disorders such as restless leg syndrome are common in CTDs such as scleroderma and rheumatoid arthritis, affecting 30% of patients in one study.¹²⁶

Although not rigorously studied in CTD-ILD, the prevalence of obstructive sleep apnea in other forms of ILD is high and does not seem to be directly related to symptoms of excessive daytime sleepiness or obesity.¹²⁷ One recent study of patients with various forms of ILD found that 55% of patients with scleroderma-ILD had obstructive sleep apnea on polysomnography. Interestingly, daytime symptoms in these patients were not severe (assessed by the Epworth sleepiness scale) and did not differ between those with and without obstructive sleep apnea, suggesting that this scale may not be sufficiently sensitive to identify those at high risk of this condition.¹²⁵ Treatment of obstructive sleep apnea with continuous positive airway pressure in these patients may improve sleep quality and quality of life.¹²⁸ Nocturnal hypoventilation related to either respiratory muscle weakness or severe restrictive lung disease (typically with FVC $<45\%$ predicted) can lead to hypoxia and hypercapnia that contributes to daytime symptoms.¹²⁹ Thus, it is reasonable to consider sleep testing for patients with CTD-ILD, even in those without traditional risk factors for obstructive sleep apnea.

Dyspnea and cough

Patients with CTD-ILD commonly have dyspnea and chronic cough related to physiologic impairment of respiratory function as a result of progressive fibrosis of the parenchyma. However, dyspnea can also result from pleural effusions, pulmonary hypertension, or skeletal muscle weakness (with respiratory muscle involvement), and this may be most common in IIM-ILD; directed therapy for each of these may improve symptoms. Pulmonary rehabilitation is an important adjunctive therapy to consider because it can improve dyspnea, depression, anxiety, and quality of life.¹³⁰ Medical therapy for dyspnea specifically in CTD-ILD has not been well described; however, low dose opiates and anxiolytics may alleviate symptoms in fibrotic lung disease in general and should be considered.^{131 132}

Cough is common and difficult to treat effectively in ILD. Given the likely contribution of gastroesophageal reflux and its high prevalence in certain patients with CTD-ILD, such as those with scleroderma, aggressive therapy for reflux including dietary and lifestyle modifications and drugs should be considered. This is especially true given the observed association between the severity of gastroesophageal reflux and ILD in patients with scleroderma and MCTD.¹³³ However, a study of 14 patients with IPF who underwent baseline and follow-up

24 hour esophageal manometry studies after high dose acid suppression found a reduction in acid reflux events but increases in non-acid reflux events and no change in cough counts after eight weeks of therapy.¹³⁴ Nonetheless, the association between gastroesophageal reflux disease and ILD in CTD may differ from that seen for IPF, and our practice is to offer therapeutic and lifestyle modifications for refractory cough.

Patients with Sjögren's syndrome may develop throat dryness that can be associated with cough; treatment with nebulized isotonic saline may improve airways dryness.¹³⁵ Other causes of cough such as post-nasal drip or drug effects (for example, angiotensin converting enzyme inhibitors) should be sought and addressed. An RCT of patients with IPF found a significant reduction in cough in response to thalidomide, although no studies in CTD-ILD have been reported.¹³⁶ However, thalidomide is associated with an increased risk of pulmonary embolism in certain patient populations and may cause edema and should therefore be used with caution.¹³⁷

Palliative care

Recent studies showing improvements in quality of life and even survival benefits in patients with terminal diseases such as lung cancer who participate in palliative care programs have led to investigations of the utility of such interventions in ILD.¹³⁸ An RCT of 105 consecutive patients with chronic dyspnea and various lung diseases, including 19 (18%) with ILD, randomized patients to breathless support training and palliative care versus usual care. Treatment significantly improved six month survival in the overall population and in the ILD population alone.¹³⁹ However, the small number of patients with ILD and the short study duration limit the inferences that can be drawn. Nonetheless, palliative care probably has an important role to play in the management of chronic diseases with no cure, such as ILD, and referral to palliative care specialists is supported by the ATS/ERS guidelines.⁵⁸ Further studies are needed to define the role of palliative care in CTD-ILD.

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation has been studied in patients with scleroderma as part of the Autologous Stem Cell Transplantation International Scleroderma Trial.¹⁴⁰ This open label, parallel group study compared the safety and efficacy of autologous hematopoietic stem cell transplantation versus 12 months of intravenous pulse cyclophosphamide in 156 patients with early diffuse scleroderma. Of note, most of these patients had ILD (>85%). Although long term event-free survival, modified Rodnan skin scores (a marker of severity of skin disease), FVC, and patient important outcomes improved in the transplant group, there were more events, including deaths (8 v 0) in the first year in this group. Furthermore, 22% of patients in the transplant group experienced relapse of disease at 12-24 months, requiring the need for immunosuppressive therapy. This suggests that transplantation is not curative for a large proportion of patients and that although it may improve long term survival, short term survival may be negatively affected. Further

studies of hematopoietic stem cell transplantation in scleroderma are under way and may help clarify the role of this intervention in scleroderma-ILD (Stem Cell Transplant vs Cyclophosphamide (SCOT); NCT00114530).

Lung transplantation

Owing to concerns about the impact of pre-existing conditions on post-transplant outcomes, CTD-ILD is a relative contraindication to lung transplantation at many centers. Potential contributors to poor outcomes include gastroesophageal reflux (thought to cause bronchiolitis obliterans syndrome), renal disease (complicates management of immunosuppressive and antimicrobial agents commonly used after transplantation), and extra-pulmonary disease such as myositis (complicates management of immunosuppression and rehabilitation after transplantation). Because of these concerns, fewer than 2% of all lung transplants worldwide between 1995 and 2010 were given to patients with CTD associated lung disease.¹⁴¹ However, recent studies suggest that post-transplant outcomes in patients with CTD-ILD do not differ significantly from those in patients with non-CTD-ILD.¹⁴²⁻¹⁴⁶ Patients with CTD-ILD should therefore be referred to centers with experience in the evaluation and management of lung transplantation in this population.

Guidelines

Although no guidelines on the management of CTD-ILD are available, we extrapolated certain recommendations from the joint American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines for the management of IPF.¹⁴⁷ We also reviewed treatment guidelines for PAH for the recommendations in this review.^{148 149}

Emerging treatments for CTD-ILD

The role of recently approved treatments for IPF in the treatment of CTD-ILD remains unknown. A case report of pirfenidone in a patient with scleroderma-ILD suggested improvement in lung function but additional studies are needed to confirm this observation.¹⁵⁰ A recently completed open label, randomized, parallel group safety and tolerability study of pirfenidone in scleroderma-ILD (LOTUSS trial; NCT01933334) suggested that patients with scleroderma experience similar side effects with pirfenidone as patients with IPF. Similar studies are planned for nintedanib, an intracellular inhibitor of tyrosine kinases that decreases the rate of decline in lung function in patients with IPF.

Novel inhibitors of pro-inflammatory and profibrotic mediators, such as receptor inhibitors of lysophosphotidic acid, a mediator released by platelets during epithelial injury, are currently being studied in IPF. Targeting T helper type 2 inflammatory pathways is also of interest; recent translational research in patients with IPF suggests a role for the inhibition of interleukin 13 (IL-13) using anti-IL-13 monoclonal antibodies.¹⁵¹ These and other pathways thought to be integral to the pathogenesis of IPF will probably be explored in CTD-ILD as well. Specific studies in CTD-ILD have recently been completed or are ongoing. For example, pomalidomide (CC-4047), a

derivative of thalidomide and an inhibitor of angiogenesis, was studied in scleroderma-ILD (NCT01559129) but was stopped at interim analysis because it failed to meet its primary endpoint of change in FVC. Combination trials, such as the use of bortezomib, a proteasome inhibitor used to treat multiple myeloma, together with mycophenolate mofetil (NCT02370693) in scleroderma-ILD, as well as trials of drugs such as dabigatran that target the thrombotic processes involved in scleroderma-ILD (NCT02426229), will begin enrollment in the near future. These and other studies of novel anti-inflammatory, antifibrotic, and anti-angiogenic drugs may offer additional evidence based treatment options for CTD-ILD in the near future.

Conclusion

Lung disease is a common complication or presenting feature of CTD. Despite increased awareness of CTD-ILD, proper diagnosis can be challenging and is based on the synthesis of clinical, physiologic, radiographic, hemodynamic, laboratory, and pathologic data. Immunosuppression remains the mainstay of treatment for ILD, although few data from RCTs are available to support specific drugs in most forms of CTD-ILD. Supportive therapies, including treatment of comorbidities, such as pulmonary hypertension and sleep disordered breathing, and institution of pulmonary rehabilitation may improve symptoms in these patients. Similarly, PAH and PH-ILD commonly complicate CTD and can lead to high morbidity and mortality. RCTs of novel antifibrotic and immunomodulatory agents for CTD-ILD and of vasoactive and antiproliferative agents for PH-CTD are needed to improve our understanding and the management of these progressive diseases.

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