Interstitial Lung Disease 2

Interstitial lung disease in connective tissue disorders

Aryeh Fischer, Roland du Bois

Some of the most pressing challenges associated with interstitial lung disease (ILD) are how best to define, diagnose, and treat connective tissue disease-associated ILD (CTD-ILD)—disorders with potentially substantial morbidity and mortality. In this focused review, we address aspects of prognosis for CTD-ILD and what indices might predict outcome, together with lessons that can be learnt from clinical trials of systemic sclerosis-associated ILD and idiopathic pulmonary fibrosis and how these lessons might be applied to future studies of CTD-ILD.

Introduction

The interstitial lung diseases (ILDs) are a group of diffuse parenchymal lung disorders that are classified according to specific clinical, radiological, and histopathological features (panel).1 Often, ILD has no identifiable underlying cause and is regarded as idiopathic. Frequently, however, it is associated with a specific environmental exposure or underlying connective tissue disease (CTD). CT has made it possible to characterise ILD with great precision. As a result, the defining features of nearly all ILDs, including the idiopathic interstitial pneumonias, are well described,2,3 which has helped to predict outcome and decide on best treatment.

Arguably one of the most pressing challenges in ILD is to better define the nature and importance of CTD-associated ILD (CTD-ILD)—disorders with substantial morbidity and mortality and controversies about prognosis and best treatment. Challenges include how best to define the various subgroups of CTD-ILD, especially those that present as formes frustes of systemic disease, and how to measure the effects of the ILD, particularly with regard to prognosis and treatment. Matters are further complicated by the eclectic nature of lung involvement in CTD and the many combinations of abnormal changes to the lung—notably, airway disease and ILD.

The designations CTD and collagen vascular disease are used interchangeably, and refer to various systemic autoimmune diseases characterised by immune-mediated organ dysfunction, including: rheumatoid arthritis; systemic lupus erythematosus; systemic sclerosis (scleroderma); primary Sjögren’s syndrome; polymyositis, dermatomyositis, and antisynthetase syndrome; mixed CTD; and undifferentiated CTD. Substantial heterogeneity exists between CTDs, and each is associated with various clinical features. These disorders manifest with autoimmune-mediated organ damage, frequently targeting the lungs, and are associated with many pulmonary manifestations of varied incidence and prevalence—essentially, every component of the respiratory tract is at risk (table 1). Some CTDs (eg, systemic sclerosis, antisynthetase syndrome, and rheumatoid arthritis) are more likely to be associated with ILD than are others, but all patients with CTD are at risk of ILD, which might be the first or only manifestation of their CTD.4-8 Many patients with CTD have subclinical ILD defined by the presence of interstitial lung abnormalities on high-resolution CT in asymptomatic individuals, complicating matters further. Because ILD occurs in many patients with CTD and can be identified subclinically, longitudinal studies of precisely phenotyped cohorts could be developed to better understand causes of disease progression, therapeutic responsiveness, and outcome.9

Although CTD-ILD is frequently encountered in the clinic and has been intensely studied, several questions relating to prognosis and the choice and timing of therapeutic intervention remain. The prevalence of CTD-ILD is unknown, as is the value of screening assessments for detection of ILD. Questions about diagnosis and classification remain—eg, whether patients should be classified by ILD type or by CTD type, what autoimmune aspects in idiopathic ILD are characteristic of CTD-ILD, and whether such a designation matters.

Classification of CTD-ILD

Whether an individual’s ILD is associated with CTD or is idiopathic is only worth deducing if the result affects disease outcome, choice of treatment, or probable response to treatment, or will help to define cohorts in which to study disease mechanisms or to undertake high-quality trials of treatments.

Most importantly, CTD-ILD is associated with a more favourable prognosis than is idiopathic interstitial pneumonia of equivalent severity.10-21 In the case of systemic sclerosis, precise disease classification has helped to successfully enrol patients in, and complete, two trials of

Search strategy and selection criteria

We searched PubMed with the terms “interstitial lung disease”, “connective tissue disease”, “idiopathic pulmonary fibrosis”, and “treatment” and selected the citations for this focused review on the basis of their specific applicability to areas pertinent to prognosis and therapy of connective tissue disease-associated interstitial lung disease. We largely focused on recent publications and those that have provided pivotal insights into the subject of this review. Our reference list was modified on the basis of comments from peer reviewers.
therapy for ILD.\textsuperscript{20,21} Additionally, an association with CTD provides a context for extrathoracic disease manifestations, emphasises the need for surveillance of specific extrathoracic features, and guides management decisions.

Improved survival in patients with CTD-ILD (compared with those with idiopathic ILD)\textsuperscript{8–10} could be attributed to the earlier detection of lung disease in patients at risk for ILD and the fact that subclinical or non-progressive ILD is common in CTD-ILD. Furthermore, by contrast with idiopathic interstitial pneumonia (particularly idiopathic pulmonary fibrosis), individuals with CTD-ILD are more likely to be given anti-inflammatory or immunosuppressive treatment, which might affect survival. Mis-diagnosis of idiopathic pulmonary fibrosis in a patient who has CTD-ILD could deprive that individual of anti-inflammatory therapy—treatment that is no longer recommended for patients with idiopathic pulmonary fibrosis.\textsuperscript{22} The only circumstance in which having a CTD might not confer a better outcome is if an individual has rheumatoid arthritis and the usual interstitial pneumonia histopathological pattern of ILD.\textsuperscript{11,12,14} In this situation, outcome is no better than with the idiopathic form of usual interstitial pneumonia (ie, idiopathic pulmonary fibrosis). Importantly, however, the presence of usual interstitial pneumonia in rheumatoid arthritis might be associated with smoking,\textsuperscript{11} which might account for the worse prognosis.

Because CTD-ILD is generally associated with improved survival, doctors might have an inherent desire to find reasons to define disease as CTD-ILD. However, to establish whether ILD is truly associated with CTD is a process of elimination. Patients with pre-existing CTD need a thorough assessment to exclude alternative causes of lung disease, such as respiratory infection, toxic effects of drugs, environmental exposure, or aspiration-induced lung injury. Similarly, an association with CTD can be difficult to define because ILD might be the presenting manifestation of systemic disease—about 15% of individuals presenting with an idiopathic interstitial pneumonia are ultimately identified as having an associated CTD.\textsuperscript{25,26} In some of these individuals, a serum autoantibody known to be highly specific for a specific CTD (eg, anticyclic citrullinated peptide antibodies and rheumatoid arthritis) might be present despite the absence of overt systemic features, and this complication poses further diagnostic challenges.\textsuperscript{4,15,27,28} Physicians need to be acutely aware of the potential presence of occult CTD when assessing patients with idiopathic interstitial pneumonia, particularly women and those with extrathoracic features of CTD (eg, Raynaud’s phenomenon) or positive autoantibodies.\textsuperscript{27}

By contrast with the improved survival associated with well characterised, established forms of CTD-ILD, whether occult or probable forms of this disease are associated with a better outcome is unknown. Idiopathic interstitial pneumonias could all be pulmonary manifestations of occult CTD, especially when the histopathological pattern is classified as non-specific interstitial pneumonia.\textsuperscript{25,29,31}

Patients can present with some aspects of CTD, but not enough to justify a rheumatological diagnosis to be made according to accepted criteria.\textsuperscript{7} These patients, in whom it seems that the lung is the only or most clinically important manifestation of an occult CTD, are suspected of having a systemic autoimmune disease, identified by the presence of circulating autoantibodies, specific histopathological features on surgical lung biopsy samples, or subtle extrathoracic manifestations, and could be

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**Panel: Classifications of interstitial lung diseases**

**Known causes**
- Drugs
- Connective tissue diseases
- Environmental exposures
- Genetics

**Idiopathic interstitial pneumonias**
- Idiopathic pulmonary fibrosis
- Non-specific interstitial pneumonia
- Respiratory bronchiolitis interstitial lung disease
- Acute interstitial pneumonia
- Desquamative interstitial pneumonia
- Cryptogenic organising pneumonia
- Lymphocytic interstitial pneumonia

**Granulomatous diseases**
- Sarcoidosis
- Fungal infection
- Mycobacterial infection
- Diseases associated with environmental exposures (eg, chronic beryllium disease, hypersensitivity pneumonitis)

**Other forms**
- Pulmonary alveolar proteinosis
- Langerhans’ cell histiocytosis
- Eosinophilic pneumonia
- Langerhans’ cell histiocytosis
- Pulmonary capillaritis

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**Table 1: CTDs and common pulmonary manifestations**

<table>
<thead>
<tr>
<th>CTDs</th>
<th>ILD</th>
<th>Airways</th>
<th>Pleural</th>
<th>Vascular</th>
<th>DAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic sclerosis</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Primary Sjögren’s syndrome</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Mixed CTD</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>+++</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

The signs show prevalence of each manifestation (−=no prevalence; + =low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.
classified as having lung-dominant CTD rather than idiopathic disease.6 Furthermore, despite recognition that ILD might be the forme fruste presentation of CTD, American College of Rheumatology criteria do not have a specific CTD designation for isolated ILD. Classification of such individuals as unique, or as having CTD-ILD, is justified only if such designations affect management decisions or if the natural history of each disease differs. Strategies for identification and classification of these patients are controversial and inadequate. Proposed terminology to classify such patients includes undifferentiated CTD,5,11 lung-dominant CTD,4 and autoimmune-featured ILD5 (table 2, figure 1).

Kinder and colleagues31 proposed that all patients with idiopathic non-specific interstitial pneumonia actually have undifferentiated CTD, but this suggested reclassification is not straightforward. The classification of undifferentiated CTD is well established within the rheumatology community and describes evolving, or partial presentation of, milder forms of the disease, and is not traditionally regarded to be manifested by ILD or other organ-threatening diseases12–16 (table 2). Furthermore, the broader criteria proposed by Kinder and colleagues31 (table 2) will lead to inappropriate diagnoses of CTD-ILD—eg, patients with non-specific interstitial pneumonia, gastro-oesophageal reflux disease, and a high erythrocyte sedimentation rate could be inappropriately classified as having CTD-ILD.

Corte and colleagues32 have also questioned the clinical relevance of defining patients with idiopathic interstitial pneumonia as having undifferentiated CTD. They retrospectively studied 45 patients with biopsy-proven non-specific interstitial pneumonia and 56 patients with biopsy-proven usual interstitial pneumonia. They

<table>
<thead>
<tr>
<th>Symptoms or clinical features</th>
<th>Autoantibodies, laboratory abnormalities, or histopathology findings</th>
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<tbody>
<tr>
<td><strong>Undifferentiated CTD, strict definition</strong>31†</td>
<td>One or more of these symptoms: dry eyes or dry mouth; joint pain or swelling; Raynaud’s phenomenon; proximal muscle weakness; morning stiffness</td>
</tr>
<tr>
<td><strong>Undifferentiated CTD, broad definition</strong>31‡</td>
<td>One or more of these symptoms: dry eyes or dry mouth; gastro-oesophageal reflux disease; weight loss; recurrent unexplained fever; joint pain or swelling; rash; photosensitivity; dysphagia; non-androgenic alopecia; mouth ulcers; Raynaud’s phenomenon; morning stiffness; proximal muscle weakness</td>
</tr>
<tr>
<td><strong>Lung-dominant CTD</strong>31†</td>
<td>All of these three clinical features: (1) non-specific interstitial pneumonia, usual interstitial pneumonia, lymphocytic interstitial pneumonia, organising pneumonia, or diffuse alveolar damage (or desquamative interstitial pneumonia if no smoking history), determined by surgical lung biopsy or suggested by high-resolution CT; (2) insufficient extrathoracic features of a definite CTD; and (3) no identifiable alternative cause for interstitial pneumonia</td>
</tr>
<tr>
<td><strong>Autoimmune-featured ILD</strong>32*</td>
<td>One or more of these symptoms: dry eyes or dry mouth; gastro-oesophageal reflux disease; weight loss; foot or leg swelling; joint pain or swelling; rash; photosensitivity; dysphagia; hand ulcers; mouth ulcers; Raynaud’s phenomenon; morning stiffness; proximal muscle weakness</td>
</tr>
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</table>

CTD=connective tissue disease. ILD=interstitial lung disease. ANA=antinuclear antibody. dsDNA=double-stranded DNA. CCP=cyclic citrullinated peptide. *At least one clinical feature and one laboratory finding should be present for diagnosis. †All three listed clinical features and either (a) or (b) from the final column should be present for diagnosis.

Table 2: Proposed diagnostic criteria for possible subtypes of CTD-ILD

![Figure 1: Management schema for interstitial pneumonia in CTD](https://example.com/figure1.png)

CTD=connective tissue disease. ILD=interstitial lung disease. ANA=antinuclear antibody. dsDNA=double-stranded DNA. CCP=cyclic citrullinated peptide. *At least one clinical feature and one laboratory finding should be present for diagnosis. †All three listed clinical features and either (a) or (b) from the final column should be present for diagnosis.
reported that features of CTD are common in patients with idiopathic interstitial pneumonia, with 31% of patients with non-specific interstitial pneumonia and 13% of those with idiopathic pulmonary fibrosis meeting established diagnostic criteria for undifferentiated CTD (table 2). However, when the broader, less specific set of proposed diagnostic criteria for undifferentiated CTD were applied (table 2), 71% of patients with non-specific interstitial pneumonia and 36% of those with idiopathic pulmonary fibrosis could be reclassified as having undifferentiated CTD. Because of its poor specificity, the investigators argued against further implementation of the broader set of criteria to define undifferentiated CTD in patients with idiopathic interstitial pneumonia.

Studies have attempted to address the prognostic implications of these somewhat nebulous designations. Corte and colleagues showed that although a diagnosis of undifferentiated CTD according to narrow criteria was associated with a histopathological pattern of non-specific interstitial pneumonia, being classified as having undifferentiated CTD did not affect survival in these patients.

Fischer and colleagues assessed the prognostic importance of antinuclear antibody (ANA) detection in patients with biopsy-proven, idiopathic, usual interstitial pneumonia. 25 of 285 patients had nucleolar-pattern ANA, and on retrospective assessment these individuals had subtle extrathoracic features suggestive of systemic sclerosis rather than idiopathic pulmonary fibrosis. Although the nucleolar-pattern ANA cohort had a lung-dominant CTD phenotype, no difference in survival was seen between patients with usual interstitial pneumonia with a positive nucleolar-pattern ANA (ie, possible CTD-ILD) and those with idiopathic pulmonary fibrosis.

Vij and colleagues described a cohort of patients with usual interstitial pneumonia-predominant ILD retrospectively identified as having autoimmune-featured ILD. Of 200 patients that presented to an ILD referral centre, 63 were thought to have autoimmune-featured ILD because they had insufficient features to define definite CTD, a sign or symptom suggestive of a CTD, and a positive serologic test result for an autoimmune process (table 2). Patients thought to have autoimmune-featured ILD had similar survival outcomes to those with idiopathic pulmonary fibrosis, but worse survival outcomes than those with definite forms of CTD-ILD. Of those with autoimmune-featured ILD, only the presence of ANA at a titre of greater than 1:1280 was associated with improved survival, which provides evidence against over-reliance on non-specific symptoms incorporated into the proposed criteria.

Other data from patients whose surgical lung biopsy samples showed a histopathological pattern consistent with usual interstitial pneumonia suggest that the presence of circulating autoantibodies is associated with specific autoimmune histopathological features, even in the absence of CTD. Song and colleagues compared secondary histopathological features between three groups of patients with biopsy-proven usual interstitial pneumonia. Group 1 (n=39) had CTD-associated usual interstitial pneumonia, group 2 (n=27) had antibody-positive (ANA or rheumatoid factor) idiopathic usual interstitial pneumonia (ie, antibody-positive idiopathic pulmonary fibrosis), and group 3 (n=34) had antibody-negative idiopathic usual interstitial pneumonia. Patients with CTD-associated usual interstitial pneumonia had more germinal centres, plasma cells, and fewer fibroblastic foci than did patients with idiopathic usual interstitial pneumonia. Histopathological features differed between groups 2 and 3 according to autoantibody status; although none of group 2 had extrathoracic features of CTD, they had more germinal centres and more plasma cells than did group 3. Notably, no histopathological features distinguished CTD-associated usual interstitial pneumonia (group 1) from antibody-positive idiopathic-usual interstitial pneumonia (group 2). Of patients with idiopathic usual interstitial pneumonia (groups 2 and 3), antibody status did not predict survival, but patients in groups 2 and 3 had a worse disease outlook than did those with CTD-associated usual interstitial pneumonia (group 1). The relation between circulating, albeit non-specific, autoantibodies and histopathological features is of interest, and raises the possibility that systemic autoimmunity might be of aetiological importance in this cohort of patients, and that the lungs might be the source of autoantibody production.

Definitive conclusions about differences in outcome cannot yet be drawn from these retrospectively identified cohorts of patients with various forms of possible or less well defined disease. However, so far, results of studies suggest that no difference exists between these groups.

Advancement in this subspecialty would be helped by increased dialogue between associated disciplines. The pulmonary and rheumatology communities need to agree on the characterisation and classification of CTD to address this interdisciplinary divide. Importantly, any of the proposed terms or criteria should be viewed as provisional. We believe that patients with possible or less well defined CTD-ILD (undifferentiated CTD) should be distinguished from those with established forms of the disease, because the natural history of less well defined disease and whether it truly behaves as a CTD-ILD have not yet been validated.

Well-organised prospective studies are needed to better answer several important questions. Do specific autoantibodies exist that play a part in the evolution from less defined to well defined CTD? Does the presence of antibodies alone in a patient with ILD carry prognostic significance, irrespective of whether the disease is associated with defined CTD? Are specific autoimmune histopathological features associated with survival, irrespective of any association with a defined CTD? How can we devise and implement a more unified, consistent
set of classification criteria to be used in multi-institutional collaborative studies of individuals with possible forms of CTD-ILD?

**Predicting outcomes**

Most knowledge about determinants of progression and prognosis in CTD-ILD comes from studies of the natural history of systemic sclerosis-associated ILD. Whether these data are applicable to other forms of CTD-ILD is not known and should be studied. Several large studies have shown that for patients with idiopathic interstitial pneumonia, a histopathological pattern of usual interstitial pneumonia is associated with worse survival than is a pattern showing non-specific interstitial pneumonia.\(^1\)\(^-\)\(^4\) For patients with CTD, the effect of having usual interstitial pneumonia rather than non-specific interstitial pneumonia on survival is less certain.

Bouros and colleagues\(^8\) reviewed 80 patients with biopsy-proven systemic sclerosis-associated ILD and reported that 5-year survival differed little between patients with non-specific interstitial pneumonia (91%) and those with usual interstitial pneumonia (82%).\(^9\) Mortality was related to severity of disease, defined by initial diffusing capacity of the lung for carbon monoxide (DLCO), initial forced vital capacity (FVC), and the rate of decline in DLCO. Similarly, Park and colleagues\(^10\) assessed prognostic variables in a diverse cohort of 93 individuals who underwent surgical lung biopsies for CTD-ILD (37 had systemic sclerosis, 28 had rheumatoid arthritis, 11 had Sjögren’s syndrome, eight had polymyositis or dermatomyositis, and nine had another form of CTD). Although age, duration of dyspnoea, and FVC predicted outcome, the distinction between non-specific and usual interstitial pneumonia did not. Subset analyses of the rheumatoid arthritis-associated ILD cohort suggested that survival in patients with usual interstitial pneumonia might be similar to that in those with idiopathic pulmonary fibrosis, and worse than that in patients with CTD-associated non-specific interstitial pneumonia or other, non-rheumatoid arthritis-associated, CTD-associated usual interstitial pneumonia. However, after adjustment for age, sex, and FVC, these differences did not persist, suggesting that survival in patients with rheumatoid arthritis-associated usual interstitial pneumonia is similar to that in patients with other forms of CTD-ILD. In a series of 18 patients with rheumatoid arthritis-associated ILD, those with usual interstitial pneumonia (n=10) had worse survival than did those with non-specific interstitial pneumonia (n=6).\(^11\) However, all patients with usual interstitial pneumonia—but none with non-specific interstitial pneumonia—had a history of smoking,\(^11\) perhaps confounding survival findings.

Kim and colleagues\(^12\) retrospectively assessed whether a diagnosis of usual interstitial pneumonia on the basis of the pattern of abnormality seen on high-resolution CT, predicted outlook in 82 patients with rheumatoid arthritis-associated ILD. The median survival time for all patients with this disease was 5 years. Patients with a definite usual interstitial pneumonia pattern had a worse median survival time than did those who did not have this pattern (3.2 years vs 6.6 years; \(p=0.04\)). Median survival time did not differ between the rheumatoid arthritis-associated usual interstitial pneumonia and idiopathic pulmonary fibrosis groups (\(p=0.66\)). Male sex, low baseline FVC and DLCO, and a definite usual interstitial pneumonia pattern on high-resolution CT were associated with worse survival in rheumatoid arthritis-associated ILD. In view of these data, the investigators suggested that knowledge of underlying histopathology in this disease will help to guide management—patients with rheumatoid arthritis-associated non-specific interstitial pneumonia should be given immunosuppressives, and those with rheumatoid arthritis-associated usual interstitial pneumonia should be counselled about their worse outlook and considered for lung transplantation.

In systemic sclerosis-associated ILD, loss of lung function and extent of fibrosis seem to be the most important prognostic variables.\(^12\) Importantly, patients with systemic sclerosis-associated ILD seem likely to lose lung function and have progression of fibrosis early in the disease course. Steen and colleagues\(^13\) showed that a major decline in FVC occurs within the first 4–6 years of onset of systemic sclerosis.

77 patients with systemic sclerosis-associated ILD randomly assigned to receive placebo in the Scleroderma Lung Study\(^*\) had a 4.2% decline in FVC and 8.2% decline in DLCO over 12 months. The rates of decline in FVC and DLCO were similar across the categories of disease duration (0–2 years, 2–4 years, and 4–7 years). A greater extent of maximum fibrosis on high-resolution CT at baseline was associated with a greater decline in FVC, and this effect was most evident during the first 2 years after disease onset.

Goh and colleagues\(^14\) proposed that the extent of fibrosis, as seen on high-resolution CT, and FVC in patients with systemic sclerosis-associated ILD provide enough discriminatory prognostic information to subclassify this disease as either limited or extensive (figure 2). Disease is classified as limited if less than 10% of the lungs is affected, extensive if more than 30% is affected, but indeterminate if 10–30% is involved. When indeterminate, an FVC of 70% or greater (predicted) signifies limited disease, whereas an FVC of less than 70% suggests extensive disease. This distinction with this simple staging system provided a more accurate prognostic separation of systemic sclerosis-associated ILD than had been achieved with any other index alone. We believe this staging system should feature in management decisions in clinical care and future clinical treatment trial design.

Early reports based on small series of patients with systemic sclerosis-associated ILD seemed to suggest that neutrophilia and eosinophilia, detected by broncho-alveolar lavage, were associated with an increased
probability of ILD progression.46 Findings from studies of two large systemic sclerosis-associated ILD cohorts challenge this notion. Goh and colleagues46 assessed the prognostic importance of bronchoalveolar lavage cellular profiles in 141 patients. The presence of neutrophilia in bronchoalveolar lavage samples was not associated with time to decline in pulmonary function or progression-free survival. Similarly, neither eosinophilia nor lymphocytosis detected by bronchoalveolar lavage was associated with mortality, rapidity of functional deterioration, or progression-free survival. Bronchoalveolar lavage neutrophilia was weakly associated with early mortality, and more strongly associated with disease severity (defined as the extent of fibrosis on high-resolution CT) and greater functional impairment (measured by pulmonary function testing). After disease severity has been quantified by high-resolution CT and pulmonary function testing, bronchoalveolar lavage findings are no longer independent predictors of prognosis in systemic sclerosis-associated ILD. Similarly, Strange and colleagues18 assessed whether or not bronchoalveolar lavage neutrophilia or eosinophilia predicted disease progression or treatment responsiveness in 141 patients enrolled in the Scleroderma Lung Study.39 They reported that although bronchoalveolar lavage neutrophilia and eosinophilia were associated with poor lung function and severe fibrosis on high-resolution CT, they were not predictive of disease progression or response to cyclophosphamide treatment after 1 year.

In view of these studies, the routine use of bronchoalveolar lavage to solely predict the likelihood of disease progression or treatment responsiveness in CTD-ILD is no longer necessary. Bronchoalveolar lavage, however, is often done to exclude infection, and could also be used as a component of research protocols.

Serum concentrations of a MUC1 mucin, Krebs von den Lungen 6 (KL-6), and surfactant protein D (SFTPD)—glycoproteins secreted by type II pneumocytes—are regarded as possible biomarkers for the presence of various ILDs, including ILD associated with systemic sclerosis.48,51,52 SFTPD seems to participate in a range of innate immune and inflammatory responses, and its expression is increased in response to lung injury. Serum concentrations of SFTPD rise when the alveolar epithelium is damaged and seem to be linked to the presence of ILD in patients with systemic sclerosis. Similarly, serum concentrations of KL-6 are associated with alveolar damage and activation. KL-6 enters the circulation as a result of increased pulmonary vascular and epithelial permeability. Serum concentrations of SFTPD and KL-6 in 66 patients with systemic sclerosis-associated ILD enrolled in the Scleroderma Lung Study48 (44 with alveolitis defined by bronchoalveolar lavage or high-resolution CT) were significantly increased compared with the ten healthy controls, and of those with systemic sclerosis, concentrations were higher in patients with high resolution CT-defined alveolitis than in those without. SFTPD and KL-6 were positively correlated with extent of fibrosis on high-resolution CT, but not with ground-glass opacity. Several investigators have suggested that measurement of both SFTPD and KL-6 could help to diagnose and monitor systemic sclerosis-associated ILD.48,51,52 Although many studies of alveolar cell proteins and ILD have been correlatively, rather than predictive, findings from studies from the Royal Brompton Hospital (unpublished) have shown that higher baseline serum KL-6 concentrations were associated with a more rapid subsequent decline in FVC in patients with systemic sclerosis-associated ILD than were lower KL-6 concentrations.

Management dilemmas and challenges to CTD-ILD treatment trials

Management of CTD-ILD is challenging. Other than for systemic sclerosis-associated ILD, no controlled clinical trial data are available to guide management decisions. Available therapeutic options are scarce, and therapies that are available could potentially be very toxic. The heterogeneity of diseases within this broad group and the scarcity of well defined outcome measures contribute to the challenge.

Since subclinical ILD is often identified in patients with CTD, not all patients with CTD-ILD need treatment. The decision to treat often depends on whether the patient is clinically impaired by the ILD, whether disease is progressive, and what mitigating factors exist. Assessment of the extent of fibrosis on CT and FVC reduction—as has been proposed for systemic sclerosis-associated ILD—might help to decide whether or not to treat other forms of CTD-ILD. Immunosuppressive treatment is generally reserved for patients with clinically important, progressive disease, identified by a range of assessment methods that include both subjective and objective measures of respiratory impairment.

Recruitment of sufficient numbers of patients for clinical trials (or other research studies) of CTD-ILD is difficult. Generally, CTDs are rare disorders, and the
prevalence of ILD varies with each. Because ILD occurs more often with systemic sclerosis than with any other CTD, and because patients with systemic sclerosis tend to be referred to specialty centres, efforts to study systemic sclerosis-associated ILD have been more successful than for others. In fact, the only controlled clinical trial data for CTD-ILD are for systemic sclerosis-associated disease,20,21,54 and these studies were only able to enrol relatively few patients. Whether randomised, multicentre, controlled treatment trials for rheumatoid arthritis-associated or myositis-associated ILD are feasible is not known; if successful, such trials will undoubtedly set new benchmarks for the management of lung disease associated with CTD.

So far, all controlled clinical trials for the treatment of systemic sclerosis-associated ILD have used cyclophosphamide as at least the first phase of treatment.20,21,54 The evidence on which choices of treatment for other forms of CTD-ILD can be based is largely restricted to small series and retrospective data suggesting the potential role of several drugs (eg, cyclophosphamide, azathioprine, ciclosporin, tacrolimus, and mycophenolate mofetil).20,21,54–62

Cyclophosphamide is one of the most potent steroid-sparing immunosuppressive drugs used to treat autoimmune-mediated organ-threatening damage. It is cytotoxic to both resting and dividing lymphocytes, and suppresses both humoral and cellular immune responses. White and colleagues61 retroactively assessed whether oral cyclophosphamide affected lung function or survival in patients with systemic sclerosis-associated ILD and alveolitis (defined by bronchoalveolar lavage or lung biopsy). 39 patients received cyclophosphamide (35 orally, four intravenously) and 30 did not receive cyclophosphamide. During a 13–16 month follow-up, FVC in patients given cyclophosphamide was more likely to have stabilised or improved than in those given nothing (43% increase in FVC in cyclophosphamide group vs 71% decline in untreated group), and patients given cyclophosphamide had improved survival (89% vs 71%).

Two prospective placebo-controlled trials of cyclophosphamide have been done in patients with systemic sclerosis-associated ILD. The Scleroderma Lung Study was a multicentre, randomised, placebo-controlled trial of 158 patients with systemic sclerosis-associated ILD from 13 centres across the USA.21,54 Tashkin and colleagues39 reported that a 1 year course of oral cyclophosphamide improved FVC, dyspnoea, skin thickening, functional disability, and quality of life compared with placebo, albeit with more adverse events than with placebo. The greatest treatment effect was seen in patients with the most severe lung fibrosis on high-resolution CT. A major limitation of this study is that only 54 of 79 patients in the cyclophosphamide group, and 55 of 72 in the placebo group, completed the study.

The Fibrosing Alveolitis in Scleroderma Trial30 was a multicentre, randomised, placebo-controlled trial of 45 patients with systemic sclerosis-associated ILD from five centres across the UK randomly assigned to receive an intravenous infusion of cyclophosphamide or placebo (once a month for 6 months) followed by oral azathioprine or placebo. The investigators noted more of an improvement in FVC in the cyclophosphamide cohort than in the placebo cohort, but this difference was not significant (p=0.08). Adverse events with active treatment were few, generally not sustained, and resulted in withdrawal of therapy in only two patients.

Taken together, these studies emphasise that: prospective, randomised, placebo-controlled, multicentre studies can be successfully done in systemic sclerosis-associated ILD; the treatment effect seems to be mainly prevention of progression of fibrotic disease rather than any reversal of fibrotic change; stabilisation of disease in systemic sclerosis-associated ILD should be viewed as a therapeutic success; and because none of the treatment effects seen in the Scleroderma Lung Study were sustained at 24 months, a longer-term plan for immunosuppression will probably be needed to manage systemic sclerosis-associated disease. However, although cyclophosphamide was stopped at 12 months, the difference in disease behaviour between groups lasted for 18 months,61 which suggests that cyclophosphamide might affect disease behaviour for as long as 6 months after drug cessation.

The specific role of cyclophosphamide for systemic sclerosis-associated ILD continues to be controversial. Indeed, the accompanying editorial63 to the Scleroderma Lung Study concluded that the slight therapeutic response and the potential for substantial toxic effects do not support the conclusion that 1 year of daily cyclophosphamide should be considered for all individuals with systemic sclerosis-associated ILD. Furthermore, whether the findings from trials of cyclophosphamide in patients with systemic sclerosis-associated ILD can be applied to other forms of CTD-ILD is not known.

The choice of a clinical trial endpoint that is clinically meaningful, is indicative of change in disease status, and can be measured accurately is a challenge.64 FVC has robust performance characteristics that justify its use in trials of ILD. In patients with idiopathic pulmonary fibrosis, categorical change in predicted FVC is consistently associated with changes in other clinically important outcomes and is a strong predictor of mortality.65,66 The difficulty with all physiological endpoints is that patients do not progress or worsen at the same rate—many patients have long periods of disease stability that punctuate periods of decline. Many patients lose a lot more lung function than is implied by the change in group mean from baseline to end of study if some of the individuals in their group stay stable. The absence of a significant between-group difference in the changes in group mean often causes much misunderstanding, because observers extrapolate the amount of group change to the same change in an individual’s
disease status and conclude that the change is too small to matter. For example, in the Scleroderma Lung Study,27,44 the mean absolute difference in adjusted 12-month FVC (predicted) between the cyclophosphamide and placebo groups was 2·53%. This value seems small, and would certainly be regarded as within the limits of measurement error if this difference was the amount of change seen in one patient over time. However, this value is a group mean difference that comprises various amounts of change, including no change at all, resulting in an underestimate of change for individuals who lost large amounts of lung function. Because of this effect, the investigators subsequently explored ways in which future studies might use population enrichment so that cohorts are selected with criteria that can predict whose disease might rapidly worsen during the time of the study, thereby increasing the likelihood of recording any positive drug effects on that change.44 Although the entry criteria for the Scleroderma Lung Study attempted to enrich the population for active disease by use of bronchoalveolar lavage and high-resolution CT criteria, these criteria have now been clearly shown to not accurately predict evidence of activity or probable progression. However, secondary analyses of the dataset have identified a potentially more robust enrichment strategy. Future studies should recommend that patients meet a severity threshold on the basis of high-resolution CT and FVC criteria (as discussed above) and one or both of two minor criteria: short duration of systemic disease (defined as first 6 years after onset of signs or symptoms attributable to systemic sclerosis from first non-Raynaud’s signs or symptoms); or recorded progression (>10% decline of predicted FVC over the past 3–12 months). Those most at risk of decline will therefore be included in any trials, increasing the likelihood that the trial drug will have a positive effect. However, enrichment in this way is not guaranteed to be successful, needs to be tested, and reduces the number of patients eligible for inclusion.

Of all the ILDs, idiopathic pulmonary fibrosis has had by far the most trials of new therapy.44 Results of these studies have often been disappointing, but positive pirfenidone studies have resulted in approval of pirfenidone in Europe, Japan, China, and India.56–71 The many negative studies have prompted debate on several issues of trial design—most notably that of choice of endpoint, particularly whether all-cause mortality and all-cause hospital admissions should be used.72,73 What has become increasingly clear from idiopathic pulmonary fibrosis studies is that even in this disease, which has a much greater rate of mortality than do nearly all CTD-ILDs, the numbers of patients and the length of trial needed to show a reasonable reduction in mortality are too prohibitive. Other suggested endpoints, including patient-reported outcomes or all-cause hospital admissions, are too noisy, with potential confounding from non-pulmonary factors, variable hospital practices, and reasons for hospital admissions. FVC does seem to be the most balanced endpoint in idiopathic pulmonary fibrosis trials, and in a continuing study of pirfenidone in the USA, an enrichment approach has been taken in recruitment that should maximise the chance of recording a drug effect (if an effect is present), with FVC as the primary endpoint.

Without well designed, thoughtful clinical trial implementation, several fundamental questions will go unanswered. Can we extrapolate the findings from studies of systemic sclerosis-associated ILD to other forms of CTD-ILD? Should the presence of specific autoimmune features affect management decisions? Should physicians make management decisions without taking into account the specific patterns of ILD (eg, non-specific interstitial pneumonia vs usual interstitial pneumonia)? Or should treatment be varied according to the underlying pattern,73 so that patients with rheumatoid arthritis-associated non-specific interstitial pneumonia are given immunosuppression whereas those with rheumatoid arthritis-associated usual interstitial pneumonia are told that their outlook is worse than other ILD patterns and that they should be considered for lung transplantation (as is often recommended in idiopathic pulmonary fibrosis)? What specific drugs should be used for CTD-ILD? Would these drugs vary according to CTD type, ILD type, or both? These and other questions need a sustained and coordinated multicentre network to be answered. The notion of a CTD-associated lung, in which all forms of lung disease associated with CTD are lumped together, is outdated. Since CTD-ILD is associated with substantial morbidity and mortality, the knowledge base needs to keep increasing and the challenges need to be met to move forward for the benefit of patients.

Contributors
Both authors contributed equally to the development, content, writing, and final preparation of this manuscript.

Conflicts of interest
AF is a speaker, advisory board member, and consultant for Actelion Pharmaceuticals; a speaker and advisory board member for Gilead Pharmaceuticals; and an investigator for the Scleroderma Lung Study II. In the past 3 years, R&D has served on scientific advisory boards for InterMune, Actelion, and Boehringer-Ingelheim, and has been a consultant to Bayer, Novartis, and Merck and a lecturer at symposia organised by InterMune, Boehringer-Ingelheim, and GlaxoSmithKline.

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